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DEVELOPMENT OF PROMETHAZINE MUCOADHESIVE TABLETS FOR BUCCAL DELIVERY: *IN VITRO, EX VIVO* AND *IN VIVO* CHARACTERIZATION

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ABSTRACT

Promethazine Hydrochloride (PMZ), a low bioavailabe drug, used for the management of emesis. The purpose of the present investigation was to develop buccoadhesive tablets for PMZ and to evaluate for their physicochemical, in vitro, ex vivo and in vivo parameters. Ex vivo drug permeation through porcine buccal membrane from the drug solution was conducted to know the permeation characteristics of the PMZ. The controlled-release PMZ tablets were produced by direct compression method using Sodium CMC and Carbopol 934P as mucoadhesive polymers and evaluated for in vitro drug release, in vitro bioadhesion, in vivo residence time, swelling and erosion studies, surface pH, ex vivo drug permeation through porcine buccal membrane from the optimized buccal tablet (F10) and stability studies. Formulation F10 showed maximum drug release (96.3 %) in 6 h, with the Higuchi model release profile and permeated 49.8 % of the drug with flux 1.45 mg $h^{-1}cm^{-2}$ through porcine buccal membrane. The optimized formulation showed peak detachment force (1.64 N), work of adhesion (0.36 mJ), in vivo residence time (287 min), swelling index (204%), erosion (53.1%) and surface pH (6.92). In vivo mucoadhesive behaviour of the optimized formulations was studied in healthy human volunteers and subjective parameters were evaluated. The stability of the optimized formulation was studied and no significant changes were detected in drug content and in vitro release after 6 months. PMZ mucoadhesive tablets for buccal delivery could be prepared with required permeation, bioadhesive and in vivo residence properties.

Keywords: Promethazine HCl, buccal tablets, *in vitro* release, bioadhesion, *ex vivo* permeation

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INTRODUCTION

The interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of those drugs that undergo first-pass effect. Drug delivery via the buccal route using bioadhesive dosage forms offers such a novel route of drug administration. This route has been used successfully for the systemic delivery of number of drug candidates[1, 2] Problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route[3, 4]. Moreover, buccal drug delivery offers a safe and easy method of drug utilization, because drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity. It is an alternative route to administer drugs to patients who are unable to be dosed orally. Therefore, adhesive mucosal dosage forms are suggested for buccal delivery, including adhesive tablets [5, 6], adhesive patches[7, 8] and adhesive gels[9].

During the past decade, bioadhesive polymers have received considerable attention for platforms of buccal controlled delivery because of their ability to localize the dosage form in specific regions to enhance drug bioavailability[10]. Bioadhesive polymers can not only cause the adhesion effects but can also control the release rate of the drug[11]. From a technological point of view, an ideal buccal dosage form must have 3 properties. It must (1) maintain its position in the mouth for a few hours; (2) release the drug in a controlled fashion, and (3) provide the drug release in a unidirectional way toward the mucosa. In regard to the first requirement, strong adhesive contact to the mucosa is established by using mucoadhesive polymers as excipients. If the mucoadhesive excipients are able to control drug release, the second requirement can also be achieved. The third objective can be fulfilled by preparing a system having uniform adhesiveness and impermeable backing layer[12].

Promethazine Hydrochloride (PMZ) is a first-generation H_1 receptor antagonist of the phenothiazine chemical class used medically as an antihistamine antiemetic and is effective in preventing motion sickness. PMZ is well absorbed from the gastrointestinal tract and undergoes for extensive first-pass metabolism leading to poor bioavailability[13] (25%). From both, physicochemical (low molecular weight 320.9 g mol^{-1}, low dose 25 mg) and pharmacokinetic (absolute bioavailability 25%) perspective, PMZ was considered to be a suitable candidate for buccal delivery.

A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a

predictable manner to elicit the required therapeutic response. The aim of present study was to develop buccoadhesive buccal tablets using Sodium carboxymethyl cellulose and Carbopol 934P either alone or in combination and to evaluate for in vitro drug release, in vitro bioadhesion, in vivo residence time, swelling and erosion studies, surface pH, ex vivo drug permeation through porcine buccal membrane from the optimized buccal formulation and stability studies.

MATERIALS AND METHODS

Materials

Promethazine Hydrochloride and PVP K 30 were gifted by Dr.Reddy's Laboratories, Hyderabad, India. Carbopol 934P and Pearlitol SD 200 were gifted by Zydus Cadila, Ahmadabad, India. Mucin (Crude Type II) was procured from Sigma-Aldrich (Germany) and was used without further purification. Phenol red was obtained from Hi Media Laboratories Pvt., Mumbai, India. All other chemicals and reagents used were of analytical grade and purchased from Merck Ltd., Mumbai, India.

