Development of Promethazine Hydrochloride Mucoadhesive Patches for Buccal Delivery: *In vitro, Ex vivo* and *In vivo* Characterization

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**ABSTRACT**

Promethazine hydrochloride (PMZ HCl), an antiemetic, undergoes extensive first-pass metabolism (bioavailability 25%). The purpose of the present investigation was to develop mucoadhesive patches for transbuccal delivery of PMZ HCl using solvent casting technique with Hydroxy ethyl cellulose (Natrosol 250 E) and hydroxylpropyl methyl cellulose as mucoadhesive polymers and propylene glycol as the plasticizer and evaluate their physicochemical characteristics, *in vitro* drug release, moisture absorption, surface pH, mechanical properties, *in vitro* bioadhesion, *in vivo* residence time, and *ex vivo* drug permeation through porcine buccal membranes from optimized buccal patch and stability studies. The physicochemical interaction between PMZ HCl and polymers was investigated by Fourier Transform Infrared Spectroscopy. *Ex vivo* drug permeation through porcine buccal membrane was performed and 83.7% of the drug permeated in 6 hours with flux $0.19 \text{ mg h}^{-1} \text{ cm}^{-2}$. The optimized formulation AA4 showed maximum drug release (98%) in 6 hours in the Higuchi model release profile. Moisture absorption, surface pH, tensile strength, elongation at break, peak detachment force and work of adhesion values of the optimized formulation were found to be 68.1%, pH 6.7, 12.3 kg/mm$^2$, 69.2 % mm$^2$, 7.5 N and 2.73 mJ respectively. Formulation AA4 showed 77.6% of the drug permeated through porcine buccal membrane in 6 hours and flux calculated to be $0.45 \text{ mg h}^{-1} \text{ cm}^{-2}$. FTIR studies showed no evidence of interaction between the drug and polymers. *In vivo* mucoadhesive behaviour of the optimized formulation 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, *in vitro* release and *ex vivo* permeation after 6 months.

**KEYWORDS:** Promethazine hydrochloride; buccal patches; bioadhesion; *ex vivo* permeation; *in vivo* residence time.

**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 a novel route of drug administration. This route has been used successfully for the systemic delivery of a number of drug candidates (Anders and Merkle, 1989; Chen and Hwang, 1992). 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 (Nagai and Konishi, 1987; Harris and Robinson, 1992). 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 patches (Guo, 1994), adhesive tablets (Dortunc et al., 1998), and adhesive gels (Ishida et al., 1983). However, buccal films are preferable over adhesive tablets in terms of flexibility and comfort.

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 (Gu et al., 1988). Bioadhesive polymers not only cause adhesion effects but also control the release rate of the drug release (Duchene et al., 1988). From a technological point of view, an ideal buccal dosage form must have 3 properties: (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 an impermeable backing layer (Remunan-Lopez et al., 1998).
Promethazine hydrochloride (PMZ) is a first-generation H<sub>1</sub> receptor antagonist of the phenothiazine chemical class used medically as an antihistamine antiemetic, taken before travelling, and is effective in preventing motion sickness (Windholz et al., 1983). Although it is well absorbed in the gastrointestinal tract, its bioavailability is low, at approximately 25% as a result of extensive first-pass metabolism, so its bioavailability may be improved when delivered through buccal route. Its biphasic solubility, low dosage and low molecular weight 320.9 make it a suitable candidate for administration through the buccal route (Schwinghammer et al., 1984). 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 objective of the present investigation was to develop buccoadhesive patches of PMZ using hydroxy ethyl cellulose (Natrosol 250 E) and hydroxy propyl methyl cellulose (HPMC E 15) as mucoadhesive polymers, propylene glycol as the plasticizer and to evaluate for in vitro drug release, in vitro bioadhesion, in vivo residence time, moisture absorption studies, surface pH, and ex vivo drug permeation through porcine buccal membranes from the optimized buccal formulation and stability studies.

