Development of Mucoadhesive Patches for Buccal Administration of Prochlorperazine: Evaluation of In Vitro Release and Mechanical Properties

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Introduction

Buccal delivery of drugs provides an attractive alternate to the oral route of drug administration, particularly in overcoming deficiencies associated with the oral administration. It has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. The direct entry of the drug into the systemic circulation avoids the first-pass hepatic metabolism leading to increase in bioavailability (Senel and Hincal, 2001; Choi et al., 2000). Various mucoadhesive formulations were suggested for buccal delivery that includes buccal patches (Anders and Merkle, 1989; Vanshi et al., 2007), adhesive tablets (Owens et al., 2005; Jafar et al., 2004) and adhesive gels (Ishida et al., 1983). Buccal patches over come some of the drawbacks of other dosage forms. They have unique characteristics including flexibility, relatively rapid onset of drug delivery, sustained drug release and rapid decline in the serum drug concentration when the patch is removed. The patch is confined to the buccal area over which it is attached and therefore the absorption profile may have less inter and intra-individual variability.

PCPZ is a piperazine derivative, used to treat dizziness due to labyrinthine disorder, postoperative vomiting and emesis related to chemotherapy. It is also used in treatment of psychosis and manic phase of bipolar disorder (Hao et al., 2002). Oral administration was the most common route of administration however, PCPZ undergoes extensive intestinal and first-pass hepatic metabolism. The oral route of administration of PCPZ is also impractical for patients who are vomiting or who have impaired gastric emptying. Both parenteral and suppository formulations have also been used, but these approaches have low patient acceptability. From both, physicochemical (low molecular weight 373.9 g/mol, low dose 15-30 mg, Log P 2.4) (Clarke, 1986) and pharmacokinetic (T1/2 4-8 h, absolute bioavailability about 5.7 %) (Finn et al., 2005) views PCPZ is considered to be suitable for buccal delivery. Buccal tablets are available for PCPZ, but buccal films are preferred over adhesive tablets in terms of flexibility and comfort (Peh and Wong, 1999).

In this investigation we developed PCPZ buccal patches with a dissolvable matrix using HPMC E 15, with an insoluble backing membrane. The developed patches were evaluated for in vitro release, in vitro permeation through porcine buccal membrane and mechanical properties. The in vitro release characteristics of the prepared systems were evaluated using Franz diffusion cells and the adhesion measurement was carried out using

KEY WORDS: Buccal, Prochlorperazine, Bioadhesion, Mechanical properties.

ABSTRACT: The aim of this investigation was to develop and evaluate mucoadhesive buccal patches of prochlorperazine (PCPZ). Permeation of PCPZ was calculated in vitro using porcine buccal membrane. Buccal formulations were developed by solvent-casting technique using hydroxypropylmethyl cellulose (HPMC) as mucoadhesive polymer. The patches were evaluated for in vitro release, moisture absorption and mechanical properties. The optimized formulation, based on in vitro release and moisture absorption studies, was subjected for bioadhesion studies using porcine buccal membrane. In vitro flux of PCPZ was calculated to be 2.14 ± 0.01 µg.h⁻¹.cm⁻² and buccal absorption was also demonstrated in vivo in human volunteers. In vitro drug release and moisture absorbed was governed by HPMC content. Increasing concentration of HPMC delayed the drug release. All formulations followed Zero order release kinetics whereas the release pattern was non-Fickian. The mechanical properties, tensile strength (10.28 ± 2.27 kg mm⁻² for formulation P3) and elongation at break reveal that the formulations were found to be strong but not brittle. The peak detachment force and work of adhesion for formulation P3 were 0.68 ± 0.15 N and 0.14 ± 0.08 mJ, respectively. The results indicate that suitable bioadhesive buccal patches of PCPZ with desired permeability and suitable mechanical properties could be prepared.
an ultra test, Mecmesin equipment with porcine buccal membrane.

