Development of Mucoadhesive Patches for Buccal Administration of Propranolol Hydrochloride

M.D. Dhanaraju, K.R. Senthil kumar and G. Poovi

Abstract: The objective of this work was to prepare and evaluate the controlled release of patches in buccal drug delivery system using the model drug propranolol hydrochloride (D). The mucoadhesive patches containing propranolol hydrochloride were developed by using the casting method with the use of film forming polymer Eudragit NE30D (ED) and different proportions of water swellable polymers Carbopol 934P (Cp934p), sodium carboxy methyl cellulose (SCMC), hydroxyl propyl methyl cellulose (HPMC). Then these formulations were evaluated for swelling study, weight variation, thickness uniformity, mucoadhesive strength, in-vitro drug release and kinetics study. The results showed that patches properties depended significantly on both relative amount of hydrophilic polymer and ED. The rank orders of ED patches for the processes evaluated were as follows: Swelling (increase in area) and Mucoadhesion- D:ED:SCMC> D:ED:Cp934p >D:ED:HPMC; Swelling (in weight)- D:ED:SCMC> D:ED:HPMC> D:ED: Cp934p. The in vitro release study shown that the drug released from the formulation was sustained and the drug release was controlled by swelling and diffusion mechanism. The present investigation shown that the patch composed of ED and SCMC with 1:5:10 ratio showed the significant characteristics for buccal administration.

Key words: Buccal drug delivery system • Eudragit NE30D • Carbopol934p • Sodium carboxy methyl cellulose • Hydroxyl propyl methyl cellulose

INTRODUCTION

In the last decade considerable interest has been focused on buccal drug delivery systems [1-5]. The buccal method is one of the most attractive ways to deliver drugs into the organism [6-11]. Because the oral cavity has been shown to be an attractive site for drug delivery due to ease of administration and active molecules administered through the buccal mucosa pass directly into the systemic circulation [12-14] there by avoiding possible drug degradation in the gastro-intestinal tract as well as first-pass metabolism [15, 16] and also excellent accessibility, high patient acceptance and compliance are attractive features of buccal mucosa [17-19]. And then this route is well vascularized with venous blood draining the buccal mucosa reaching the heart directly via the internal jugular vein. In addition, when compare to the sublingual route of permeability barrier and relative immobility, the buccal musculature makes perfectly suited site for mucoadhesive sustained release dosage forms [20]. The oral mucosa portion is an ideal surface for the placement of retentive delivery systems for patches since it contains a larger expanse of smooth, immobile tissue [21, 22]. The first step in the development of such a patch is the selection and characterization of an appropriate bioadhesive. Hence bioadhesive formulations have been developed to enhance the bioavailability [23, 24] of drugs that undergo substantial first-pass hepatic effect and to control the drug release to a constant rate [25].

A wide variety of adhesive polymers [2] have been investigated with the aim of developing adhesiveness [26] permeability [27] and bioavailability [28]. These mucoadhesive polymers are pivotal in the development of buccal delivery systems which enable retention at the buccal mucosal surface so providing intimate contact between the dosage form and the absorbing tissue. The polymers employed to develop mucoadhesiveness in
this study were gel forming polymers, as poly acrylic acids (Carbopol 934P), sodium carboxy methyl cellulose [SCMC], hydroxyl propyl methyl cellulose (HPMC) and film-forming polymer, as Eudragit NE30D [29, 30] in different percentages [31] and combinations. The HPMC, SCMC and carbopol [32, 33] swells in contact with a liquid medium forming a gel that controls drug release and reduces irritation in the mouth [34].

Propranolol HCl (PHCl), a β-blocker, used in the treatment of various cardiovascular disorders is an ideal model drug for incorporation into a controlled release buccal formulation due to its short half-life (3–6hrs), low molecular weight and its extensive and highly variable first pass metabolism following oral administration [35]. In the present study, a flexible buccal patch or new mucoadhesive films for the controlled delivery of propranolol was developed by using the casting method. In order to prepare films having the appropriate characteristics, film-forming polymers (water insoluble Eudragit NE 30D as the matrix) were initially used alone and successively in combination with mucoadhesive polymers that the several above mentioned polymers with known bioadhesive properties were incorporated into Eudragit patches, both to provide the patches with bioadhesive properties and to modify the rate of drug release.