Materials and Methods

Materials

Promethazine hydrochloride, HEC (Natrosol 250 E) and HPMC E 15 were donated by Dr. Reddy’s Laboratories, Hyderabad, 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., India.

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. The delipidized membrane was allowed to equilibrate for approximately one hour in receptor buffer to regain lost elasticity.

Ex vivo drug permeation studies through porcine buccal membrane

The oral mucosa of pigs resembles that of humans more closely than any other animal in terms of structure and composition (Van Eyk and Vander, 2004; Squier et al., 1991) and therefore porcine buccal mucosa was selected for drug permeation studies. Ex vivo permeation studies were performed with porcine buccal membranes using a 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<sup>2</sup> area) with a receptor compartment volume of 25 ml. 25 ml of phosphate buffer pH (7.4) was placed in the receptor compartment. The donor compartment contained a solution of 1 ml of phosphate buffer pH 6.6 in which 5 mg of PMZ was dissolved. The donor compartment also contained phenol red at a concentration of 20 µg/ml. This is because phenol red acts as a marker compound and is not supposed to permeate through the porcine buccal mucosal. The entire setup was placed over a magnetic stirrer and temperature was maintained at 37°C. Samples were collected at predetermined time intervals from receptor compartment and replaced with an equal volume of the buffer. After performing the experiment in triplicate (n=3), mean values were calculated (Chinn Reddy et al., 2011). The cumulative amount of the drug permeated was plotted against time. The flux (J) was calculated by using the following equation (1).

\[
J = \frac{dQ}{dt} \cdot A \quad \ldots (1)
\]

Where \(J\) is flux (mg h<sup>−1</sup> cm<sup>−2</sup>); \(dQ/dt\) is the slope obtained from the steady-state portion of the curve; \(A\) is the area of diffusion (cm<sup>2</sup>).

Estimation of Drug Content in the Sample by HPLC Method

Quantitative HPLC was performed on an isocratic high performance liquid chromatograph (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 25 cm and internal diameter of 4.6 mm, packed with particles of 5 µ diameter) was used for chromatographic separation. The composition of the mobile phase was acetonitrile, water, and 0.375% v/v triethylamine (pH adjusted to 2.5 with orthophosphoric acid) in the ratio of 41:59 v/v. The mobile phase was pumped from the solvent reservoir to the column at a flow rate of 1 ml/min<sup>−1</sup>, with a run time of 5 minutes and an ambient column temperature. The volume of the injection loop was 20 µL. Prior to the injection of drug solutions, the column was equilibrated for at least 30 min with the mobile phase run. The eluents were monitored at 254 nm and data was acquired, stored, and analyzed with the LC 10 software. The sensitivity was set to 0.0005 AUFS. 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 (\(r^2 = 0.998\)).

Preparation of Adhesive Polymeric Buccal Patches

Buccal patches were prepared using solvent casting technique with HPMC E 15 and HEC (Natrosol 250 E) as
mucoadhesive polymers and propylene glycol as the plasticizer. The polymer was added to 20 mL of solvent mixture [Dichloromethane (DCM): Alcohol 1:1 for HPMC E 15 and distilled water for HEC] and allowed to stand for 6 hours to swell. Propylene glycol and PMZ HCl were dissolved in 5 mL of solvent mixture and added to the polymer solution. This was set aside for 2 hours to remove entrapped air, transferred to a petri plate, and dried at 40°C in an oven. The developed patches were removed carefully, cut to size (each having an area of 2.26 cm²), and stored in a desiccator. The composition of the patches is shown in Table 1. Patches were subjected to weight variation, thickness variation and content uniformity. Formulations AA1 to AA5 were prepared using HPMC E 15 and AB1 to AB4 were prepared using HEC (Natrosol 250 E).

**TABLE 1**

Composition of promethazine hydrochloride buccal patches.

