Formulation and evaluation of a bioadhesive patch for buccal delivery of tizanidine

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Abstract  Tizanidine hydrochloride (THCl) is an antispasmodic agent which undergoes extensive first pass metabolism making it a possible candidate for buccal delivery. The aim of this study was to prepare a monolayered buccal patch containing THCl using the emulsification solvent evaporation method. Fourteen formulations were prepared using the polymers Eudragit® RS 100 or Eudragit® RL 100 and chitosan. Polymer solutions in acetone were combined with a THCl aqueous solution (in some cases containing chitosan) by homogenization at 9000 rpm for 2 min in the presence of triethyl citrate as plasticizer and cast in novel Teflon molds. Physicochemical properties such as film thickness, in vitro drug release and in vitro mucoadhesion were evaluated after which permeation across sheep buccal mucosa was examined in terms of flux and lag time. Formulations prepared using a Eudragit® polymer alone exhibited satisfactory physicochemical properties but lacked a gradual in vitro drug release pattern. Incorporation of chitosan into formulations resulted in the formation of a porous structure which did exhibit gradual release of drug. In conclusion, THCl can be delivered by a buccal patch formulated as a blend of Eudragit® and chitosan, the latter being necessary to achieve gradual drug release.

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1. Introduction

Buccal drug delivery is a highly effective way to improve bioavailability. This is because the buccal mucosa has a rich blood supply which facilitates direct entry of drug molecules into the systemic circulation. Buccal drug delivery is well accepted by patients as the buccal cavity is easily accessible for self-medication. In addition, buccal dosage forms allow drug absorption to be rapidly terminated in case of an adverse reaction. Formulations of buccal dosage forms include adhesive tablets, gels, and patches, of which patches are preferable in terms of flexibility and comfort.

Tizanidine hydrochloride (THCl) is a centrally acting \( \alpha_2 \)-receptor agonist which regulates myotonolytic effects on skeletal muscle. It exhibits a short half-life of 2.5 h, a low bioavailability of around 40% and a wide distribution in the body. Tizanidine undergoes extensive first pass metabolism leading to breakdown of the imidazole ring and oxidation of the aromatic ring and sulfur atom. In an attempt to overcome such extensive first-pass metabolism, tizanidine was selected as a candidate for formulation in a bioadhesive buccal patch.

A bioadhesive THCl tablet for buccal delivery has been formulated and evaluated by Shanker et al. and Giradkar et al. but THCl buccal patches have not been investigated. Buccal patches must be flexible, elastic and strong to withstand the mechanical activity inside the mouth. They must also possess good mucoadhesion in order to be retained in the mouth for the desired duration. Buccal patches offer greater flexibility and comfort than adhesive tablets and a monolayered buccal patch was chosen for development in this study. The patch was designed to provide unidirectional drug release, a large contact surface area and good buccal penetration of drug. Various formulation variables and their effect on patch properties were evaluated. The hydrophobic polymers Eudragit RS and RL-100 were used as base matrices and chitosan (CHT) was incorporated as a hydrophilic polymer to modify the rate of drug release. Ethyl cellulose was used as the backing layer.

2. Materials and methods

2.1. Materials

THCl was supplied by Endoc Pharma (India), CHT (MW: 110,000) was purchased from Marine Chemicals (Cochin, India). Eudragit RS 100 and RL 100 were provided by Vikram Thermo India Pvt Ltd. Acetone was purchased from Sigma Aldrich (USA). Triethyl citrate was purchased from Merck Specialties Pvt Ltd (India).

2.2. Preparation of patches

To prepare patches, the required quantity of Eudragit RS 100 or RL 100 was dissolved in acetone and 30% or 35% w/w triethyl citrate (dry polymer weight), respectively added to the acetone solutions. The required quantity of THCl was dissolved in water and the acetone and aqueous solutions combined by homogenization at 9000 rpm for 2 min. Finally 1 mL aliquots of the resulting polymeric solution (4 mg/mL) were pipetted into individual Teflon molds. Patches comprising different ratios of THCl, Eudragit and CHT were prepared as described in Table 1. In patches containing CHT, CHT was dissolved in the aqueous solution of THCl.

