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Research article

FORMULATION AND EVALUATION OF BUCCOADHESIVE BI-LAYER TABLET OF PROPRANOLOL HYDROCHLORIDE

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ABSTRACT

The purpose of the study was to formulate and evaluate mucoadhesive bi-layer buccal tablets of propranolol hydrochloride tablets using the bioadhesive polymers such as sodium alginate and carbopol 971 P along with ethyl cellulose as an impermeable backing layer. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling index, *in vitro* drug release. Tablets containing sodium alginate and carbopol 971 P in the ratio of 5:1 showed the maximum percentage of *in vitro* drug release without disintegration in 12 hours. The swelling index was proportional to sodium alginate content and inversely proportional to carbopol 971 P content. The surface pH of all tablets was found to be satisfactory, close to neutral pH; hence, no irritation would observe with these tablets. The mechanism of drug release was found to be zero-order kinetics.

Keywords : Mucoadhesion bi-layer tablet, Buccal drug delivery, Propranolol hydrochloride.

INTRODUCTION

Buccal delivery of drug provides an alternative to the oral route of drug administration. In recent years, delivery of therapeutic agents through various trans-mucosal routes gained significant attention owing to their pre-systemic metabolism or instability in the acidic environment associated with oral administration[1]. Buccal delivery provides direct entry of drug into the systemic circulation, thus avoiding the hepatic first-pass effect, ensuring ease of administration, and making it possible to terminate delivery when required[2]. Attempts have been made to formulate various buccal mucoadhesive dosage forms, including tablets[3], films[4], patches[5], disks[6] and gels[7]. 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 and should release the drug in a unidirectional way toward the mucosa, in a controlled and predictable manner, to elicit the required therapeutic response. This unidirectional drug release can be achieved using bi-

layer tablet dosage form[6,8]. Propranolol hydrochloride, a nonselective beta-adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. Propranolol hydrochloride is subjected to an extensive and highly variable hepatic first pass metabolism following oral administration, with a reported systemic bioavailability of between 15% and 23%.[9, 10]. The physicochemical properties of propranolol hydrochloride, its half-life of 3 to 5 hours, and its low molecular weight of 295.81 make it a suitable candidate for administration by the buccal route[11].

MATERIALS AND METHODS

Propranolol hydrochloride, carbopol 971 P (CP), and ethyl cellulose (EC) were obtained as a gift samples from Glenmark pharmaceuticals Ltd, Nashik, Sodium-alginate (300-400 cps) (Na-Alginate), polyethylene glycol 6000 (PEG 6000), polyvinyl pyrrolidone K-30 (PVP), and Perlitol (Spray dried mannitol) were purchased from local vendor. All other reagents and chemicals used were of analytical grade.

EXPERIMENTAL

Preparation of buccal tablets

Bi-layer buccal tablets were prepared by a direct compression method using two steps. Various batches were prepared by varying the ratio of CP and Na-alginate to identify the most effective formulation. The mucoadhesive drug/ polymer mixture was prepared by homogeneously mixing the drug with CP, Na-alginate, PVP, Perlitol, and PEG 6000 in a polybag for 15 minutes as shown in Table 1. The mixture 100 mg was then compressed using a 12 mm diameter die in a single stroke multistation tablet machine (Rimek Minipress I, Ahmedabad, India). The upper punch was raised and the backing layer of EC was placed on the above compact; the two layers were then compressed into a mucoadhesive bi-layer tablet. Each tablet weighed 150 mg with a thickness of 1.5 to 1.6 mm.

Table 1 : Formulation of buccoadhesive tablets.

Sr. no.	Ingredients (mg/tab)	F1	F2	F3	F4	F5
	Adhesive layer					
1	Propranolol hydrochloride	20	20	20	20	20
2	Sodium alginate	34.3	33.4	32	30	26.7
3	Carbopol 971P	5.7	6.6	8	10	13.3
4	PVP K30	30	30	30	30	30
5	Perlitol	8	8	8	8	8
6	PEG 6000	2	2	2	2	2
	Backing layer					
7	Ethyl cellulose	50	50	50	50	50
	Total	**150**	**150**	**150**	**150**	**150**

Content uniformity

Drug content uniformity was determined by dissolving the tablets in ethyl alcohol and filtering with whattman filter paper (0.45 µm). The filtrate was evaporated and the drug residue dissolved in 100 ml phosphate buffer pH 6.8. The 5 ml solution was then diluted with phosphate buffer pH 6.8 up to 20 ml, filtered through whattman filter paper, and analyzed at 290 nm using a UV Double beam spectrophotometer (Shimadzu 2501 PC, Japan.)[11]. The experiments were performed in triplicate, and average values reported.