**MATERIAL AND METHODS**

**Materials:** Propranolol hydrochloride was given as a gift sample from Lupin Labs Pvt. Ltd, Aurangabad, India, eudragit NE 30D was obtained from Rohm Pharma, Germany, Hydroxypropyl methyl cellulose was procured from Dow Chemicals, India and carbopol 934 was purchased from Himedia, Mumbai, India. Sodium carboxy methyl cellulose was from Lobachemie, Mumbai. All chemicals used were of analytical grade.

**Methods**

**Preparation of Bioadhesive Buccal Patches:** The patches were prepared from different compositions as shown in Table 1. Patches containing different proportions of propranolol and eudragit NE 30D were prepared by dissolving the propranolol hydrochloride in the eudragit dispersion and then cast onto a Petri dish and dried in the oven at 45°C until completely dry [36, 37]. The drug to eudragit ratio studied were 1:1, 1:5, 1:10 different hydrophilic polymers SCMC, Methanol K4M and Cp 934p were incorporated into the eudragit patches to modify the drug release profile and the bioadhesiveness of the buccal patch. Hydrophilic polymers were prepared as 2% solution and hydrated for 24 hrs before being incorporated into the drug eudragit mixture. However, in the case of corbopol, the gel solution was neutralised to pH 6.5 – 7.5 before being added, to avoid incompatibility.

**Content Uniformity:** The patches containing drug was cut into 1.1 cm² were taken in a small mortar and triturated with a little amount of buffer for about 10 minutes and dissolved and the volume was made upto 50ml with buffer. The solutions were diluted appropriately and the absorbance measured at 290nm.

**Weight Variation and Thickness Uniformity:** Weights of each patch were determined and average was calculated. Thickness of the patches was measured with the help of a screen gauge, measurements were taken at different positions of the patches and the average was calculated.

**Studies of Swelling:** The patch area of swelling was measured by placing 1.1 cm² of the patches containing drug in a petridish of diameter of 7 cm under which a graph paper was placed to measure the increase in area. This film was weighed (W₁) and 50ml of buffer pH 6.2 was poured into the petridish. Weight increases due to swelling of patch. After every 5 minutes interval the increase in length and breadth of the patch was noted and the patch was taken out from the petridish and excess water is removed with the help of a tissue paper and the weight was measured (W₂). The difference gives the weight of swelling of the patch.

**In vitro Release Studies:** The in vitro propranolol release was evaluated [38, 39] using USP dissolution test apparatus (6 peddle over disk). The dissolution medium comprised 500ml of buffer maintained at a temperature of 37±0.5°C and paddle rotation speed of 100 rpm/min was used. 5ml of sample were collected at predetermined time

<table>
<thead>
<tr>
<th>Composition</th>
<th>Ratios*</th>
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<tbody>
<tr>
<td>Propranolol Hydrochloride (mg)</td>
<td>1:1</td>
</tr>
<tr>
<td>EUD NE30D (mg)</td>
<td>50</td>
</tr>
<tr>
<td>Carbopol (mg)</td>
<td>-</td>
</tr>
<tr>
<td>Methocel K4M (mg)</td>
<td>-</td>
</tr>
<tr>
<td>SCMC (mg)</td>
<td>-</td>
</tr>
<tr>
<td>Water (ml)</td>
<td>2.4</td>
</tr>
</tbody>
</table>

intervals over 14 hrs. The drug concentration was measured by UV spectrophotometer at a detection wavelength of 290 nm.

Studies on Mucoadhesive Strength: The strength of the bond formed between the formulation and the mucous membrane exercised from the porcine chick pouch was determined using tensile experiments on a specially fabricated assembly slightly modified from the method described by Gupta et al. in 1992 [40].