**Materials and Methods**

**Materials**

Prochlorperazine maleate was gifted by Anphar Laboratories Pvt Ltd., Jammu, India. Polyester backing membrane was gifted by 3M, St. Paul, USA. Hydroxypropyl methylcellulose E 15 was procured from Loba Chemie Pvt. Ltd., 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. Ltd. Mumbai, India. All reagents used were of analytical grade.

**Preparation of PCPZ from Prochlorperazine Maleate**

Weighed amount, about 10 g of prochlorperazine maleate was taken in a conical flask; 100 mL of 5 % w/v sodium bicarbonate solution was added, kept for shaking for 30 min on rotary shaker. Diethyl ether, 50 mL was added and kept for shaking for 15 min. The organic layer was separated and dried in vacuum oven. A clear, pale yellow, viscous liquid was obtained and it was used for the fabrication of patches.

**Tissue Preparation (Isolation)**

Porcine buccal tissue from domestic pigs was obtained from local slaughterhouse and used within 2 hours of slaughter. The tissue was stored in Krebs buffer at 4 °C after collection. The epithelium was carefully mounted in between an ultra test, Mecmesin equipment with porcine buccal membrane. The delipidized membrane was allowed to equilibrate for approximately one hour in receptor buffer to regain the lost elasticity.

**In vitro Drug Permeation Studies**

The buccal epithelium was carefully mounted in between the two compartments of a Franz diffusion cell with internal diameter of 2.1 cm (3.46 cm² area) with a receptor compartment volume of 12.0 mL. Distilled water containing 20 % v/v of ethanol (12 mL) was placed in receptor compartment. The epithelium was 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 the lost elasticity.

**Estimation of Drug Content in the Sample by HPLC**

Analysis of samples for PCPZ was performed using an HPLC system (Shimadzu, Japan) according to the reported method (Miller et al., 1988). The HPLC system was equipped with a LC-10AT pump, SPD-10A Spectrophotometric detector. Samples were eluted on a RP C18 column (150 × 4.6mm ID, particle size 5 µ) cyano analytical column at ambient temperature using a mobile phase consisting of a mixture of 50 mM sodium acetate buffer pH 4, with 40 % methanol and 18 % acetonitrile (v/v). The detection was carried out at 250 nm at a flow rate of 1.2 mL per minute. Sample preparation briefly involved addition of 300 µL of acetonitrile to 100 µL of sample, vortexed, centrifuged to precipitate the proteins and 20 µL of supernatant was spiked. A calibration curve was plotted for PCPZ in the range of 50-500 ng/mL. A good linear relationship was observed between the concentration of PCPZ and the peak area of PCPZ with a good correlation coefficient (r² = 0.999). The required studies were carried out to estimate the precision and accuracy of the HPLC method of analysis of PCPZ.

Phenol red was estimated spectrophotometrically by alkalizing with sodium hydroxide. Acetonitrile (250 µL) was added to 250 µL of sample to precipitate the proteins, vortexed followed by addition of 1 mL of 0.2 M sodium hydroxide. The solution was then made up to 5 mL, vortexed, centrifuged and absorbance of supernatant was measured at 563 nm using UV-Vis spectrophotometer.

**Buccal Absorption Studies**

Buccal absorption test was performed for PCPZ solution in eight healthy male volunteers aged between 24 and 29 years and weighing between 59 to 75 kg. The ethics committee of the University College of Pharmaceutical Sciences, Kakatiya University, India approved the protocol. Volunteers participated in the study after signing informed consents. This method uses phenol red, a non-absorbable marker for determining saliva volumes. It is assumed that phenol red is lost neither by absorption nor by swallowing (Schurmann and Turner, 1978; Tucker, 1988). Before test, the volunteers were asked to moisten their mouth with 20 mL of buffer solution containing 20 % v/v of ethanol. Phosphate buffer solution (20 mL, pH 6.6) containing 3 mg PCPZ and phenol red (20 µg/mL) was given to the volunteers and they were asked to swirl the solution about 60 swelling/min. The samples of 1 mL were collected from the floor of the mouth at 2, 4, 6, 8, 12, 14 and 16 min using a micropipette. While collecting the samples, volunteers were asked to stop swirling momentarily and draw solution to the floor of the mouth. After the last sample was collected, all the solution was expelled into a beaker, volunteers were asked to rinse their
mouth twice with 20 mL of phosphate buffer (pH 6.6) and the washings were pooled with the original sample. Volume was noted and the quantity of PCPZ present in the samples was estimated by HPLC. Phenol red was estimated as described in the earlier section.

