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Diltiazem-loaded buccoadhesive patches for oral mucosal delivery: Formulation and *in vitro* characterization

Sanju Manhar and Preeti K. Suresh*
Pt. Ravishankar Shukla University, Raipur (C.G.)- 492 010, India.

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ABSTRACT

The objective of the present study was to develop and evaluate bioadhesive buccal patches for mucosal delivery of diltiazem. The antihypertensive agent, diltiazem, undergoes first pass metabolism which compromises its bioavailability and the buccal route is a viable alternative to bypass this metabolism. In the present study, the buccal patches were fabricated with Eudragit L100 as the film forming polymer and hydroxypropyl methylcelluose, Carbopol 934 and sodium carboxymethylcellulose as the mucoadhesive polymer. The patches were characterized for various physicochemical attributes *viz.*, weight uniformity, surface pH, folding endurance, swelling profile, content uniformity, permeability study, *in vitro* drug release profile and stability study in saliva. The results indicate that the Carbopol 934 is suitable for fabricating buccoadhesive patches with requisite release and stability profile.

INTRODUCTION

The mucosal layer lining the oral cavity has been used as a site for attachment of bioadhesive systems for localized drug delivery for the treatment of conditions of oral cavity. The buccal mucosa is the epithelial lining the inside of the cheek, the gums and also the upper and lower lips. This site has been investigated as an alternative route for systemic drug delivery. There are many advantages associated with the use of the buccal mucosa as a site for the delivery of drugs into the systemic circulation. Primarily the blood flow from the buccal epithelium drains directly into the internal jugular vein, first-pass metabolism in the liver and intestine can be avoided. Additionally, it offers a relatively large surface area with high vascularity, low metabolic activity, accessibility, low variability and patient acceptability. Oral bioadhesive patches/films have been developed and reported for propranolol hydrochloride (Patel *et al*., 2007), nystatin (Aksungu *et al*., 2004), valdecoxib (Averineni *et al.*, 2009), triclosan (Dinge *et al.*, 2008), clotrimazole (Prodduturi *et al.*, 2007), metronidazole benzoate (El-Kamel *et al.*, 2007) and myoglobin (MHb) protein (Colonna *et al*., 2006). Diltiazem, a benzothiazepine is a calcium channel blocker used as a first line drug for management of hypertension. It is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina. They lower the blood pressure by decreasing peripheral resistance without compromising cardiac output. Diltiazem HCl also has vasodilation action due to its antagonism of the actions of the calcium ion in membrane functions. The drawbacks of diltiazem hydrochloride include its substantial hepatic first-pass effect, interaction with foods which cause reduction of bioavailability up to 30-40%, short half life of 3–4.5 hrs, protein-binding 70–80% and the need for a large dose (120 – 240 mg) to be administered once a day for 14 day chronic therapy which causes various side effects. The aim of the present study was to prepare bioadhesive buccal drug delivery system to enhance drug bioavailability with a minimum dose of 30-40mg. Drug delivery via buccal mucosa offers distinct advantages of this transmucosal route over peroral administration.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was a generous gift from Zeim Lab Pvt.Ltd. Eudradit L100 was kindly provided as a gift sample by Evonik Degussa India Pvt. Ltd. Hydroxypropyl methylcellulose, Carbopol 934 (CP 934) and Sodium carboxymethyl cellulose (CMC) were purchased from Loba Chemie Pvt. Ltd., Mumbai, India. Triethanolamine was obtained from Mark Pvt. Ltd. All reagents were of analytical grade and were used as received.

* *Corresponding Author;*
Preeti K. Suresh, Email: suresh.preeti@gmail.com

Methods

Buccal bioadhesive films were prepared by casting method. Accordingly, Eudragit L100 was dissolved (40%) in water and subsequently ethanol was added to achieve a ratio of water:ethanol of 1:5.

To this dispersion was added diltiazem hydrochloride and triethanolamine (plasticizer). An aqueous solution of the mucoadhesive polymer (2%) was added to the film-forming polymer mixture.

The mixtures were prepared with a magnetic stirrer without heating and cast onto a mercury containing petridish. The petridish was kept at 4°C for 24 hrs to remove all the air bubbles entrapped and air dried. Prepared film was cut into patches (2cm×1cm) having 1mm thickness and wrapped in aluminium foil and stored at room temperature (Perioli *et al*., 2004).