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<tr>
<th>Code</th>
<th>PMZ (mg)</th>
<th>HPMC E 15 (mg)</th>
<th>HEC (mg)</th>
<th>PG (μL)</th>
<th>Solvent system DCM: Alcohol 1:1 (mL)</th>
<th>Water (mL)</th>
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<tr>
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<td>25</td>
<td>-</td>
</tr>
<tr>
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<td>-</td>
<td>1280</td>
<td>240</td>
<td>25</td>
<td>-</td>
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<td>-</td>
<td>1920</td>
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<td>25</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: Each patch (2.26 cm²) contained 10 mg of PMZ. 15 % v/w of propylene glycol to the total polymer weight, incorporated as plasticizer.

**Moisture Absorption Studies**

The moisture absorption studies gave an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture. Moisture absorption studies were performed in accordance with the procedure reported earlier (Chinna Reddy et al., 2010). Briefly, 5 % w/v agar in distilled water, which in hot condition was transferred to petri plates and allowed to solidify. Then 6 patches from each formulation were weighed and placed over the surface of the agar and left for 2 hours at 37°C and the patch was weighed again. The percentage of moisture absorbed was calculated using the equation 2:

\[
\% \text{ Moisture absorbed} = \left[ \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \right] \times 100 \quad \cdots(2)
\]

**Surface pH Study**

The method adopted by Bottenberg et al. (Bottenberg et al., 1991) was used to determine the surface pH of the patches. A glass electrode was used for this purpose. The bioadhesive buccal patches were allowed to swell by keeping them in contact with 1 ml of distilled water (pH 6.5) for 2 hours at room temperature, and the pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute.

**Measurement of Mechanical Properties**

Mechanical properties of the patches were evaluated using a microprocessor-based advanced force gauze with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK) fitted with a 25 kg load cell. Strips from the patch with dimensions of 6 x 10 mm and no visual defects were cut and positioned between two clamps separated by a distance of 3 cm. Clamps were designed to secure the patch without crushing it. During tests, the lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2.0 mm/seconds until the strip broke. The force and elongation of film at the point where the strip broke were recorded. The tensile strength and elongation at break values were calculated using the equation 3 & 4:

\[
\text{Tensile strength (kg.mm}^{-2}) = \frac{\text{[Force at break(kg)/Initial cross sectional area of the sample (mm}^2\text{)]}}{} \quad \cdots(3)
\]

\[
\text{Elongation at break} \% = \frac{[\text{Increase in length} (\text{mm}) \times 100]}{[\text{Original length} \times \text{Cross sectional area (mm}^2\text{)]}} \quad \cdots(4)
\]

**In vitro Bioadhesion Studies**

The adhesive binding of the patches containing PMZ 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) fitted with a 5 kg load cell. In this test, the 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 patch 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 μL 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 seconds. At the end of contact time, the upper support was withdrawn at a speed of 0.5 mm s⁻¹ to detach the membrane from the patch. 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 patches (Wong et al., 1999). The work of adhesion was determined from the area under the force-distance curve while the peak detachment force was the maximum force required to detach the patch from the mucosa.
In vivo Residence Time

Six healthy volunteers aged between 22-25 years participated in the study. The optimized formulation was applied manually by pressing them against the cheek for about 30 seconds without moistening before application (Chinna Reddy et al., 2011). Volunteers were instructed to record the time of the patch application, and the time and circumstances of the end of adhesion (erosion or detachment of the patch).

In vitro Release Studies

The drug release from buccal patches was studied using the USP type II dissolution test apparatus (Electrolab TD-08L Dissolution tester). Patches were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the patch. The patch was further fixed to a 2 × 2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 ml of phosphate buffer pH 6.6 at 50 rpm at a temperature of 37 ± 0.5°C. Samples of 5 ml were collected and replenished with fresh buffer at different time intervals up to 6 hours and samples were analyzed using a UV-Vis Spectrophotometer at 249 nm.

Ex vivo permeation of PMZ through Porcine Buccal Membrane from Buccal Patch

The ex vivo permeation of PMZ from buccal patch for the optimized formulation through porcine buccal membranes was studied. The buccal membrane was isolated as described in the tissue preparation section. The membrane was mounted over a Franz diffusion cell whose internal diameter was 2.1 cm. The buccal patch was sandwiched between the buccal mucosa and the dialysis membrane, so as to secure the patch tightly from getting dislodged from the buccal membrane. Phosphate buffer pH 7.4 was placed in the receptor compartment. The entire setup 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.