Selection of Model Surface: The porcine cheek pouch was selected for the bioadhesive testing, the cheek pouch was selected from the sacrificed animal of the slaughter house. The pouch was excised and trimmed evenly from the sides. It was then washed in the buffer pH 6.2 and then preserved in the same buffer.

Fabrication of Test Assembly: The working of a double beam physical balance form the basis of bioadhesion test apparatus. The left pan of a balance was removed. On the left side a wire made of copper was hung and was used to support a plastic cylinder base having a flat surface at the bottom. The height of the whole step was adjusted to accommodate a 500ml beaker below it. Another 50ml beaker was kept inverted in the 500ml beaker in such a way that the cylinder base hanging from the balance is almost touching the bottom of 50ml beaker. The two sides of balance was balanced such that the right hand side was exactly 5g lighter than the left by placing weights on the left side of the balance. The two sides of the balance were balanced with a 5g weight on the right hand side.

The porcine pouch, excised and washed was tied tightly with the mucosal surface facing upwards using a rubber band on the bottom of the 50ml beaker. The beaker was then lowered into the 500ml beaker and was filled with buffer pH 6.2 such that the buffer just surface of the mucosal membrane and keeps it moist. That was then kept at the left hand set up of the balance. The patch was then stuck to the bottom surface of the plastic cylinder portion hanging on the left hand set up portion of the balance. The balance beam was raised with 5g weight on the right pan and removed. This lowered plastic cylinder along with the patch over the mucosa with the weight of 5gms. The balance was kept in position for 3 minutes and then slowly the weights were increased in the right pan, till the patch separated from the mucosal surface. The excess weight on the pan that is total weights minus 5 gms is the force required to separate the patch from the mucosa. This gives bioadhesive strength of the patch. The tissue is then washed with buffer and left for 5 minutes before the next measurement.

Kinetics and Mechanism of Drug Release: The in vitro release profiles were tested for their kinetic behavior in order to establish the kind of mechanism possibly involved in propranolol hydrochloride release from the film matrix. Data were analyzed using the following equation [41]:

\[ M_t = M_8 \frac{kt}{1 + kt} \]

Where \( M_t/M_8 \) is the drug fraction released at time \( t \), \( k \) is a constant depending upon structural and geometric characteristics of the system, \( n \) is an exponent value is indicative of the drug release mechanism.

RESULT AND DISCUSSION

The various formulations of mucoadhesive patches containing propranolol hydrochloride were developed by using the casting method [36, 37] with the use of film forming polymer Eudragit NE30D and different proportions of waterswellable polymers HPMC, SCMC and corbopol 934p (Table 1).

Eudragit NE 30D is a neutral co polymer and is widely used in the development of controlled release delivery systems and film coating technology. This aqueous colloidal dispersion is insoluble and inert in aqueous media at all pH values and is preferred over the use of organic solvents casting which posed undesirable hazards to environment and overall health. This polymer dispersion has a low minimum film formation temperature and does not require plasticizers, resulting in flexible films [42]. The reasons for using swellable polymers are that it swells and dissolves slowly in the presence of aqueous medium giving rise to a prolonged release of drug when the ratio of swellable polymers is high. HPMC polymer [43] have good binding property and low solubility can maintain the integrity of the patches for a longer period of time and Carbopol is known to be excellent bioadhesive polymers [44-47]. Addition of Eudragit NE 30D to highly acidic polymer like coabopol into the drug polymer dispersion resulted in latex coagulation [37]. This incompatibility could be overcome by neutralizing the carbopol solution to pH 6.5-7.5 prior to addition of the drug and latex dispersion, where a no incompatibility was observed when HPMC and SCMC were added.

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In vitro swelling profile (increase in weight) of different formulation. D-Drug, E-Eudragit NE 30D, CP- Carbopol 934p, SCMC- sodium carboxy methyl cellulose & HPMC- hydroxyl propyl methyl cellulose polymer (n = 3, mean ± standard deviation).