The composition of the various patches is presented in Table 1.

Characterization of Buccoadhesive Patch

Weight uniformity

The formulated patches were evaluated for their uniformity in weight. Ten patches were weighed individually and the average weight of patch was calculated from the collective weight. The weight variation of the individual weight from the average weight was calculated and presented in Table 2.

Thickness

Uniform thickness is vital for the patches composed of potent drugs. The thickness of the patches was measured at different positions (centre and four corners) with the screw-gauge micrometer. The measurement was done for three patches of each formulation and average values are given in Table 2.

***Surface* pH**

Weighed patches were placed in glass beaker and allowed to swell in contact with phosphate buffer pH 6.8 (15mL). Thereafter, surface pH measurements at predetermined intervals of 0.5, 1.0, 1.5, 2, 3, 4, 5 and 6 h were recorded (Table 3).

Folding endurance

The folding endurance of patches was determined by repeatedly folding 1 patch at the same place till it cracked (Table 2).

Swelling study

The buccal patches were weighed individually (W1) and placed separately in 2 % agar gel plates, incubated at 37 °C ± 1 °C, and examined for any physical changes. At regular 15 min time intervals until 1 hour, patches were removed from the gel plates and excess surface water was removed carefully using the filter paper.

The swollen patches were then reweighed (W2) and the swelling index (SI) were calculated using the following formula:

$$SI = (W2 - W1) / W1 \times 100$$

The results are reported in Table 2.

Content uniformity

Content uniformity test was performed to ensure uniform distribution of drug in the patch. The patch was placed in a 500 ml beaker and 200 ml of ethanol:phosphate buffer saline pH 6.8 (20:80) was added. The medium was stirred at 300 rpm with a teflon coated magnetic bead for 3 h over a magnetic stirrer at 37 °C. A 5 ml aliquot solution was withdrawn and analysed for the drug content by using UV spectrophotometer (Table 3).

Permeability study

The permeation study with the pure drug, solid dispersions and the physical mixtures were carried out using two different membranes viz. egg membrane and cellophane membrane by beaker method.

Specially designed diffusion tubes with an internal diameter of 2.25 cm having cellophane membrane at one end were used. The membrane was previously soaked in distilled water, alcohol, 0.3% sodium sulfide and 0.2% H_2S0_4 solution for 24 h. The patch was attached inside the tube with adhesive tape and tube was filled with 15 ml of ethanol: Phosphate buffer pH 6.8 (20:80). This assembly was immersed in a beaker containing 200 ml of Ethanol:Buffer (20:80; Phosphate buffer saline pH 6.8) and was placed over a thermostatically controlled magnetic stirrer set at 37±2 °C.

The contents in the beaker were stirred with the help of a teflon coated bead at 300 rpm. The release study was carried out for 6 h. The samples (5 ml) were withdrawn and filtered through 0.45 µ membrane filter at predetermined intervals of 1, 2, 3, 4, 5 and 6 h and replaced with equal volume of Ethanol: Buffer (20:80 Phosphate buffer saline pH 6.8) to maintain the sink conditions. The drug content was analyzed with the help of a UV spectrophotometer at 238 nm (Table 3).

Drug release study

The USP rotating paddle method was used to study the drug release profile from the buccal patches, 200 ml of phosphate buffer (pH 6.8) was used as the dissolution medium, at 37.0±0.5°C, and a rotation speed of 50 rpm was used. One side of patch was attached at the bottom of cylinder with the help of adhesive tape. Samples (5 ml) were withdrawn at 0.25, 0.5, 1, 2, 3, 4, 5, and 6 h intervals and replaced with equal volumes of fresh medium. The concentration of the drug in the medium was assayed spectrophotometerically (Figure 1).

Stability study in saliva

The stability study of patches was performed in natural human saliva. Human saliva was collected from volunteers. Patches were placed in separate petridishes containing 5 ml of human saliva and placed in a temperature-controlled oven at 37 °C ± 0.2 °C for 6 h.