FTIR Studies

The FTIR studies were carried out for pure drug, physical mixture of PMZ and HPMC E 15, physical mixture of PMZ and HEC. The FTIR spectra for the samples were obtained using KBr disk method using an FTIR spectrophotometer (PERKIN ELMER FT-IR 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

The optimized formulation (AA4) was stored in borosilicate glass bottles, flushed with nitrogen, and kept under stability at 40°C/75%RH for a period of six months. A known amount of sample from the formulations subjected to stability was analyzed at predetermined time intervals for the drug content, in vitro release and ex vivo permeation through porcine buccal membranes.

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 its availability in large quantities from slaughterhouses. The cumulative percentage amount permeated in 6 hours was found to be 83.77 ± 9.1% and the flux was calculated to be 0.192 mg h⁻¹cm⁻². The permeation of drug through the porcine buccal epithelium was found to be rapid up to first 3 hours followed by a slow penetration in the next 3 hours (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.

![Fig. 1. Ex vivo permeation of PMZ through porcine buccal mucosa, the values represented Mean ± S.D (n=3).](image-url)
Weight, Thickness and Drug Uniformity

The prepared patches were smooth in appearance, uniform in thickness, weight, and drug content shown in Table 2 and showed no visible cracks. The mass of patches ranged from 62 ± 5 to 110 ± 4 mg for AA series, and from 43 ± 3 to 73 ± 3 mg for AB series and the thickness ranged from 350 ± 70 to 510 ± 50 µm for AA series and from 270 ± 30 to 390 ± 40 mg for AB series. The drug content in the buccal patches ranged from 95.1 ± 0.8% for AB series, indicating the favorable drug loading and patches uniformity with respect to drug content.

Moisture Absorption Studies

In order to investigate the possibility of any side effects, in vivo. Since an acidic or alkaline pH may cause irritation to the buccal mucosa, we attempted to keep the surface pH as close to neutral as possible. Hence this parameter assumes significance while developing a mucoadhesive formulation. The results (Table 2) revealed that the formulations were in an acceptable pH range of 5.8 to 7.4 (salivary pH). Hence, they may not produce any local irritation to the mucosa.

Surface pH

The surface pH of the patches was determined in order to investigate the possibility of any side effects, in vivo. Since an acidic or alkaline pH may cause irritation to the buccal mucosa, we attempted to keep the surface pH as close to neutral as possible. Hence this parameter assumes significance while developing a mucoadhesive formulation. The results (Table 2) revealed that the formulations were in an acceptable pH range of 5.8 to 7.4 (salivary pH). Hence, they may not produce any local irritation to the mucosa.

Moisture Absorption Studies

Moisture absorption studies evaluated the integrity of the formulation upon exposure to moisture. The results of moisture absorption studies were presented in Table 3. Formulations AA1, AA2, AB1 were eroded in 2 hours. Results showed that there were differences in moisture absorption, percentage moisture absorbed ranged from about 64.16 to 171% w/w for various formulations. When the patches were placed without the backing membrane complete swelling followed by erosion was observed, indicating that the drug release mechanism involves swelling of the polymer initially followed by drug release from the swollen matrix by diffusion.

