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Controlled release from bisoprolol fumarate buccal patches

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ABSTRACT

The aim of the present work is to investigate the formulation of Bisoprolol Fumarate buccal patches for controlled release medication in order to treat blood pressure and cardiac diseases. The half life of Bisoprolol Fumarate is 10 hrs and Bisoprolol fumarate is acid labile, in order to treat the angina pectoris which required 24hr controlled drug release and to avoid degradation of drug in GIT, the buccal patches were prepared. The patches were prepared by solvent casting method using hydroxyl propyl methyl cellulose (HPMC K15) and Carbopol 974. The patches were found to be smooth in appearance, uniform in thickness, weight uniformity, drug content, swelling index, folding endurance, surface pH and in vitro diffusion study using Keshery chien diffusion cell. The optimized patch of 1% HPMC K15 exhibit in vitro release of 80% through cellophane membrane and in vivo release 73.4% through egg membrane and the optimized patch of 1% Carbopol 974 exhibit in vitro release of 75.2% through cellophane membrane and in vivo release 71.1% through egg membrane in 8 hrs showing good mucoadhesive strength and mucoadhesive time.

Key words: Bisoprolol fumarate, Buccal patch, HPMC K15, Carbopol 974.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route [1]. Buccal delivery offers a safer mode of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity [2-5]. 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 [5-7]. Bisoprolol Fumarate is a classical example of β- adrenergic blocking agent and is approved by FDA for the treatment of cardiac disease. The half life of Bisoprolol Fumarate is 10 hrs and Bisoprolol Fumarate is acid labile in order to treat the angina pectoris which required 24hr controlled drug release and to avoid degradation of drug in GIT the buccal patches were prepared [8]. Drugs administered by buccal route offers several advantages such as rapid absorption through oral mucosa and high blood level due to high vascularisation of the region; thereby avoiding first pass effect [9-20].

MATERIALS AND METHODS

Materials

Bisoprolol fumarate was obtained as gift sample form Unichem laboratories Ltd. Raigad, HPMC K15 and Carbopol 974 was procured from Oxford chemical, Mumbai. All other reagents and materials were of analytical or pharmacopoeial grade.

Preparation of Bisoprolol fumarate buccal patch

The buccal patches were prepared by solvent casting method. HPMC K15 and Carbopol 974 polymers in ratio of 0.5 to 1.5 % were incorporated in different buccal patches. The concentration of plasticizer was finalized differently for the two polymers from the plasticity of the film. It is varied from 10% to 20% for the patch. The composition of different formulation is shown in Table no.1.

The component of each formulation were mixed and poured in the mould and dried in oven then removed from the mould and cut in to pieces of 1 × 1 cm and finally packed in aluminium foil.

Evaluation

Folding Endurance

Folding endurance was determined by repeatedly folding at the same place until it broke. The number of times the film folded at the same place without breaking was the folding endurance value.

Patch thickness

Patch thickness measured at five different randomly selected spots using screw gauge.

Content uniformity

The buccal Patch dissolved in phosphate buffer pH 6.8. The n solution is diluted and filtered through whattman filter paper, and analyzed at 271 nm using a UV Double beam spectrophotometer.

Surface pH study

The Patch was allowed to swell by keeping it in contact with 2% agar gel plate for 2 hrs at room temperature. The pH was measured by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 min.

Swelling study

Buccal patches were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37 ± 1°C. At regular intervals (1, 2, 3, 4, 5& 6 hours) the patches were removed from Petri dishes and excess water removed carefully using filter paper. The swollen patch was then reweighed (W2) and the swelling index (SI) were calculated using the formula given in equation. $SI = [(W2-W1) \div W1] \times 100$ Where, W1 = initial weight of the patch W2 = final weight of the patch.

In Vitro Drug Release

The in vitro drug permeation study was carried out using Keshery chien diffusion glass cell. The upper and lower compartment was filled with saline phosphate buffer solution. Cellophane membrane was kept in between two compartment and whole assembly kept at 37 ± 0.2°C. The amount of drug permeated was determined by removing an aliquot of 1ml sample at appropriate time interval and stirred at 50 rpm on magnetic stirrer.