**Fabrication of PCPZ patches**

Buccal patches were prepared using solvent casting technique with HPMC as polymer and propylene glycol as plasticizer. Polymer was added to 20 mL of dichloromethane and methanol (1:1) solvent system and allowed to stand for 6 h to swell. PCPZ and propylene glycol were dissolved in 5 mL of solvent system and added to the polymeric solution. This was set aside for 2 h to remove entrapped air, transferred to a petri plate and dried at room temperature for overnight and then in vacuum oven for 8-12 h. The formed patches were removed carefully, cut to size and stored in a desiccator. The composition of the patches is shown in Table 1. Patches with any imperfections, entrapped air, differing in weight or PCPZ content were excluded from further studies.

**In vitro Release Study from PCPZ Patches**

The drug release rate from buccal patches was studied using Franz diffusion cells. Patches were supposed to release the drug from one side only; therefore an impermeable polyester backing membrane was placed on the other side of the patch. The patch was sandwiched in dialysis membrane (Hi Media molecular weight 5000) and, was further placed between receptor and donor compartments. The entire set up was placed over magnetic stirrer and temperature was maintained at 37°C by placing the diffusion cell in a water bath. The contents of receptor compartment were stirred with teflon bead at a speed of 500 rpm. One mL sample was collected at predetermined time intervals from receptor compartment and replaced with an equal volume of the buffer. The samples were analyzed by using UV-visible spectrophotometer (Elico, India) at 254 nm. The experiment was performed in six replicates.

**Moisture Uptake Studies**

The moisture uptake studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture. The study was carried out as per procedure reported earlier (Vamshi et al., 2007). Briefly, agar (5% w/v) was dissolved in hot water, transferred into petriplates and allowed to solidify. Six patches from each formulation series were placed in vacuum oven overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. They were then incubated at 37°C for one hour over the agar surface. The initial and final weights were recorded and percentage moisture absorption was calculated by using the formula:

\[
\% \text{Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

**Measurement of Mechanical Properties**

Mechanical properties of the patches were evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with a 25 kg load cell. Film strip with the dimensions 60 x 10 mm and without any 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 the test, the lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip broke. The force and elongation of the film at the point when the strip broke was recorded. The tensile strength and elongation at break values were calculated using the formula.

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

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

**Table 1. Formulation ingredients off mucoadhesive buccal patches of Prochlorperazine.**

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>PCPZ (mg)</th>
<th>HPMC E 15 (mg)</th>
<th>Propylene glycol (µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>78</td>
<td>2000</td>
<td>300.0</td>
</tr>
<tr>
<td>P2</td>
<td>78</td>
<td>2250</td>
<td>337.5</td>
</tr>
<tr>
<td>P3</td>
<td>78</td>
<td>2500</td>
<td>375.0</td>
</tr>
<tr>
<td>P4</td>
<td>78</td>
<td>2750</td>
<td>412.5</td>
</tr>
<tr>
<td>P5</td>
<td>78</td>
<td>3000</td>
<td>450.0</td>
</tr>
</tbody>
</table>

*Note*: 25 mL of solvent system, 1:1 ratio of dichloromethane and methanol was used.
**In vitro Bioadhesive Strength**