Buccoadhesive tablets preparation

Buccoadhesive tablets of PMZ were prepared by direct compression of the drug with mucoadhesive polymers using a flat-faced, single punch (8 mm diameter) tableting machine (Cadmach, India) (Table 1). Sodium carboxy methyl cellulose and Carbopol 934P were used as mucoadhesive polymers and Pearlitol SD 200 as diluent, PVP K30 as channeling agent and sodium stearyl fumarate (SSF) as lubricant. The mass of the tablets were determined using a digital balance (Shimadzu, Japan) and thickness with a digital screw gauge (Mitutyo, Japan).

Table 1. Composition of Promethazine Hydrochloride buccal tablets

Ingredient	Formulation (mg per tablet)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Promethazine HCl	10	10	10	10	10	10	10	10	10	10
Carbopol 934P	25	20	15	10	15	10	5	2.5	2.5	1.5
Sodium CMC	35	40	45	50	25	30	35	37.5	27.5	28.5
PVP K-30	6	6	6	6	5	5	5	5	5	5
Pearlitol SD 200	23	23	23	23	44	44	44	44	54	54
SSF	1	1	1	1	1	1	1	1	1	1

Assay of tablets

Twenty tablets were taken and powdered; powder equivalent to one tablet was taken and was allowed to dissolve in 100 mL of double distilled water on a rotary shaker overnight. The solution was centrifuged and the supernatant was collected. The absorbance was measured using a UV-Vis Spectrophotometer (Elico, India) at 254 nm[19].

Tissue isolation (Isolation)

Porcine buccal tissue from domestic pigs was obtained from a local slaughterhouse and used within 2 hours of slaughter. The tissue was stored in Krebs buffer pH 7.4 [sodium chloride (118 mM), potassium chloride (5.4 mM), sodium hydrogen phosphate (1 mM), magnesium sulfate (1.2 mM), calcium chloride (1.9 mM), sodium hydrogen carbonate (25 mM), and dextrose (11.1 mM)] at 4°C after collection, and separated from the underlying connective tissue with surgical technique and the delipidized membrane was allowed to equilibrate for approximately one hour in receptor buffer to regain lost elasticity[6].

Ex vivo drug permeation

The oral mucosa of pigs resembles that of humans more closely than any other animal in terms of structure and composition[14] and therefore porcine buccal mucosa was selected for drug permeation studies. Ex vivo permeation of PMZ solution studies were performed with porcine buccal membrane using Franz diffusion cell. The buccal epithelium was carefully mounted in between the two compartments of a Franz diffusion cell with an internal diameter of 2.1 cm (3.46 cm^2 area) with a receptor compartment volume of 25.0 mL. Phosphate buffer pH 7.4 was placed in the receptor compartment and the donor compartment contained a solution of PMZ. The donor compartment also contained phenol red at a concentration of 20µg/mL and it acts as a marker compound. The entire set up was placed over magnetic stirrer and temperature was maintained at 37°C. Samples of 1 mL were collected at predetermined time intervals from the receptor compartment and replaced with an equal volume of the fresh buffer. After performing the experiment in triplicate (n=3), mean values were calculated[8].The cumulative amount of permeated drug (Q), per unit surface area was plotted versus time (t). In a steady state situation the flux, J, is defined as the slop of this line. The flux (J) was calculated by using the following Equation (1).

$$J = dQ/dtA \text{ ---------- (1)}$$

Where J is flux (mg h^{-1} cm^{-2}); dQ/dt is the slope obtained from the steady-state portion of the curve; A is the area of diffusion (cm^2).

Estimation of Drug Content by HPLC Method

Quantitative HPLC was performed on an isocratic high performance liquid chromatography (Shimadzu, Japan) consisting of a LC–10AT solvent module, SPD–10A, and UV-Visible spectrophotometric detector with LC 10 software. The analytical column C18 Inertsil ODS–3V (Column of length 25cm and internal diameter of 4.6mm, packed with particles of 5µ diameter)

was used for chromatographic separation. The mobile phase used was a mixture of acetonitrile, water and triethylamine (40.7:59:0.3% v/v) and pH was adjusted to 2.5 with orthophosphoric acid. The flow rate was maintained at 1mLmin^{-1}, with a run time of 5 min and the entire analysis was carried out at an ambient temperature. The volume of the injection was 20 µL and the eluents were monitored at 254 nm. Prior to injection of drug solutions, the column was equilibrated for at least 30 min with the mobile phase. A calibration curve was plotted for PMZ in the range of 50-1000 ng/mL. A good linear relationship was observed between the concentration of PMZ and the peak height of PMZ with a correlation coefficient (r^2 = 0.998). The required studies were carried out to estimate the precision and accuracy of the HPLC method[19]