Mechanical Properties of Patches

The ideal buccal patch, apart from good bioadhesive strength, should be flexible, elastic, and strong enough to withstand breakage due to stress caused during its residence in the mouth. The tensile strength (TS) and elongation at break (E/B) shows the strength and elasticity of the film. A soft and weak polymer is characterized by a low TS and E/B; a hard and brittle polymer is defined by a moderate TS, and low E/B; a soft and tough polymer is characterized by a moderate TS and a high E/B; whereas a hard and tough polymer is characterized by high TS and E/B (Aulton et al., 1981). An ideal buccal film should have a relatively high TS and E/B. The results of the mechanical properties, i.e., TS and E/B, are presented in Table 3. TS and E/B increased with the increase in polymer content. In AA series, the maximum TS was exhibited by AA5 (17.31 ± 1.14 kg/mm²). Maximum E/B was seen with AA1 (113.0 ± 7.6% mm²). In AB series, the maximum TS was exhibited by AB4 (10.21 ± 1.25 kg/mm²). Maximum E/B was seen with AB1 (85.66 ± 5.21% mm²). Optimized formulation AA4 exhibited tensile strength and elongation at break values 12.35 ± 2.00 kg/mm² and 69.23 ± 4.36 % mm² respectively.

In vitro Bioadhesion Studies

In vitro bioadhesion measurements are performed routinely for mucoadhesive dosage forms, and the most commonly used technique for the evaluation of buccal patches is the measurement of adhesive strength. Work of adhesion, calculated from the area under the force-distance-curve, is a measure of work that must be done to remove a patch or film from the tissue. Peak detachment force is the maximum applied force at which the patch detaches from tissue. For formulation AA4, the peak detachment force and work of adhesion were found to be 4.75 ± 0.64 N and 0.925 ± 0.38 mJ, respectively. The work of adhesion and peak detachment force values were within the range for suitable bioadhesion as reported for various films (Peh and Wong, 1999). In addition, all formulations were found to have similar values since the basic surface environment of the patch, which is essential for the bioadhesion, remains the same and it is only the thickness that varies. However, differences do exist due to changes in polymer type or composition of the film.
**In vivo Residence Time**

*In vivo* residence time for the optimized formulation (AA4) in healthy human male volunteers was found to be 327 ± 32 minutes. After completion of the *in vivo* residence time study, volunteers were asked to score parameters such as irritancy, discomfort, dry mouth, salivation, dislodgment of the buccal patch during study, and heaviness of the buccal patch 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 patch at the place of attachment because of the moderate thickness, light weight, and sufficient surface area of the patch.

**In vitro Drug Release Studies**

The drug release profiles of PMZ from buccal patches are shown in Figures 2 & 3. It was clear from the plots that the drug release was governed by polymer content. No lag time was observed as the patch was directly exposed to the dissolution medium. An increase in the polymer content was associated with a decrease in drug release rates. Increasing the amount of the polymer in the patches produced the water-swollen gel like state that could substantially reduce the penetration of the dissolution medium into the patches and retard the drug release.

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**Fig. 2.** Release profiles of PMZ from mucoadhesive buccal patches of AA series in phosphate buffer pH 6.6. Values represent the mean ± S.D (n=3).

**Fig. 3.** Release profiles of PMZ from mucoadhesive buccal patches of AB series in phosphate buffer pH 6.6. Values represent the mean ± S.D (n=3).
There appeared no significant difference in the final percentage of drug release in the case of the AA series which might be due to the fact that in all the formulations the drug dissolved completely in the dissolution medium. AA series formulation AA4 showed 98.3 ± 5.1% drug releases in 6 h, whereas AA1, AA2, AA3 formulations showed > 95% within 4 hours. In the case of the AB series drug release ranged from 72% (AB4) to 101% (AB1) in 6 hours. Though AB1 showed a good release profile, the drug was diffused from the patches onto the surface after one week of fabrication. The formulation AA4 was selected as the optimized formulation and was used further for the evaluation of ex vivo permeation studies across porcine buccal membranes, in vitro bioadhesion and in vivo residence time in healthy human volunteers.

Mathematical Model Fitting of in vitro Drug Release

Data of the in vitro release was fit into different equations and kinetic models to explain the release kinetics of PMZ from buccal patches. The kinetic models (Korsmeyer et al., 1983; Peppas, 1985) used were zero-order equation, first-order equation, Higuchi Korsmeyer-Peppas models. Correlation coefficients ($R^2$) and release exponents ($n$) calculated through various models were depicted in Table 4. All formulations (correlation coefficient values ranging from 0.917 to 0.988) followed the Higuchi model.