### Table 1 Relative amounts of Eudragit\textsuperscript{\textregistered} RS 100, Eudragit\textsuperscript{\textregistered} RL 100 and chitosan (CHT) in patch formulations based on THCl=1.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Eudragit\textsuperscript{\textregistered} RS 100</th>
<th>Eudragit\textsuperscript{\textregistered} RL 100</th>
<th>CHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F2</td>
<td>8</td>
<td>–</td>
<td>–</td>
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<tr>
<td>F3</td>
<td>10</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F4</td>
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<td>–</td>
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<td>F5</td>
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<td>2</td>
</tr>
<tr>
<td>F6</td>
<td>15</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>F7</td>
<td>15</td>
<td>–</td>
<td>0.5</td>
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<tr>
<td>F8</td>
<td>–</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>F9</td>
<td>–</td>
<td>8</td>
<td>–</td>
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<tr>
<td>F10</td>
<td>–</td>
<td>10</td>
<td>–</td>
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<tr>
<td>F11</td>
<td>–</td>
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<td>–</td>
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<td>F12</td>
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<tr>
<td>F13</td>
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<td>1</td>
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<tr>
<td>F14</td>
<td>–</td>
<td>15</td>
<td>0.5</td>
</tr>
</tbody>
</table>

2.3. Evaluation of patches

2.3.1. Thickness and weight

The thickness of patches was assessed using a micrometer screw gage (Mitutoyo, Japan). For each formulation, three randomly selected patches with surface area 1 cm\(^2\) were used. Each patch was weighed individually on an analytical balance (Shimadzu, Japan) and the average weights calculated.

2.3.2. Assay of THCl

A complete patch from a Teflon mold was cut into pieces and crushed in a pestle and mortar under a water/ethanol solvent system with continuous agitation. The contents were then filtered through a Whatman filter paper (Whatman International Ltd, England) into a volumetric flask. After appropriate dilution with phosphate buffer (pH 6.8), solutions were analyzed by determination of absorption at 320 nm (UV 1800 spectrophotometer, Shimadzu, Japan) against a solvent blank. Drug content was estimated from a calibration curve in the range 2–12 µg/mL (regression equation \( Y=0.050X, R^2=0.9990 \)).

2.3.3. Folding endurance

Folding endurance of patches was determined manually by repeatedly folding a film at the same place until it ruptures. The number of folding required to break or crack a patch was taken as the folding endurance.

2.3.4. Surface pH

Patches were placed in glass tubes containing 10 mL phosphate buffer (pH 6.8) and the pH at the surface measured after 1, 2, 3, 4, 5, 6, 7 and 8 h by placing the tip of the glass microelectrode of a digital pH meter (Elico LI 120, India) close to the surface of the patch and allowing it to equilibrate for 1 min prior to recording. Experiments were performed in triplicate.
2.3.5. Swelling and erosion
Swelling and erosion of patches were determined under conditions identical to those for the dissolution tests. The degree of swelling (water uptake) and extent of erosion (mass loss) were determined gravimetrically according to the equations:

\[
\text{Degree of swelling} = \frac{\text{Wet weight} - \text{original dry weight}}{\text{Original dry weight}}
\]

\[
\text{Erosion (mass loss)} = \frac{\text{Original weight} - \text{remaining dry weight}}{\text{Original weight}} \times 100\
\]

2.3.6. In vitro drug release
Experiments were performed in triplicate using an orbital shaker maintained at 37 ± 0.5°C and 100 strokes per min. Patches were firmly secured in modified glass bottles (125 mL) placed on the shaker platform and 100 mL phosphate buffered saline (PBS, pH 6.8) added as the dissolution medium. At specified times, 2 mL aliquots were removed using a syringe and replaced with equal volumes of fresh PBS to maintain the total volume. Samples were filtered through a 0.45 μm Millipore Filter (Whatman International Ltd, England) and THCl concentration determined by measuring absorbance at 320 nm.