In vitro release studies

The drug release from buccal tablets was studied using the USP type II dissolution test apparatus (Electrolab TDT-08L Dissolution tester). Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive sealant. The dissolution medium was 500 mL of phosphate buffer pH 6.6 at 50 rpm and temperature was maintained at 37 ± 0.5 °C. Samples of 5 mL were collected at predetermined time intervals and analyzed utilizing UV-Visible Spectrophotometer at a wavelength of 254 nm.

In vitro bioadhesion studies

The adhesive binding of the tablets containing PMZ HCl to porcine buccal mucosa was studied in triplicate using a microprocessor based advanced force gauze with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK) and fitted with a 5 kg load cell. In this test, porcine buccal membrane was secured tightly to a circular stainless steel adaptor (diameter 2.2 cm) provided with the necessary equipment. A backup membrane was placed over the buccal tablet to be tested and fixed with the help of cyanoacrylate adhesive to the cylindrical stainless steel adaptor of similar diameter. The entire setup was mounted onto the platform of a motorized test stand. All measurements were conducted at room temperature. During measurement, 100 mL of 1% mucin solution (crude mucin procured from Sigma Chemical Co, USA) was used to moisten the porcine buccal membrane. The upper support was lowered at a speed of 0.5 mm s^{-1} until contact was made with the tissue at the predetermined force of 0.5 N for a contact time of 180 s. At the end of contact time, the upper support was withdrawn at a speed of 0.5 mm s^{-1} until detach from the membrane. Data collection and calculations were performed using the data plot

software package of the instrument. Two parameters, namely the work of adhesion and peak detachment force, were used to study the buccal adhesiveness of tablets[6, 15].

In vivo residence time evaluation of buccal tablets

Six healthy male volunteers aged between 20 and 25 years participated in the study. This study design was approved by the institutional human ethical committee (No. UCPSc/KU/BA/2011-02) and informed consents were received by all the volunteers participated in the study. Eating was restricted during the study, whereas drinking was allowed 1 h after administration of the buccoadhesive drug-free tablet. Tablets were applied manually by pressing them against the cheek for about 30 sec, without moistening before application[6]. Volunteers were instructed to record the time of the tablet application, and the time and circumstances of the end of adhesion (erosion or detachment of the tablet). After completion of the study, a questionnaire was given to volunteers to score the parameters such as irritancy, comfort, taste, dry mouth, salivation, dislodgment of the system during the study, and heaviness of the system at the place of attachment.

Swelling and erosion Studies

Water uptake of the tablets was determined gravimetrically in phosphate buffer, pH 6.6. The tablets were attached to pre-weighed glass supports using a cyanoacrylate adhesive sealant. The supports with tablets were immersed into the phosphate buffer at 37 $^{\circ}$C. At predetermined time intervals, (0.5, 1, 2, 3, 4h) the devices were removed from the media, blotted with tissue paper to remove excess water and weighed. After determining the wet weight, the tablets were dried at 40°C until constant mass (noted as remaining dry weight, W_3). Swelling index (S.I) and mass loss were determined gravimetrically according to the following equations. Water uptake or Swelling index (S.I) was calculated according to the equation [2]

$$S.I. = W_2\text{-}W_1/W_1 * 100 \text{ ---------- (2)}$$

Where W_2 and W_1 are wet weight and original dry weight, respectively. The swelling of the formulations were dependant on both, the type and concentration of the polymer included in the formulations. Erosion or % mass loss was calculated by following equation (3).

$$\text{Erosion (\% mass loss)} = W_1 - W_3/W_1 * 100 \text{---------- (3)}$$

Where W_3 is remaining dry weight.

Surface pH study

A combined glass electrode was used for this purpose[16]. The bioadhesive buccal tablets were allowed to swell by keeping them in contact with 1 mL of distilled water (pH 6.5 ± 0.1) for 2 h at

room temperature, and pH was noted down by bringing the electrode in contact with the surface of the tablet, allowing it to equilibrate for 1 minute.