At regular time intervals (0, 0.5, 1, 2, 3, 4, 5 and 6 hours), patches were examined for changes in colour, shape and integrity. The experiments were performed in triplicate, and average values were reported (Table 4).

Table. 1: Composition and appearance of Diltiazem HCl loaded buccal bioadhesive patch.

Patch	Film-forming polymer (FFP)	Mucoadhesive Polymer (MP)	FFP:MP ratio (w/w)	Patch Appearance	
				Color	Surface
S1	Eudragit L100	Carbopol 934	5:3	Pale yellow	Smooth
S2	Eudragit L100	Carbopol 934	7:1	Dull white	Smooth
S3	Eudragit L100	Carbopol 934	3:1	Bright white	Smooth
S4	Eudragit L100	Sodium CMC	5:3	Pale yellow	Smooth
S5	Eudragit L100	Sodium CMC	7:1	Bright white	smooth
S6	Eudragit L100	Sodium CMC	3:1	Light pale yellow	Smooth
S7	Eudragit L100	HPMC	5:3	Pale yellow	Rough
S8	Eudragit L100	HPMC	7:1	Dull white	Rough
S9	Eudragit L100	HPMC	3:1	Dull white	Rough

Patch size - 2 cm ×1 cm, volume of mixture solution – 16ml, plasticizer 0.65 ml for Carbopol 934 and 0.55 ml for Sodium CMC and HPMC.

Table. 2: Important physicochemical parameters of patches containing diltiazem hydrochloride.

Patch	Weight of patches (in gm)*	Thickness (in mm) #	Folding Endurance #	Swelling (%) #
S1	0.177 ± 0.0055	0.91± 0.0011	>20	104.46 ± 0.1190
S2	0.156 ± 0.0013	0.86±0.0023	>20	102.28 ± 0.1003
S3	0.168 ± 0.0014	0.94±0.0102	>20	148.20 ± 0.0213
S4	0.134 ± 0.0059	0.83±0.0043	>20	177.03 ± 0.9923
S5	0.139 ± 0.0011	0.80±0.0101	>20	98.24 ± 0.9823
S6	0.133 ± 0.0045	0.87±0.0032	>20	111.86 ± 0.5310
S7	0.135 ± 0.0041	0.85±0.0041	>20	86.45 ± 0.2313
S8	0.146 ± 0.0068	0.78±0.0004	>20	68.44 ± 0.2098
S9	0.149 ± 0.0024	0.89±0.0021	>20	74.10 ± 0.2314

The values represent mean ± SD (* n = 10; # n = 3).

Table. 3: Content uniformity, permeability study, surface pH of the developed formulations.

Patch	Content Uniformity (%)	Permeability (%)	Surface pH
S1	99.36	79.95 ±0.0021	6.75
S2	98.68	74.13 ±0.2301	6.81
S3	99.72	81.11 ±0.1025	6.76
S4	99.77	79.45 ±0.0210	7.23
S5	96.79	74.23 ±0.0325	6.90
S6	98.99	87.23 ±0.0210	5.88
S7	99.98	80.56 ±0.0321	7.11
S8	97.26	76.53 ±0.0862	7.02
S9	98.45	89.21 ±0.5087	6.98

Table. 4: Stability studies of various buccoadhesive patches.

Patch	Time (h)							Stability
	0.5	1	2	3	4	5	6	
S1	No change in color, shape, size	Starts to swell	Increase in size	Increase in size	Increase in size	Increase in size	Size increased up to ¾ times, no fragmentation	S2<S1<S3
S2	No change in color, shape, size	Starts to swell	Increase in size	Increase in size	Increase in size.	Increase in size	Increase in size ¾ times. No fragmentation; light yellow color	S2 < S1 S2 < S3
S3	No change in color, shape, size	Starts to swell	Increase in size	Increase in size	Increase in size	Increase in size	Increase in size more than ¾ times; no fragmentation	S3 > S1 S3 > S2
S4	After 15 min starts to swell & fragment	Fragments dispersed in saliva	Particles dispersed in saliva	particles of patch dispersed in saliva	Fragmented particles disappeared	-	-	S5<S4< S6
S5	Stable for 15 min Particles start to swell, fragment	Fragments dispersed in saliva	Particles dispersed in saliva	Particles disappear	-	-	-	S5 < S4 S5 < S6
S6	Stable for 15 min Particles swell, fragment	Fragments dispersed in saliva	Fragmented particles dispersed in saliva	Fragments disappear	-	-	-	S6 > S4 S6 > S5
S7	Rough surface, swell, fragmented within 15-30 min	Fragments dispersed in saliva	Fragmented particles dispersed in saliva	Fragments disappear	-	-	-	Poor stability
S8	Rough surface, swell, fragmented within 15-30 min	Fragments dispersed in saliva	Fragmented particles dispersed in saliva	Fragments disappear	-	-	-	Poor stability
S9	Rough surface, swell, easy fragmentation within 15-30 min	Fragments dispersed in saliva	Fragmented particles dispersed in saliva	Fragments disappear	-	-	-	Poor stability