***In-vitro* mucoadhesion time**

Adhesion time of formulations were determined by using rotating cylinder method USP type VI apparatus (Disso Lab India, India) at 37 ± 0.5^0 C at 100 rpm using phosphate buffer pH 6.8.[6, 12]. The goat buccal mucosa was adhered to the cylinder by using cynoacrylate glue. The disk was pressed on the mucosa gently with the finger for 1 minute. The time of disk adhered to mucosa was measured and results are given in Table 2.

Table 2: *Ex-vivo* mucoadhesion time of formulation

Formulation	Adhesion time Hours ± SD
F1	7 ± 0..98
F2	9 ± 0.76
F3	11 ± 1.34
F4	10 ± 1.98
F5	8 ± 0.98

Table 3 : Evaluation of tablet parameter

Formulation	% weight variation	Thickness (mm)	Hardness (kg/cm^2)	% Friability	%Drug content
F1	0.82±0.15	1.6±0.98	4.32±0.16	0.65±0.05	100.6±0.3
F2	0.72±0.21	1.5±0.34	4.23±0.34	0.65±0.09	98.45±0.5
F3	0.86±0.17	1.6±0.75	4.00±0.35	0.74±0.03	99.4±0.4
F4	0.63±0.12	1.7±0.56	4.23±0.46	0.75±0.06	97.56±0.5
F5	0.84±0.12	1.5±0.86	3.98±0.32	0.76±0.04	100.5±0.8

Swelling study

Buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37 ± 0.1^0 C. The tablet was removed from the petri dish and excess surface water was removed carefully using filter paper. The swollen tablet was then reweighed (W2), and the swelling index (SI) or percent hydration was calculated using the following formula[6] and given in Fig. 2

% of hydration = (W2-W1) X 100 / W2

Where,

W1- initial weight of tablet

W2- weight of disks at time t

Surface pH study

The surface pH of the buccal tablets was determined.

***In-vitro* drug release**

USP type II rotating paddle method was used to study the drug release from the bi-layer tablet. The dissolution medium consisted of 600 ml of phosphate buffer pH 6.8. The release study was performed at 37 ± 0.5^0 C, with a rotation speed of 50 rpm. The backing layer of the buccal tablet was attached to the glass slide with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. 5 ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.2-µm Whatman filter paper and analyzed after appropriate dilution by UV Double beam spectrophotometer at 290 nm[11]. The results are shown in Fig. 1.