Ex vivo permeation of PMZ through porcine buccal membrane from buccal tablet

Ex vivo permeation of PMZ from buccal tablets for the selected formulation through porcine buccal membrane was studied. Buccal membrane was isolated as described in tissue preparation section. The membrane was mounted over a Franz diffusion cell whose internal diameter is 2.1 cm. The buccal tablet was sandwiched between the buccal mucosa and the dialysis membrane, so as to secure the tablet tightly from getting dislodged from the buccal membrane and 25 mL of phosphate buffer pH 7.4 was placed in the receptor compartment. The entire set up was placed over magnetic stirrer and temperature was maintained at 37° C. Samples of 1 mL were collected at predetermined time points from receptor compartment and replaced with an equal volume of buffer. Estimation of drug content in the sample was done by HPLC method.

FTIR studies

The FTIR studies were carried out for pure drug, physical mixtures of PMZ and Carbopol 934P, PMZ and Sodium carboxyl methyl cellulose and optimized formulation. The FTIR spectra for the samples were obtained using KBr disk method using an FTIR spectrophotometer (PERKIN ELMER FT-I Insf. USA). Samples were mixed with dry crystalline KBr in a 1:100 (sample: KBr) ratio and pellets were prepared. A spectrum was collected for each sample within the wave number region 4,000–400 cm^{-1}.

Stability studies

Stability studies were carried out for optimized formulation F10 according to the International Conference on Harmonization (ICH) guidelines. The samples were stored at 40 ± 2°C/75 ± 5% R.H. (Skylab Instruments and Engineering Pvt Ltd., Mumbai, India) for 6 months. Samples were withdrawn after 1, 2, 3, and 6 months, and were evaluated for drug content and in vitro percentage drug release.

RESULTS AND DISCUSSION

Drug permeation studies through porcine buccal membrane

Porcine buccal mucosa has been the most frequently chosen model for ex vivo permeation studies because of its similarity to human tissue and is available in large quantities from slaughterhouses. Cumulative percentage amount permeated in 6 h was found to be 83.7 ± 9.1% and the flux and permeability coefficient was calculated to be 0.192 mg $h^{-1}cm^{-2}$ 0.019 cm/h respectively. The permeation of drug through the porcine buccal epithelium was found to be

rapid during first 3 h followed by a slow permeation throughout the experiment (Figure 1). The tissue could be isolated successfully because no detectable levels of phenol red (marker compound) were found in the receiver compartment; whereas PMZ could penetrate freely.

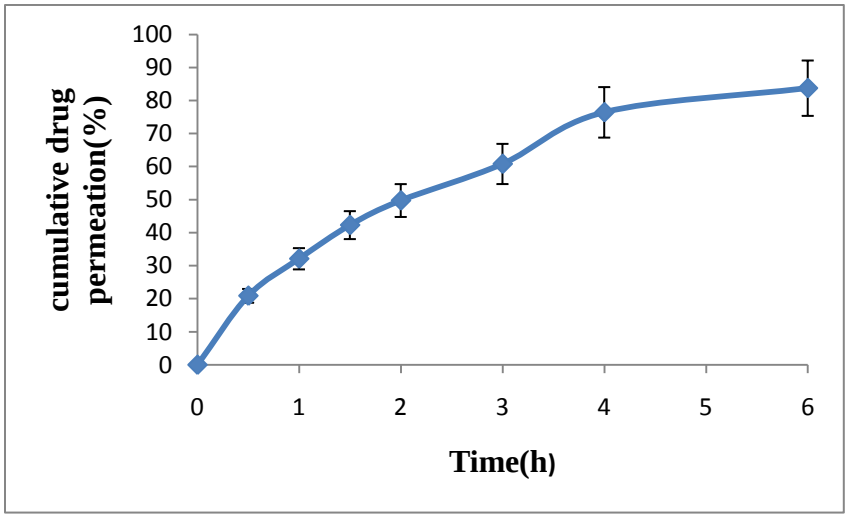

Figure 1 *Ex vivo* permeation of PMZ HCl through porcine buccal mucosa, the values represented mean ± S.D (n=3)

Mass, thickness, content uniformity and surface pH

The prepared tablets were evaluated for physicochemical properties such as mass, thickness, friability, drug content and surface pH (Table 2). The values of mass (99 - 103 mg), thickness (1.82 – 2.0 mm) and friability (0.05 - 0.13%) were found to be within the limits of conventional oral tablets stated in the Indian Pharmacopoeia 1996. Prepared tablets demonstrated uniform assay and content uniformity, with a mean drug content of ~ 98% and relative standard deviation of less than 2%. The surface pH of the prepared tablets were determined in order to investigate the possibility of any irritation effects in vivo, as acidic or alkaline pH may cause irritation to the buccal mucosa. Surface pH of all the prepared tablets were represented in Table 2 and the optimized formulation F10 was found to be 6.92 (near to neutral pH). It was inferred that neutral pH of the formulation does not cause any irritation to the mucosa and it is in agreement with the responses of healthy human male volunteers who participated during the in vivo residence time study.