The bioadhesive strength of the buccal patches was determined using an ultra test (Mecmesin, UK) equipped with a 5 kg load cell. The fresh porcine buccal mucosa obtained from slaughterhouse was stored in simulated saliva solution (2.38 g Na$_2$HPO$_4$, 0.19 g KH$_2$PO$_4$ and 8.00 g NaCl in 1000 mL of distilled water at pH 6.75). The porcine buccal mucosa was secured tightly to a circular stainless steel adapter of a diameter 2.2 cm provided with the equipment. This was fixed to advanced force gauze. The buccal patch to be tested was placed over another cylindrical stainless steel adaptor of similar diameter and mounted on the platform of motorized test stand. Buccal patch with a backing membrane was adhered on to it using a solution of cyanoacrylate adhesive. All measurements were made at room temperature. During measurement 100 µL of 1 % w/v mucin solution was used to moisten the porcine buccal membrane. The upper support was lowered at a speed of 0.5 mm/s until contact was made with the tissue at the predetermined force of 0.5 N for a contact time of 180 sec. At the end of the contact time upper support was withdrawn at a speed of 0.5 mm/s 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 force distance curve while the peak detachment force required detaching from tissue.

**Result and Discussion**

**Drug Permeation Studies through the Porcine Buccal Membrane**

Porcine buccal mucosa has been the most frequently chosen model for *in vitro* permeation studies because of its similarity to human tissue and is available in large quantities from slaughterhouses (de Vries et al., 1991; Squier and Hall, 1985). Cumulative amount of PCPZ permeated through the porcine buccal epithelium is shown in Fig. 1. The isolated membrane was intact as no detectable level of phenol red, which was used as a non-absorbable marker compound, was found in the receiver compartment. The thickness of the isolated membrane, measured with a digital micrometer (Mitutoyo, Japan), ranged from 1040 to 1880 µm. Cumulative amount of PCPZ permeated in 6 h was about 71.52 ± 4.12 % and flux was calculated to be 2.14 ± 0.01 µg. h$^{-1}$.cm$^{-2}$.

**Buccal Absorption Test**

Buccal absorption test was conducted to substantiate the results from the *in vitro* permeation studies and in addition, it gives information regarding the irritant nature of the drug to oral mucosa. The results of buccal absorption study (Fig. 2) revealed that PCPZ could be absorbed through the oral mucosal membranes. It was found that about 36.71 ± 4.14 % of the drug was absorbed in 16 min. The drug was absorbed at a slow rate for first 6 min, after which the drug absorption was rapid. The volunteers did not swallow the solution and this was evident from the observation that the total quantity of phenol red (396.20 ± 6.27 µg) calculated from the expelled solution after 16 min and quantity of phenol red present in the 8 collected samples was nearly equivalent to the initial quantity of phenol red (400 µg) in solution given to the volunteers for swirling. The loss of phenol red (approximately 3.80 µg) may be due to binding of phenol red to the oral mucosa. This was calculated from the change in the phenol red concentration. Volunteers did not report any discomfort or irritation. Visual observation of the mucosa after the test did not show any evidence of mucosal irritation or damage.

The results were in accordance with the results of *in vitro* permeation studies and show that PCPZ could permeate through the human buccal membrane. Hence there is a scope for the development of a buccal dosage form for PCPZ.

**Fig 1.** *In vitro* permeation of PCPZ (3.0 mg) through porcine buccal mucosa values represented as mean ± S.D (n = 6).
In vitro Drug Release Studies

The drug release profiles of PCPZ patches were shown in Fig. 3. The drug release was governed by the amount of matrix forming polymer. A short lag time of about 15 min was observed. 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; however, the difference is insignificant among the formulations. Formulation P1 showed maximum drug release (83.61 ± 7.52 %) with a short lag time (<15 min), while formulation P5 showed lowest release of 57.93 ± 4.36 % (lag time 20 min), among the series. Data of the in vitro release was fit into different equations and kinetic models to explain the release kinetics of PCPZ from buccal patches. The kinetic models used were zero-order equation, first-order equation, and Korsemeyer-Peppas models (Korsmeyer et al., 1983; Peppas, 1985). Zero order model seemed to be the most appropriate model describing release kinetics from all patches (0.993 for formulation P1 to 0.999 for formulation P5). On the other hand ‘n’ values (0.51 ≤ n ≤ 0.97) indicated that amount of released drug was by non Fickian diffusion (Peppas, 1985). Increasing the concentration of the polymer in the formulations showed a sustained effect on PCPZ release, but the difference is insignificant (p>0.05). This is because, 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. Zero-order release from swellable hydrophilic matrices occurs as a result of constant diffusional pathlengths. When the thickness of the gelled layer and thus the diffusional pathlengths remain constant, zero-order release can be expected. In this investigation similar behavior was predicted and obtained.
Moisture Uptake Studies