2.3.7. Kinetics of drug release
The fit of the drug release data to the Higuchi expression was evaluated. According to this model, the cumulative amount of drug released per unit area is proportional to the square root of time:

\[
Q = k_H t^{1/2}
\]

where \( Q \) is the amount of drug released after time \( t \) and \( k_H \) is the release rate constant.

2.3.8. Scanning electron microscopy (SEM)
The cross section of dried films was examined using a scanning electron microscope (JEOL, JSM 840, Japan) after coating the dried films with gold sputter.

2.3.9. In vitro mucoadhesion
The mucoadhesive strength of patches was measured in triplicate on a modified physical balance (Fig. 1) using the method described by Gupta et al.21. A piece of sheep buccal mucosa was tied to the mouth of a glass vial filled completely with PBS pH 6.8. The glass vial was tightly fitted in the center of a beaker filled with PBS at 37 ± 1°C. Patches were stuck to the lower side of rubber stoppers with glue and the mass (g) required to detach the patches from the mucosal surface was taken as the mucoadhesive strength (shear stress). The following parameters were calculated from the mucoadhesive strength:

\[
\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength (g)}}{1000} \times 9.81 \quad (4)
\]

\[
\text{Bond Strength (N/m²)} = \frac{\text{Force of adhesion (N)}}{\text{Surface area (m²)}} \quad (5)
\]

2.3.10. In vitro permeability
The rate and extent of mucosal permeation of tizanidine through sheep buccal mucosa was determined using a modified Franz diffusion cell (Fig. 2). Briefly, the receptor compartment (40 mL) was filled with PBS (pH 6.8) at 37 ± 0.5°C and stirred at 50 rpm. The patch was sandwiched between the donor and receptor compartments of the diffusion cell on the sheep buccal mucosa. Aliquots (3 mL) of the receptor medium were withdrawn at regular intervals and replaced immediately with equal volumes of PBS (pH 6.8). The amount of tizanidine released into the receptor medium was determined by measurement of absorption at 320 nm against a blank.

2.3.11. Statistical analysis
Statistical analysis of all data was carried out using GraphPad prism version 5.0 (Graphpad software Inc, San Diego, California, USA).

3. Results and discussion
Initially various hydrophobic polymers were examined for film forming properties and drug release characteristics. After extensive preliminary investigation, Eudragit® RS 100 and Eudragit® RL 100 were identified as hydrophobic...
polymers with the ability to form films from which drug release was retarded. However, initial drug release was rapid rather than gradual as desired. Incorporation of CHT, a hydrophilic polymer, is able to enhance drug release in a concentration-dependent manner by promoting disintegration of the polymer matrix\(^2\). In addition, it acts as a permeation enhancer and enzyme inhibitor\(^2\). Based on these unique properties, CHT was incorporated into patch formulations to hopefully provide more controlled drug release.

The weight and thickness of patches were in the ranges 103.1 ± 0.02 to 136.2 ± 0.03 mg and 0.53 ± 0.03 to 0.64 ± 0.01 mm, respectively. Folding endurance ranged from 81 foldings for formulation F1 to 92 foldings for F11 (92) indicating patches were highly flexible. Drug content (%) of formulations varied from 98.96 ± 0.18 to 99.19 ± 0.11% indicating drug was dispersed uniformly throughout the patches.