In vitro drug release studies

The in vitro release profiles of PMZ from buccoadhesive tablets were represented in Figure 2. The optimized formulation (F10) was showed the maximum drug release (96.3 ± 4.5%) in 6 h whereas the formulation F1 showed lowest drug release (16.2 ± 1.5%) in 6 h. An increase in polymer concentration causes an increase in the viscosity of the gel as well as formation of a gel

layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate. In the present study, the results followed this predictable behavior (Figure 2). Buccal tablets that contained lower concentrations of either Sodium CMC or Carbopol tend to release the drug in shorter time periods, while the release slowed down as the concentration of the gelling polymer increased, thus confirming the dominant role of the swellable hydrophilic polymer in the release of PMZ from buccal tablets.

Table 2: Mass, thickness, drug content and surface pH of all the formulations

Code	Mass (mg)[a]	Thickness (mm)[a]	Assay (%)[b]	Friability (%)	Surface pH
F1	102.5 ± 1.2	1.82 ± 0.02	102 ± 0.4	0.05	6.10 ± 0.09
F2	100.3 ± 1.6	1.84 ± 0.03	98.0 ± 0.5	0.06	6.28 ± 0.11
F3	101.0 ± 1.3	1.82 ± 0.01	97.1 ± 1.2	0.07	6.31 ± 0.12
F4	99.10 ± 1.1	1.83 ± 0.02	103 ± 0.6	0.07	6.52 ± 0.29
F5	103.0 ± 1.4	1.86 ± 0.02	100 ± 1.1	0.08	6.68 ± 0.13
F6	100.6 ± 1.1	1.84 ± 0.01	99.5 ±0.4	0.09	6.70 ± 0.31
F7	99.70 ± 0.8	1.86 ± 0.03	97.2 ± 1.7	0.09	6.89 ± 0.32
F8	101.0 ± 1.0	1.89 ± 0.03	101 ± 1.5	0.11	6.82 ± 0.19
F9	101.4 ± 0.9	1.98 ± 0.01	97.3 ± 0.8	0.13	6.90 ± 0.22
F10	100.6 ± 0.8	2.00 ± 0.01	101 ± 0.5	0.13	6.92 ± 0.21

Mean ± SD; [a] n = 10, [b] n = 20

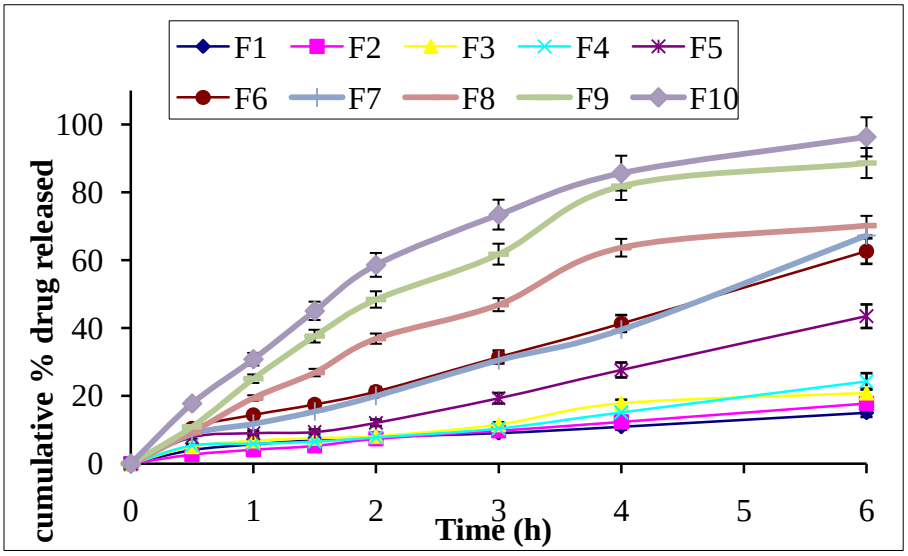

Figure 2: Release profiles of PMZ from mucoadhesive buccal tablets in phosphate buffer pH 6.6

Drug release kinetics

Data of the in vitro release was fit into different equations and kinetic models to explain the release kinetics of PMZ from buccal tablets. The release data were analyzed using the well-known semi-empirical equation shown as equation (4).

$$M_t / M_\infty = ktn \text{ ---------- (4)}$$

Where M_t/M_∞ is the fractional releasing of the drug; t denotes the releasing time; k represents a constant, incorporating structural and geometrical characteristics of the buccal devices; and n is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n value less than 0.5; for zero-order release (case II transport), n = 1; and for super case II transport, n > 1. The values of n were estimated by linear regression of log (M_t/M_∞) versus log t.