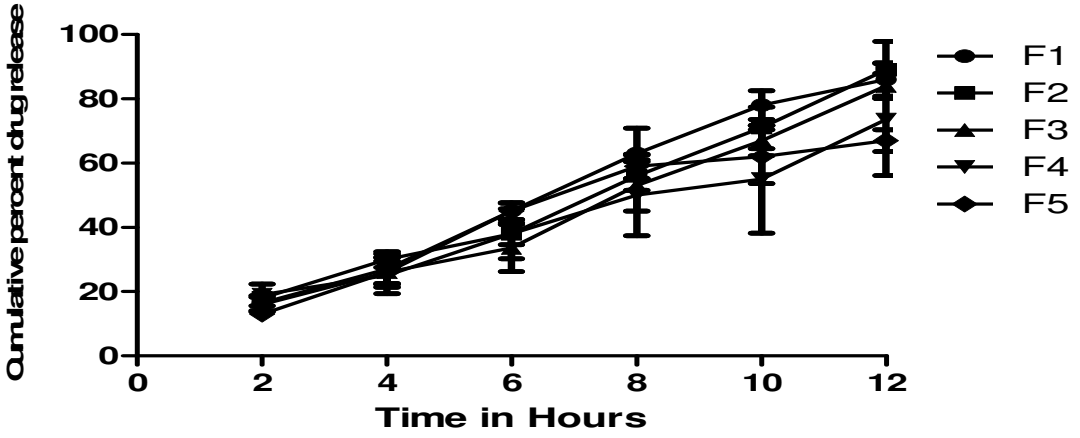

Fig. 1 : *In-vitro* drug release study

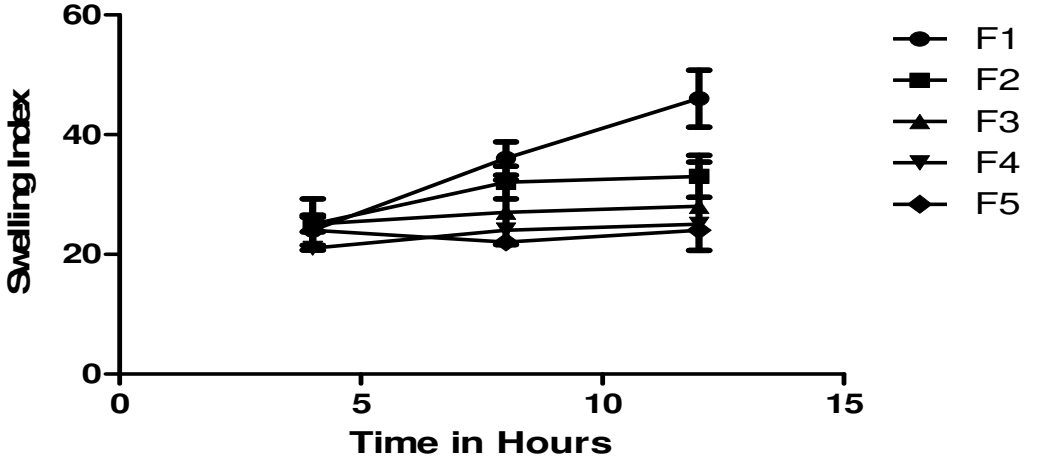

Fig. 2: Swelling index study

RESULT AND DISCUSSION

CP and Na-alginate were selected as the bioadhesive polymers because of their excellent bioadhesive properties.[6,16-18] EC has recently been reported to be an excellent backing material, given its low water permeability, hydrophobicity, and moderate flexibility[19], so it was chosen as an impermeable backing layer. Perlitol and PVP-K30 were used to improve the release of drug from polymer matrices, and the concentration was optimized during the preliminary trial to find the best formulation of bi-layer buccal tablets as shown in Table 1. Tablets were found to be satisfactory when evaluated for weight variation (0.78 ± 0.15%), thickness (1.5 ± 0.18 mm) hardness (4.005 ± 0.41 kg/cm^2), friability (0.72 ± 0.04%),and drug content (99.79 ± 0.62%). The surface pH of all the tablets was within a range of 5-6 as shown in the Table 3, close to neutral pH. Appropriate swelling behavior of a buccal adhesive system is essential for uniform and prolonged release of the drug and effective mucoadhesion.[20] The swelling study indicated that the rate of swelling was proportional to the Na-alginate content and inversely proportional to the CP content of the tablets in the initial study up to 1 hour. This finding may have been because of the fast swelling property of Na-alginate compared with CP. The maximum swelling index was found in batch F1 (48±1.23), containing a higher proportion of Na-alginate, and the lowest in F5 (22±0.23). Tablets did not show any appreciable change in their shape and form during the 8 hours they were kept on the 2% agar gel plate. This finding is owing to the hydrophilic nature of Na-alginate; it is hydrated easily with less contact time and forms a strong gel that entangles tightly with the mucin molecules. Tablets containing Na-alginate and CP in the ratio of 5:1 (F2) had the maximum percentage of *in vitro* drug release without disintegration in 12 hours.

CONCLUSION

The mucoadhesive buccal tablets of propranolol hydrochloride can help to bypass extensive hepatic first-pass metabolism and hence improve bioavailability. The buccal bi-layer tablets showed a mucoadhesion time of more than 12 hours.

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