Table 1: Composition of mucoadhesive buccal patch

Ingredients	Formulation code					
	B1	B2	B3	B4	B5	B6
Bisoprolol Fumarate (mg)	10	10	10	10	10	10
HPMC K15 (%)	0.5	1	1.5	----	----	----
Carbopol 974 (%)	----	----	----	0.5	1	1.5
Propylene glycol (%)	20	20	20	10	10	10

Table 2: Characteristics of mucoadhesive buccal patches

Code	Patch thickness (mm)	Surface pH	Folding endurance	Swelling index	% drug content	% drug release after 8 hrs
B1	0.6±0.1	6.16	224	25±0.45	95.9	76.1%
B2	0.8±0.1	6.73	275	27±0.3	97.4	80%
B3	0.9±0.1	7.2	255	31±0.3	96.7	71.2%
B4	0.7±0.3	6.23	260	34±0.5	94.9	73.1%
B5	0.8±0.2	6.4	255	41±0.6	96.3	75.2%
B6	1.1±0.2	6.7	283	37±0.7	95.4	68.9%

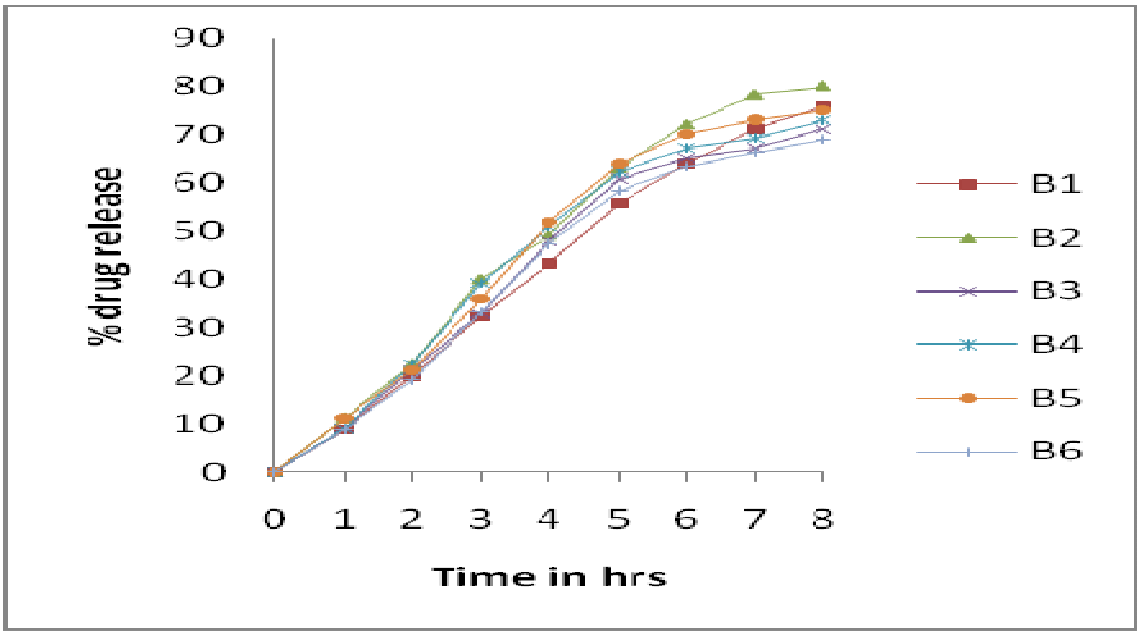

Fig.1: Graph of the % drug release v/s Time (hr)