The kinetic models[17, 18] used were zero-order equation, first-order equation, Higuchi and Korsemeyer-Peppas models. Correlation coefficients (r^2) and release exponents (n) calculated through various models were depicted in Table 3. Formulations F1 to F7 were followed zero-order release profile as evidenced from the correlation coefficient values. In the case of formulations F8 to F10 were followed the Higuchi model release profile as evidenced from the correlation coefficient values (Table 3).

Table 3: Estimated values of release exponents (n) and Correlation coefficients (r^2) for all the formulations

Code	n value	r^2(Zero order)	r^2 (First order)	r^2 (Higuchi)	r^2 (Peppas)
F1	0.590	0.984	0.561	0.943	0.014
F2	0.760	0.993	0.557	0.941	0.079
F3	0.619	0.951	0.738	0.936	0.051
F4	0.614	0.965	0.746	0.872	0.045
F5	0.845	0.977	0.929	0.860	0.149
F6	0.976	0.992	0.974	0.913	0.271
F7	0.894	0.988	0.969	0.869	0.306
F8	0.502	0.939	0.825	0.956	0.440
F9	0.511	0.924	0.785	0.957	0.546
F10	0.504	0.901	0.752	0.975	0.573

Interpretation of diffusional release mechanism from in vitro drug release data from release exponent (n) from Peppas equation, formulations F1 to F7 showed Anomalous (non-Fickian transport), F8 to F10 showed higuchi model release profile as evidenced from the correlation coefficients and release exponent value. Based on the release profile formulation F10 was selected as optimized formulation and was used further evaluation of ex vivo permeation studies across porcine buccal membrane and in vitro bioadhesion studies.

In vitro bioadhesion studies

In vitro bioadhesion measurements were performed routinely for mucoadhesive dosage forms, and the most commonly used technique for evaluation of buccal tablet is the measurement of

adhesive strength. Work of adhesion, calculated from area under the force distance-curve, is a measure of work that must be done to remove a tablet from the tissue. Peak detachment force is the maximum applied force at which the tablet detaches from tissue. The peak detachment force and work of adhesion for formulation F10 were found to be 1.64 ± 0.21 N and 0.36 ± 0.10 mJ respectively. The results revealed that the optimized formulation (F10) showed good bioadhesive property.

In vivo residence time

Swelling of the polymer contributes to the interpenetration of mucus and polymer chains, and makes bioadhesion possible. In vivo residence time for the optimized formulation in healthy human male volunteers was found to be 287 ± 28 min. After completion of the in vivo residence time study, volunteers were asked to score the parameters such as irritancy, discomfort, dry mouth, salivation, dislodgment of the buccal tablet during study, and heaviness of the buccal tablet at the place of attachment. No volunteer reported irritancy and heaviness during the study; only one volunteer felt slightly uncomfortable and slight salivary secretion during study. No volunteer felt heaviness of the buccal tablet at the place of attachment because of the moderate thickness and light weight (100 mg) of the tablet.

Swelling and erosion studies

Swelling index values of all the formulations were presented in Figure 3.The swelling index values of all the formulations were increased with increasing amounts of polymer concentration either alone or in the combination. Maximum swelling index value was observed with the formulation F1 and the optimum and desired swelling index value was observed with the formulation F10. The bioadhesion and drug release profile are dependent upon swelling behavior of the buccal tablets. As the proportion of these polymers in the matrix increased, there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer. An increase in polymer concentration causes an increase in the viscosity of the gel as well as formation of a gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate.

Erosion was investigated by comparing the initial and final tablet weight after immersion in phosphate buffer. Erosion values for all the formulations were found to be in the range of 23.9% (F1) to 53.1% (F10) and represented in Figure 4.