3.1. In vitro release

Initially THCl homopolymeric patches were made from either Eudragit\textsuperscript{®} RS 100 or RL 100 and their in vitro drug release was investigated. Patches made with THCl:Eudragit\textsuperscript{®} ratios between 1:1 and 1:5 exhibited insufficient mechanical strength to be handled. Patches made with ratios between 1:6 and 1:15, showed decreased drug release with distinct differences in drug release profiles (Fig. 3). In particular, patches made with a 1:15 ratio of either Eudragit\textsuperscript{®} exhibited significantly retarded drug release which was greater for Eudragit\textsuperscript{®} RS 100 than for RL 100. This could be attributed to the greater hydrophobicity of Eudragit\textsuperscript{®} RS 100 causing THCl to diffuse more slowly into the dissolution medium. It could also be due to the greater chloride ion content of Eudragit\textsuperscript{®} RL 100 allowing more ion exchange with ions in the dissolution medium leading to faster drug release. On the basis of these results, it was concluded that a 1:15 ratio of THCl to Eudragit\textsuperscript{®} provided the most controlled release of THCl with 40% being released after 1 h and 100% after 8 h. In an attempt to reduce the extent of release during the first hour, a hydrophilic polymer was incorporated into the formulation.

Although CHT and Eudragit\textsuperscript{®} possess very different solubilities, a homogeneous formulation with a uniform distribution of THCl was successfully prepared after emulsification. This novel method of preparation of a film overcomes the problems of content uniformity commonly encountered with conventional multilayered films. The addition of triethyl citrate also plays a prominent role in film formation since, in addition to

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**Figure 2** Schematic representation of the modified Franz diffusion cell used to determine permeation of tizanidine across sheep buccal mucosa.

**Figure 3** Drug release from buccal patch formulations: (A) Eudragit\textsuperscript{®} RS 100 and Eudragit\textsuperscript{®} RS 100-CHT formulations; (B) Eudragit\textsuperscript{®} RL 100 and Eudragit\textsuperscript{®} RL 100-CHT formulations.
acting as a plasticizer, triethyl citrate also acts as an emulsifying agent. Increasing the amount of triethyl citrate relative to CHT does not lead to phase separation but can result in a monolayered film with rigidity problems.

The purpose of incorporation of CHT was to reduce the initial drug release and maintain the duration of drug release. The addition of CHT to patches made with both Eudragit® polymers at ratios of 0.5:1 and 1:1 did not provide a more gradual initial release pattern but addition of CHT at a 2:1 ratio (formulations F5 and F12) produced the desired profile. Presumably this amount of CHT leads to the formation of pores in the polymer matrix allowing the dissolution medium to freely penetrate, solubilize the THCl and facilitate its escape22. To confirm the similarity of the dissolution profiles of F5 and F12, the similarity factor (f2) was calculated and found to be 82.13 for F5 vs F12 and 83.45 for F12 vs F5. Since the f2 values are higher than 50, these results confirm that the drug release profiles are almost identical for these formulations.

### 3.2. Swelling and erosion

Swelling and erosion studies were conducted for formulations F5 and F12 (Fig. 4). Eudragit® is an insoluble, relatively impermeable, cationic copolymer of acrylate and methacrylates with quaternary ammonium groups and chloride counterions. Its chemical name is poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride). The only difference between Eudragit® RL and RS is the higher amount of methacrylate chloride in Eudragit® RL. Hydration and swelling is governed by the chloride ions which undergo exchange with the buffer anions in the dissolution medium to increase hydration and swelling of the patches.

Formulations F5 and F12 undergo swelling in the first hour with degrees of swelling of 0.53 and 0.59, respectively. The higher degree of swelling of formulation F12 is due to its greater chloride ion content. Subsequently, only minor changes in the degree of swelling took place attributed to the presence of CHT in the formulations. In the dissolution medium, CHT in the polymer leads to the formation of pores which, in turn, reduce the swelling ability of the polymer. Swelling due to gel formation does not occur at the acidic and near neutral pH of CHT. In summary, the degree of swelling of patches suggests they will cause minimal discomfort when in use.

Formulations F5 and F12 also exhibited marked reductions in size after 1 h due to erosion. The values were 25.32% erosion of formulation F5 and 27.22% erosion of formulation F12 over 8 h. The erosion data confirm that the patches maintain their integrity throughout the period of drug release.