Moisture absorption studies evaluate the integrity of the formulation upon exposure to moisture and the results were shown in Table 2. The percentage moisture observed ranged from about 62.17 ± 5.28 to 152.10 ± 28.63 % w/w for different formulations. Formulations P1 and P2 were deformed during the study. The results reveal that, percentage of moisture absorption was increased with increase in polymer content of formulations. When the patches were placed without 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

Ideal buccal film, 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). It is suggested that an ideal buccal film should have a relatively high TS and E/B (Peh and Wong, 1999).

The results of the mechanical properties i.e. TS and E/B are presented in Table 2. TS increased with the increase in polymeric content but E/B values decreased with the increase in polymer content. Maximum TS was exhibited by P5 patch (14.48 ± 2.48 kg.mm⁻²) and minimum was exhibited by P1 (4.27 ± 0.87 kg.mm⁻²). Maximum E/B was seen with P1 (120.57 ± 10.26 % mm⁻²) and the least was observed with P5 (55.60 ± 4.28 % mm⁻²). Tensile strength values indicate that there is no statistically significant difference (p < 0.05) between the next immediate formulations. But statistically significant difference was observed in elongation at break values between the next immediate formulations.

Selection of optimized formulation

Based on in vitro release and moisture absorption studies formulation P3 was selected as the best formulation. Formulation P1 showed maximum drug release (83.61 ± 7.52 %), where as formulation P3 showed 77.81 ± 5.97 % drug release. The difference is statistically insignificant (p>0.05). Formulations P1 and P2 were deformed during moisture absorption studies, these formulations could not be expected to maintain the integrity after administration. Therefore, formulation P3 was selected as best formulation and subjected for further investigation.

In vitro Bioadhesion Measurements

In vitro bioadhesion measurements are routinely performed for mucoadhesive dosage forms and, most commonly used technique for evaluation of buccal patches is the measurement of adhesive strength (He et al., 1998). Work of adhesion, calculated from 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. The peak detachment force and work of adhesion for formulation P3 were 0.68 ± 0.15 N and 0.14 ± 0.08 mJ respectively. These values for bioadhesion and peak detachment force were within the range for suitable bioadhesion as reported for various films (Peh and Wong, 1999).

### Table 2. Moisture absorption and mechanical properties of mucoadhesive buccal patches of Prochlorperazine.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Moisture absorbed (% w/w)</th>
<th>Tensile Strength (Kg.mm⁻²)</th>
<th>Elongation at Break (% mm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Deformed</td>
<td>4.27 ± 0.87</td>
<td>120.57 ± 10.26</td>
</tr>
<tr>
<td>P2</td>
<td>Deformed</td>
<td>9.23 ± 1.58</td>
<td>87.25 ± 6.52</td>
</tr>
<tr>
<td>P3</td>
<td>62.17 ± 5.28</td>
<td>10.28 ± 2.27</td>
<td>80.62 ± 5.24</td>
</tr>
<tr>
<td>P4</td>
<td>67.87 ± 3.19</td>
<td>12.41 ± 2.86</td>
<td>74.73 ± 4.87</td>
</tr>
<tr>
<td>P5</td>
<td>152.10 ± 28.63</td>
<td>14.48 ± 2.48</td>
<td>55.60 ± 4.28</td>
</tr>
</tbody>
</table>

*aValues represented are mean ± S.D (n=3)
Conclusion

HPMC E 15 shows satisfactory buccoadhesive properties. Formulation P3 using this polymer showed significant bioadhesive properties with an optimum release profile and could be useful for buccal administration of prochlorperazine. Further work is recommended to support its efficacy claims by long term pharmacokinetic and pharmacodynamic studies in human beings.

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References