During development of bioadhesive formulation, tablet hydration capacity is very important to be considered because the medium penetration is responsible for drug release. However, since

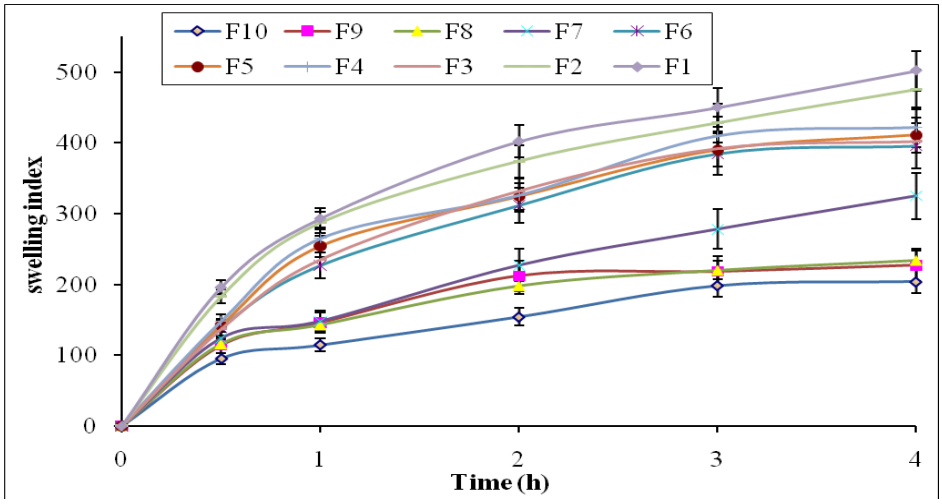

Figure 3: Swelling index values of all the formulations at different time points

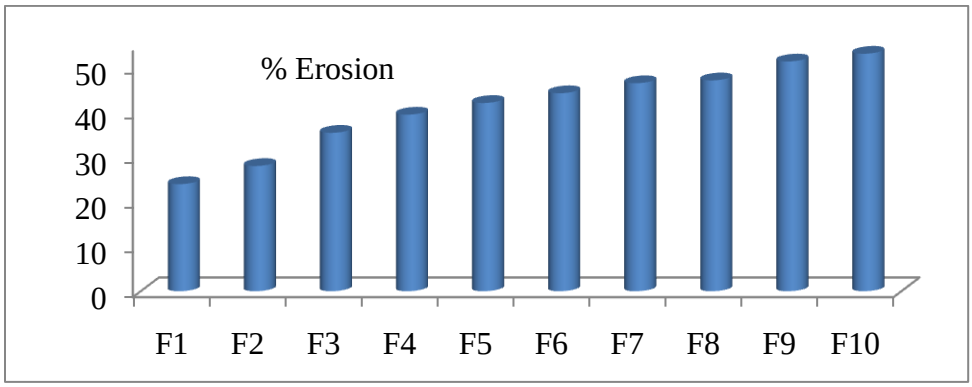

Figure 4: Percentage erosion of all the formulations at the end of 4 hrs

swelling and gel formation can make tablets erodible, it is very important to know when the formulation loses its integrity. For this purpose erosion was investigated by comparing the initial and final tablet weight after immersion in phosphate buffer. The negative erosion values initially after 1-2 hours confirmed that the good hydration of all tablets and positive erosion values for all the formulations were observed at the end of 4 h because of the erosion effect.

Ex vivo permeation of PMZ through porcine buccal membrane from buccal tablet

Based on the in vitro drug release, surface pH, swelling index and erosion studies of all the formulations, formulation F10 was selected for ex vivo permeation studies. The drug permeation profile from the optimized buccal tablet was represented in Figure 5. The cumulative percentage of drug permeated in 6h, flux and permeation coefficient from formulation F10 were found to be 49.7 %, 0.512 mg/h/cm^2, 0.051 cm/h, respectively. The results of drug permeation from buccal tablets through the porcine buccal membrane reveal that PMZ was released from the formulation and permeated through the porcine buccal membrane and could possibly permeate through the human buccal membrane.