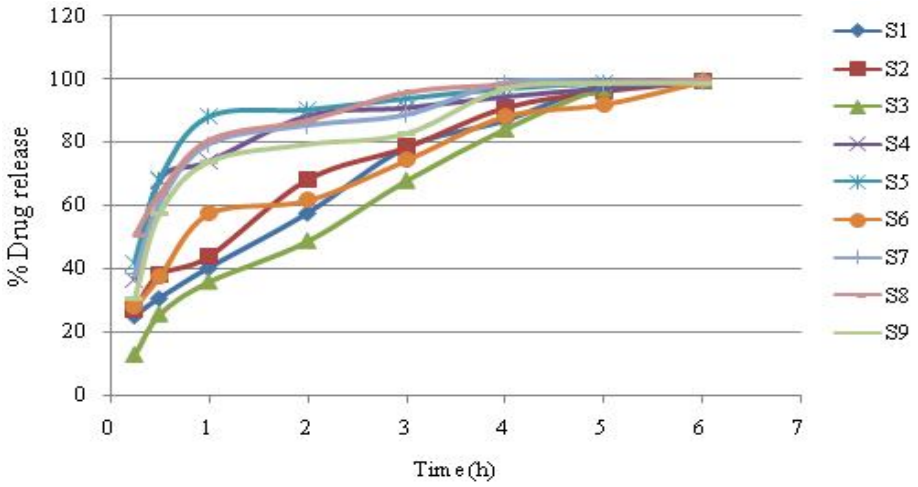

Fig. 1: Release profile of diltiazem hydrochloride in phosphate buffer pH 6.8.

RESULTS AND DISCUSSION

Weight uniformity, thickness, folding endurance study

The patches devoid of plasticizer were brittle. Films cast from alcoholic solution were transparent but on incorporation of drug in the cast film solution, it displayed a whitish to pale yellow color. Patches containing drug and Eudragit L 100 had good physical appearance, perhaps owing to the film-forming property of Eudragit. Patches prepared with CP 934 and sodium CMC had a smooth surface but HPMC containing patches had rough surface. Assessment of weight uniformity was done with randomly selected 10 patches from each batch and was found to be within limits. The thickness of patches was measured at five randomly selected spots. The means and standard deviations were calculated and were observed to be within acceptable range. Patches displayed good folding endurance and showed no visible cracks (Table 2).

Swelling Study

Patches containing hydrophilic polymers CP 934 and Eudragit L100 showed considerable swelling. The swelling index was found to be proportional to the CP 934 content and inversely proportional to the Eudragit L100 content. Examination of patches during the dissolution studies revealed that patches showed considerable swelling and gel formation, especially in the patches with higher concentration of hydrophilic polymer CP 934. Addition of a certain amount of the hydrophilic polymers increased surface wettability and, consequently, water penetration within the matrix. Patches did not show any appreciable changes in their shape and form during the 15 min when patches were kept on a 2 % agar gel plate but HPMC and sodium CMC displayed better hydration capacity and absorbed water up to 96-98 % leading to irregular shape after 15 min. The swelling index varied from 68.44 - 177.03 % (Table 2). Thus, it is apparent that the concentration of CP 934 and Eudragit L100 affected the swelling index of the Eudragit patches. Moreover, the concentration of CP 934 had a negative effect on percent swelling index; that is, as the concentration of CP 934 increased the percent swelling index decreased.