Fig. 1: In vitro swelling profile (increase in weight) of different formulation. D-Drug, E-Eudragit NE 30D, CP- Carbopol 934p, SCMC- sodium carboxy methyl cellulose & HPMC- hydroxyl propyl methyl cellulose polymer (n = 3, mean ± standard deviation).

Table 2: Patches characteristics of the different formulations. (n = 3, mean ± standard deviation)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight (mg)</th>
<th>Thickness (mm)</th>
<th>Swell weight (mg)</th>
<th>Mucoadhesive strength (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:5 D:E:HP</td>
<td>50</td>
<td>0.32</td>
<td>52±4.23</td>
<td>1.324±0.085</td>
</tr>
<tr>
<td>1:10 D:E:HP</td>
<td>50</td>
<td>0.33</td>
<td>-</td>
<td>1.382±0.070</td>
</tr>
<tr>
<td>1:5:5 cp</td>
<td>47</td>
<td>0.44</td>
<td>56±2.64</td>
<td>1.428±0.08</td>
</tr>
<tr>
<td>1:5:10 cp</td>
<td>49</td>
<td>0.47</td>
<td>52±4.98</td>
<td>1.564±0.055</td>
</tr>
<tr>
<td>1:5:5 HPMC</td>
<td>52</td>
<td>0.40</td>
<td>54±3.96</td>
<td>1.326±0.065</td>
</tr>
<tr>
<td>1:5:10 HPMC</td>
<td>55</td>
<td>0.42</td>
<td>56±3.34</td>
<td>1.502±0.07</td>
</tr>
<tr>
<td>1:5:5 SCMC</td>
<td>54</td>
<td>0.48</td>
<td>56±6.28</td>
<td>1.622±0.078</td>
</tr>
<tr>
<td>1:5:10 SCMC</td>
<td>56</td>
<td>0.48</td>
<td>61±4.98</td>
<td>1.874±0.09</td>
</tr>
</tbody>
</table>

Table 2 showed the weight, thickness, swell weight, bioadhesive strength of different formulation of the patches. The swelling rate in terms of swell weight (Figure 1) was conducted for all the patches except 1:10 ratio due to sustained drug release occur in 1:5 ratio when compare to 1:1 and 1:10 ratio (Figure 3). Hence further study was carried out on 1:5 ratio with different hydrophilic polymers. The weight was found to increase to a high extent when the concentration of SCMC was increased. These results inferred that SCMC films exhibited higher capacity of water uptake than other polymer films as expected on the basis of SCMC higher water solubility.

Figure 2 showed the swelling characteristics of the different formulation. The studies of swelling in terms of area were conducted for all the patches of different ratios of polymer for up to 10 minutes and the swellability of the patches was found to increase when the hydrophilic polymer content was increased. It can be seen that, when the relative amount of hydrophilic polymer content such as SCMC, Carbopol 934 and HPMC increased, the swelling characteristic of the patches also increased linearly. Among the Drug dispersed Eudragit film studied, D:ED:SCMC produced swelling to a much higher extent than Corbopol and HPMC, which gave reduced swelling in a dissimilar manner (rank order: SCMC>CP>HPMC) due to a Eudragit and its co-polymer is obviously related to its solubility in the medium.

Several methods have been employed to determine the in-vitro bioadhesion of mucoadhesive dosage forms. These included the texture analyzer [48] whilhemg plate method [49] adhesion weight method [50], flow channel techniques method [51]. The strength of the bond formed between the mucous membrane excised from the porcine cheek pouch was determined using tensile experiments on a special fabricated assembly from the method described.
Comparison of bioadhesive properties of these formulations with the values reported in the literature for bioadhesive materials is not meaningful unless measurements are carried out using similar methods and experimental conditions. It has been shown that the bioadhesion between hydrated block copolymer patches and tissues increases with increase in initial applied force. Similar findings have been reported by Park and Robinson and Park and Park and attributed to enhanced interaction between the hydrogel and the substrate. The maximum adhesion force of the patches were observed in the patch with D: E: SCMC (1:5:10) followed by carbopol and HPMC (Table 2). Because the strength of patches was dependent on the property of bioadhesive polymers, which on hydration, adhere to mucosal surface and also on the concentration of polymer used.