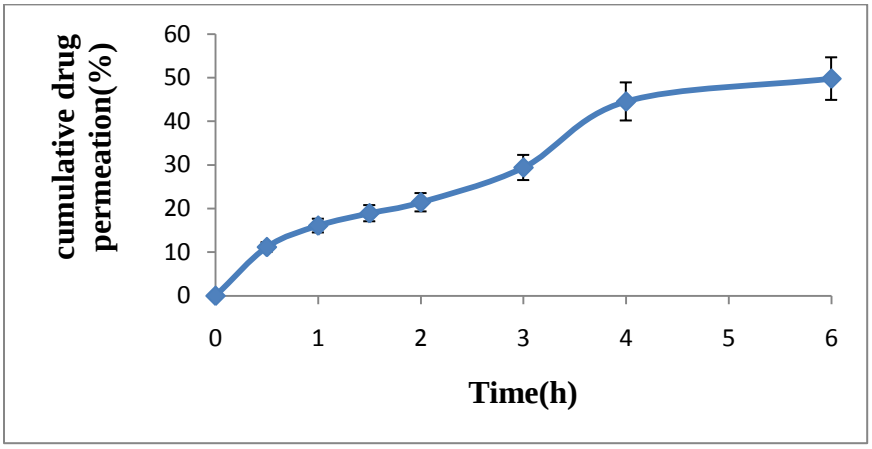

Figure 5 *Ex vivo* permeation of PMZ through porcine buccal mucosa from buccal tablet (Optimized formulation F10), the values represented mean ± S.D (n=3)

FTIR Studies

FTIR spectroscopic studies were conducted to study any interaction between the drug and polymers used in the formulation of buccal tablets. FTIR spectra of PMZ, physical mixture of PMZ and Carbopol, physical mixture of PMZ and Sodium CMC, and optimized formulation were represented in Figures 6. PMZ showed principal peaks at 2200-2480 cm^{-1} for NH^{+} stretching, at 1456 cm^{-1} for CH_3 and CH_2 bending and 757 cm^{-1} for out of plane CH bending of disubstituted aromatic respectively. The FTIR spectra of the physical mixtures and optimized formulation showed the same absorption bands as the pure drug and polymer, demonstrates that the absence of interaction between drug and mucoadhesive polymers used.

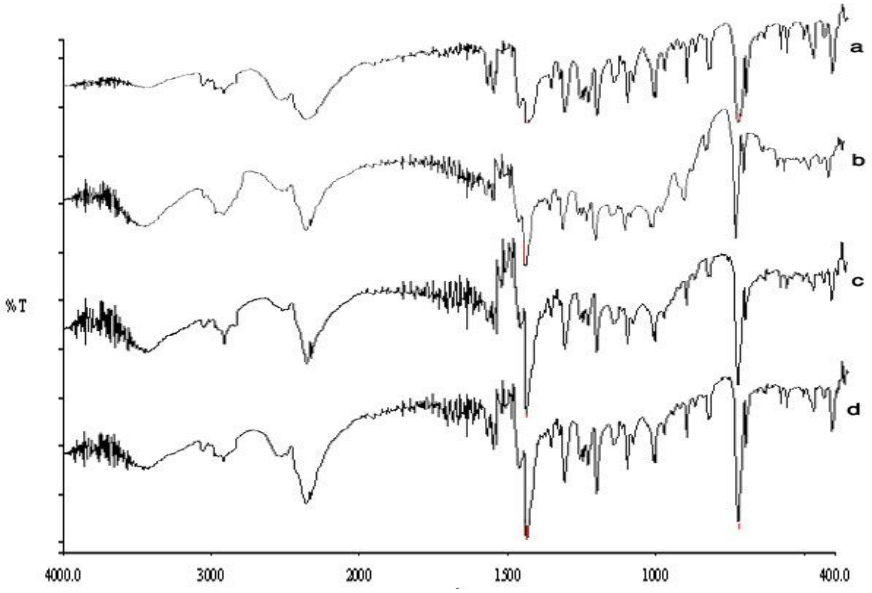

Figure 6: FTIR spectra of PMZ (a), Physical mixture of PMZ and Carbopol (b), Physical mixture of PMZ and Sodium CMC (c), Optimized formulation F10 (d).

Stability studies

The stability studies were conducted as per ICH guide lines and the results were represented in Table 4. The stability study results revealed that the optimized buccal formulation was stable for 6 months. Drug content and in vitro percentage drug release results reveal that after 6 months of the stability studies there was no significant difference in drug content and in vitro drug release.

CONCLUSIONS

The results demonstrated that PMZ could be delivered through the buccal route. Buccal delivery of PMZ tablets could be prepared using mucoadhesive polymers as Sodium CMC and Carbopol 934P. Drug to polymer ratio (1:3) showed significant bioadhesive properties with an optimum release profile and ex vivo drug permeation through porcine buccal membrane could be useful for buccal administration of PMZ. In vivo residence time in human volunteer study results revealed that the optimized formulation showed good retentive property and no irritation. Further work is recommended to support its efficacy claims by long term pharmacokinetic and pharmacodynamics studies in human beings.

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