Surface pH

Surface pH of the oral mucosal dosage forms is an important aspect for characterisation since an acidic or alkaline pH may cause irritation to the oral mucosa. It was therefore necessary to determine if any extreme surface pH changes occurred in the patch during the drug release period. The surface pH of the patches remained fairly constant at approximately 6.7–7.0 over the 6 h test period, confirming that the surface pH of the patches was with in the neutral conditions of the saliva (pH 5.8–7.1) and that no extreme changes in pH occurred throughout the test period. These results suggested that the polymeric blend identified was suitable for oral application owing to the acceptable pH measurements shown in Table 3.

Content uniformity and permeability study

Content uniformity and permeability study was performed in Ethanol: Phosphate buffer pH 6.8 (20:80). All the formulations exhibited fairly uniform drug content ranging from 96.79 - 99.98 %. Since the formulation procedures involved few processing steps, no major drug loss was observed during the preparation of the patches. The optimized formulation displayed cumulative percentage permeability rates in the range of 74.13 to 89.21 through the cellophane membrane. The CP forms a viscous hydrogel after swelling and this can be attributed to the formulation with CP 934 showing less permeability than HPMC and sodium CMC initially, but subsequently after 5, 6 h it was more permeable.

Drug release study

Drug release was controlled by the dissolution kinetics of Eudragit L100 and was affected by their higher molecular weight

and hydrophobic character. The release profile of diltiazem hydrochloride patches is illustrated in Figure 1. The cumulative percent drug release from the formulations was found to be > 98 %. From the release profile it is clearly evident that the drug release increased as the concentration of HPMC polymer increased.

This can be attributed to the hydrophilic nature of the HPMC, whereby it absorbs water quickly and helps in faster diffusion of drug from the system but Eudragit L100 film forming polymer retarded drug release in increasing concentration. Patch S9 was found to be better than S7 and S8 due to higher concentration of Eudragit L100 polymer. Similar result was obtained with sodium CMC patch. The main drawback of sodium CMC-HPMC patch was that their rapid water uptake caused fast drug release in the initial 2 – 4 h and their fragmentation. As a virtue of their hydrophilicity, CP 934 patches absorbed water, thereby promoting the dissolution, and hence the release, of the drug.

Further, the hydrophilic polymers would leach out and, create more pores and channels for the drug to diffuse out of the patches. CP 934 controlled the drug release in increasing concentration. This could be attributed to the extensive swelling of the polymers, which created a thick gel barrier, permitting drug diffusion in controlled manner. The study revealed that S3 patch was superior than the other formulations.

Stability study in human saliva

The stability studies of the patch were conducted in the saliva and the results are presented in Table 4. The stability of the patches with CP 934 was found to be far superior to the patches with sodium CMC and HPMC as the mucoadhesive polymer. The patches with CP exhibited stability in the order S2<S1<S3 and showed no signs of fragmentation for up to 6 h. The patch fabricated with sodium CMC displayed stability in the order S5<S4<S6. The patches comprising of HPMC had poor stability as compared to the other formulations. s

SUMMARY AND CONCLUSION

The mucoadhesive drug delivery systems used in the present study utilize the property of bioadhesion of certain water-soluble polymers that become adhesive on hydration and hence are useful for targeting the drug to a particular region of the body for extended periods of time.

In the present study, the polymers employed for buccal bioadhesive system were Eudragit L100 (film forming polymer) and sodium CMC, HPMC, CP 934 (mucoadhesive polymer) which help to adhere to buccal mucosa. Buccal bioadhesive films were prepared by casting method with Eudragit L100 and by using either sodium CMC, HPMC or CP 934 mucoadhesive polymer in 5:3, 7:1, 9:3 ratio using triethanolamine as plasticizer. The patches were characterized for various parameters like weight variation, thickness, surface pH, folding endurance, swelling study, content uniformity, permeability study, drug release profile and stability in saliva. The cumulative percent drug release from the formulations was high at > 98 %. The results indicate that the Carbopol 934 is suitable for fabricating buccoadhesive patches with requisite release and stability profile. Further in vivo studies may be required to extrapolate the in vitro data to the biological milieu.

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