Release data was analyzed using the well-known semi-empirical equation shown as equation (5):

$$\frac{M_t}{M_\infty} = k t^n$$

Where $M_t/M_\infty$ 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 = 0.5; for zero-order release (case II transport), n = 1; and for super case II transport, n > 1. The obtained values of n (diffusional exponent), and $R^2$ (correlation coefficient) are depicted in Table 4. The values of n were estimated by linear regression of log ($M_t/M_\infty$) versus log t. Interpretation of diffusional release mechanism from in vitro drug release data from release exponent (n) from Peppas equation, all formulations showed Anomalous (non-Fickian transport).

TABLE 4

<table>
<thead>
<tr>
<th>Code</th>
<th>Zero-order $R^2$</th>
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</table>

Ex vivo Permeation of PMZ through Porcine Buccal Membrane from Buccal Patch

Formulation AA4 was selected for the ex vivo permeation studies due to its superior drug release properties in terms of percentage drug released, capacity to retain the structure in moisture absorption studies, and in vitro bioadhesion studies. The results of drug permeation from buccal patches through the porcine buccal mucosa reveal that PMZ was released from the formulation and permeated through the porcine buccal membrane and could possibly permeate through the human buccal membrane. The drug permeation was slow and steady (Figure 4) and 77.67 ± 6.3 % of PMZ could permeate through the buccal membrane from formulation AA4 in 6h with a flux of 0.45 ± 0.26 mg h⁻¹cm⁻².

**Fig. 4.** Ex vivo permeation of PMZ from the optimized formulation AA4 through porcine buccal mucosa. Values represent the mean ± S.D (n=3).
FTIR Studies

To study any interaction between drug and polymers used in the preparation of patches, FTIR spectroscopic studies were carried out. FTIR spectra of PMZ, physical mixture of PMZ and HPMC E15, physical mixture of PMZ and HEC were shown in Figure 5. PMZ alone showed principal peaks at 2200-2480 cm⁻¹ for NH⁺ stretching, at 1456 cm⁻¹ for CH₃ and CH₂ bending and at 757 cm⁻¹ for out of plane CH bending of disubstituted aromatic, respectively. The FTIR spectra of the physical mixtures showed the same absorption bands as the pure drug and polymers used, illustrating the absence of interaction between drug and mucoadhesive polymers.

Stability Studies

The stability studies were conducted as per ICH guidelines and the results were represented in Table 5. Drug content, in vitro percentage drug release and ex vivo drug permeation through porcine buccal membrane results revealed that after 6 months of the stability studies there was no significant difference in drug content, in vitro drug release or ex vivo drug permeation study.

<table>
<thead>
<tr>
<th>Time</th>
<th>Drug content (mg)</th>
<th>% drug released (Q6)</th>
<th>Cumulative % drug permeated (Q6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>10.12 ± 0.09</td>
<td>98.3 ± 5.1</td>
<td>77.6 ± 6.3</td>
</tr>
<tr>
<td>1 Month</td>
<td>10.01 ± 0.08</td>
<td>97.9 ± 4.09</td>
<td>75.7 ± 5.3</td>
</tr>
<tr>
<td>3 Months</td>
<td>9.942 ± 0.11</td>
<td>97.4 ± 5.13</td>
<td>73.8 ± 7.2</td>
</tr>
<tr>
<td>6 Months</td>
<td>9.874 ± 0.12</td>
<td>96.8 ± 5.08</td>
<td>71.7 ± 8.1</td>
</tr>
</tbody>
</table>

Conclusions

This study demonstrated that Promethazine Hydrochloride could be delivered through the buccal route. Mucoadhesive patches for buccal delivery of PMZ could be prepared by using mucoadhesive polymers HEC and HPMC E15. Optimized formulation AA4 containing ratio of drug to polymer (HPMC E15) portion 1:8 showed significant bioadhesive properties with an optimum release profile and 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.

Declaration of Interest

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