The drug release profile of Eudragit patches with different ratios of the Eudragit to the propranolol showed in Figure 3. It is apparent from the plots that the drug release could be sustained and was governed by the polymer content when the time was increased. Poovi et al. also reported similar finding that the release of the drug mainly depended upon the polymer concentration. The patch with a drug to polymer ratio of 1:5 was chosen to evaluate the drug release and bioadhesive properties of the patches after incorporation of various hydrophilic polymers due to sustained drug release occur in 1:5 ratio when compare to 1:1 and 1:10 ratio. From the Figures 4, 5 and 6, it can be seen that the rate of drug release could be modified in a predictable manner by varying the amount of hydrophilic polymers. It shown that the release rate of the drug from the above mentioned three preparations was found to decrease on increasing the polymer concentrations due to more compact wall exist between the drug and polymer and it indicates that they have sustained drug release for prolonged period of time. Hence among the different ratio (1:5, 1:5:5, 1:5:10) the 1:5:10 ratio of hydrophilic polymers were selected for kinetic study.

In kinetic determination, data of the drug release study were used in order to investigate which mechanism could be possibly involved in drug release from the buccal patches. The parameters k and n can be obtained from the initial experimental data through a log transformation and by applying the least square regression method to the resulting linear curves. This gives log k and n as intercept and slope, respectively.
Table 3: Values of k and n (±95% confidence intervals) obtained by log plot of drug release curves from patches of different composition. r² values are also reported (n = 3, mean ± standard deviation)

<table>
<thead>
<tr>
<th>Formulation (D:E:HP)</th>
<th>N</th>
<th>K</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:5:10 SCMC</td>
<td>0.52±0.02</td>
<td>33.9±0.8</td>
<td>0.996</td>
</tr>
<tr>
<td>1:5:10 HPMC</td>
<td>0.55±0.01</td>
<td>30.4±0.3</td>
<td>0.999</td>
</tr>
<tr>
<td>1:5:10 Cp934p</td>
<td>0.54±0.06</td>
<td>32.7±0.6</td>
<td>0.997</td>
</tr>
</tbody>
</table>

The values of ‘k’ and ‘n’ obtained from the curves of the different patches of 1:5:10 ratios were reported in Table 3. The value of the diffusional exponent, n, depends on the geometry of the system. In the case of a cylinder, Fickian diffusion is defined by n=0.45 and Case II by n=0.89 [55]. These results showed that the formulations containing HPMC, SCMC and Cp934p, non-Fickian diffusion mechanism predominates (n > 0.45). In the case of an insoluble and non swellable polymer matrix, drug release has generally been expressed by a Fickian diffusion mechanism, i.e., the time dependence of the square root of time (n = 0.5). Therefore, the non-Fickian release behavior obtained here may suggest that release of propranolol hydrochloride was controlled by a combination of diffusion of propranolol hydrochloride from the matrix that the drug is released from the swollen polymeric network principally through a diffusion-controlled mechanism and three dimensional network structure which was produced by the complex formation i.e. swelling of the matrix following water penetration into the patches. Similar phenomena have been reported in the release behaviour of metronidazole from tablets consisting of Methocel K4M and Carbopol 934 [11].

CONCLUSIONS

In conclusion, the developed buccal adhesive patches of propranolol formulations showed excellent bioadhesive properties by using various polymer combinations. The incorporation of more than one polymer and the increase of the total polymer percentage into the patches resulted in increased bioadhesion. Propranolol dispersed Eudragit NE 30D polymer gave good sustained release, controlled swelling and higher mucoadhesion when combined with copolymer SCMC than Cp934p, HPMC present in the matrix at the above concentration. The non-Fickian release behaviour obtained for all the formulation, suggest that the release of propranolol hydrochloride is controlled by a combination of diffusion of propranolol hydrochloride in the matrix and swelling of the matrix followed by water penetration into the matrix. These results indicate that the patches are suitable for design of buccal mucoadhesive dosage form.

REFERENCES