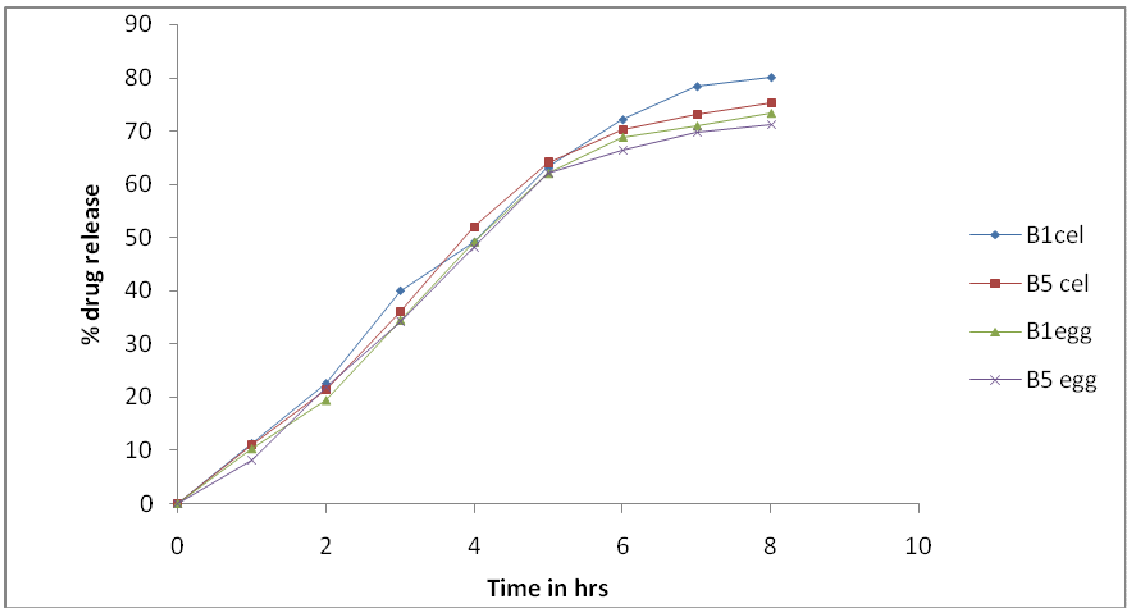

Fig.2: Diffusion study through egg membrane

RESULTS AND DISCUSSION

In the present study six formulations with variable concentration of polymers and optimized concentration of plasticizer were prepared and evaluated for physicochemical parameter and in vitro diffusion studies. All formulations gave the satisfactory results in terms of thickness, drug content, swelling index, folding endurance and surface pH as shown in table 2. Appropriate swelling behavior of a buccal adhesive system is essential for uniform and prolonged release of the drug and effective mucoadhesion.

Melting point of Bisoprolol Fumarate was found to be in the range100-101ºC, which complied with IP standards, indicating purity of the drug sample.

In-vitro release studies

From the figure 1 it depicts that % drug release from B1 was about 76.1% and drug release from B3 was 71.2% but Formulation B2 shows 80% in 8hrs. Also % drug release from B4 was 73.1% and drug release from B6 was 68.9%

but Formulation B5 shows 75.2% in 8 hrs. After the final optimization of formulation two best formulation of different polymer B2 and B5 were selected as optimized batch. The formulation batch of HPMC K15 (B2) showed higher % drug release as compared to batch of Carbopol 974 (B5). (shown in fig 1).

Swelling study

All the formulations were hydrated generally by keeping the patches in contact with 2% agar gel plate for 1-6 hr. The highest hydration (swelling) i.e. 41±0.6% was observed with the formulation B5. This may be due to quick hydration of polymers.

In-vivo Permeation Studies

The optimized formulations of 1% HPMC K15 and Carbopol 974 were taken for in-vivo (egg membrane) permeation studies. Formulation containing HPMC K15 showed the drug permeation of 73.4 % through egg membrane and formulation containing Carbopol 974 showed the drug permeation of 71.1% through egg membrane in 8 hours (shown in fig 2).

CONCLUSION

Buccal patches of Bisoprolol Fumarate using polymers like HPMC K15 and CP 974 in various proportions and combinations showed satisfactory Physico-mechanical and mucoadhesive characteristics.

The proportional amounts of various hydrophilic polymers in various formulations have influence on drug release from these formulated Bisoprolol Fumarate buccal patches.

From the present investigation, it can be concluded that such buccal patches of Bisoprolol Fumarate may provide sustained buccal delivery for prolonged periods in the management of hypertension, which can be a good way to bypass the extensive hepatic first-pass metabolism.

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