### 3.3. Kinetics of drug release

To interpret the release behavior of THCl from different patches, it is necessary to fit the data to a mathematical model. Although various mathematical models are available, the Higuchi square root model is the main one used to fit the kinetics of drug release from patches. Plotting of the data for formulations F5 and F12 gave correlation coefficients of 0.939 and 0.924, respectively confirming that drug release occurred by diffusion through the film matrix. The values of $k_H$ were found to be 532.5 and $548.7 \mu g/(cm^2 min^{1/2})$ for F5 and F12, respectively.

### 3.4. SEM

Formulations F5 and F12 were subjected to SEM studies to assess changes in their surface morphology (Fig. 5). Initially both formulations revealed smooth and compact surfaces but, after 1 h, both formulations appeared porous particularly F5. At 8 h, the surface of both formulations showed significant changes in texture and clearly visible pores. This may be due to the uptake of water resulting from the presence of CHT in the formulations. Based on these results, it can be concluded that the presence of CHT in patches significantly affects their surface morphology and leads to the formation of pores in accordance with the in vitro dissolution data.

### 3.5. Surface pH

The surface pH of a patch should be close to that of saliva (i.e., 5.8–7.1) since deviation from this pH may cause irritation to the oral mucosa. Values of surface pH for formulations F5 and F12 were in the range 6.2–6.5 indicating they are suitable for application to the oral mucosa.

### 3.6. In vitro adhesion studies

The adhesion of patches to the oral mucosa is a prerequisite for maintaining drug release. Formulation F5 was more mucoadhesive than F12 possibly due to lower concentration.
of plasticizer (triethyl citrate) used to make it. Formulation F12, containing Eudragit\textsuperscript{R} RL 100 requires 35% w/w triethyl citrate compared with 30% w/w in F5. The lower concentration of plasticizer reduces intermolecular attraction between the polymers resulting in an additive mucoadhesive force which, in turn, minimizes a polymer mucous interaction. The higher amount of plasticizer utilized for the preparation of patches may result in less mucoadhesivity but one-way ANOVA of mucoadhesion data indicated no significant differences between formulations F5 and F12 (Table 2).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Results of the in vitro mucoadhesion study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>F5</td>
</tr>
<tr>
<td>Mucoadhesive strength (g)</td>
<td>30.12 ± 1.14</td>
</tr>
<tr>
<td>Force of adhesion (N)</td>
<td>0.30 ± 0.01</td>
</tr>
<tr>
<td>Detachment force (N/m²)</td>
<td>167.24 ± 3.16</td>
</tr>
</tbody>
</table>

3.7. In vitro permeation studies

THCl permeation from formulations F5 and F12 across sheep buccal mucosa over a period of 8 h is shown in Fig. 6. The maximum permeation of drug from F5 was 83.1 ± 5.1% at 8 h compared with 80.1 ± 1.1% from F12. Regression of the linear portions of the two plots gave slopes and intercepts from which the permeation flux (slope divided by mucosal surface area) of F5 and F12 were calculated to be 5.27 ± 0.41 and 5.11 ± 0.13 μg/cm²/h, respectively. The lag times for

Figure 5  SEM photographs of formulations F5 and F12 after incubation in dissolution medium for up to 8 h.

Figure 6  In vitro drug permeation from formulations F5 and F12 over 8 h.
formulations F5 and F12, determined by extrapolation of the linear portions of the plots to the abscissa, were 1.2 and 1.3 h, respectively. Formulation F5 made from Eudragit® RS 100 gave higher permeation of drug than formulation F12 made from Eudragit® RL 100. In formulation F5, only one methacrylate chloride ion is present which allows tizanidine particles to pass from the formulation more easily than from formulation F12 which contains more methacrylate ions to hinder the passage of drug particles.

4. Conclusions

THCl can be delivered by buccal patches formulated from Eudragit® and CHT polymers where the incorporation of CHT is necessary to achieve a gradual release of drug. Although formulations F5 and F12 exhibit such in vitro release profiles, permeation of THCl from formulation F5 made with Eudragit® RS 100 across buccal mucosa is superior.

Acknowledgment

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References