RESEARCH PAPER

Accepted 30 June 2003
Revised 1 April 2004
Received 20 February 2003
Indian J. Pharm. Sci., 2004, 66(4): 438-443

Development and Evaluation of Novel Buccal Adhesive Core-in-Cup Tablets of Propranolol Hydrochloride

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The mechanism of absorption of propranolol hydrochloride through porcine buccal mucosa was evaluated. A special punch was designed and fabricated to prepare the novel buccal adhesive core-in-cup tablet. The tablets were evaluated for weight uniformity, friability, hardness, swelling, mucoadhesion strength, *in vitro* drug release, stability and *in vivo* acceptability. Swelling increases with increase in the concentration of HPMC K4M in tablets. The mucoadhesive strength of the tablets varied when different biological membranes used for the studies. Maximum mucoadhesive strength was observed for tablets containing carbopol 934 P and HPMC K4M at the ratio of 1:1 followed by 1:2, 0:1 and 1:0. Mechanism and order drug release from the tablets was by non-Fickian diffusion and first order kinetics, respectively. Propranolol hydrochloride was stable in buffer solutions having pH 6.0-7.0, normal human saliva and at accelerated temperature. *In vivo* studies indicated that tablet was comfortable in the oral cavity, not heavy, did not dislodge from the site of attachment and not caused any side effects.

Propranolol hydrochloride (PHCL) is a nonselective β-adrenergic blocking agent[1]. It inhibits response to adrenergic stimuli by competitively blocking β-adrenergic receptors within the myocardium and within the bronchial and vascular smooth muscle[2]. It has been widely used in the treatment of hypertension and many other cardiovascular disorders[3]. PHCL is subject to an extensive and highly variable hepatic first-pass metabolism following oral administration, with reported systemic bioavailability of between 15 and 23 %. As its biological half-life is about 3 h and is eliminated rapidly, repeated daily administrations are needed to maintain effective plasma levels that makes it suitable candidate to be delivered through buccal route at controlled rate[4]. Administration of drugs through buccal route bypasses the first-pass metabolism and there by increases the bioavailability.

Successful buccal drug delivery using buccal adhesive systems requires at least three of the following (a) a bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa (b) a vehicle that releases the drug at an appropriate rate under the conditions prevailing in the mouth and (c) strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery systems promote the residence time and act as controlled release dosage forms[5]. Buccal adhesive tablets consist of three layers, the core layer, the peripheral layer, and backing layer and prepared by direct compression method. The tablets prepared by this method have certain drawbacks like more number of compressions, non-uniformity in peripheral layer thickness and multidirectional release of drug in the oral cavity[6]. In order to avoid these drawbacks, it has become necessary to develop a novel tablet for the delivery of drugs through the buccal route. In our earlier publication[6], we have described the design of a special punch for the preparation of novel buccal adhesive tablets.

The goal of this investigation was to develop and characterize a novel buccal adhesive controlled release tablet for PHCL. The buccal route was chosen because of its good accessibility, robustness of the epithelium, facile removal of

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the dosage form, relatively low enzymatic activity, natural clearance mechanisms for elimination of the drug from buccal area, satisfactory patient compliance and elimination of the hepatic first pass metabolism.

MATERIALS AND METHODS

Propranolol hydrochloride was received as a gift sample from Sigma laboratories, Mumbai, Carbopol 934 P and HPMC K 4M were also received as a gift samples from BPRL, Bangalore. All other chemicals were of either reagent or analytical grade and were used as received.

In vitro permeation studies:

Porcine buccal mucosa, obtained from a local slaughterhouse, was used within 3 h of slaughter. The tissue was stored in Krebs buffer at 4° upon collection. The epithelium was separated from underlying connective tissues with surgical scissors and clamped between the donor and receiver chambers of the Franz type diffusion cell. The temperature was maintained at 37±2° by jacket surrounding the receiver chamber that was stirred with magnetic bead. After the buccal membranes were equilibrated with Krebs buffer in both chambers, the receiver chamber was filled with fresh Krebs buffer (pH 6.6) and the donor chamber was charged with PHCL, 4.5 mg/ml. The samples (n=3) were collected at every 1 h for 6 h and analyzed by UV spectroscopic method at 290 nm for PHCL content.

Preparation of novel buccal adhesive core-in-cup tablets:

Novel buccal adhesive core-in-cup tablets were prepared by direct compression method. A special punch was designed and fabricated to prepare novel buccal adhesive core-in-cup tablets. The newly designed upper 11 mm punch has protrusion and lower punch (11 mm) remains flat faced as shown in our earlier publication[6]. Buccal adhesive cups and core layer (fast release and sustained release layers) were prepared by using special punch (11 mm) and flat-faced 7 mm punch, respectively. All the ingredients were passed through ASTM sieve # 100 and blended in a mortar. The blended buccal adhesive polymer mixture was compressed on a Cadmach single station punching machine using an 11 mm specially designed and fabricated punch to obtain buccal adhesive cups. The core layer (consisting of fast release and sustain release layers) was separately compressed on a Cadmach single station punching machine using 7 mm flat-faced punches and dies. Buccal adhesive cups were placed in an 11 mm die cavity and core layers were inserted inside the cups and compressed with 11 mm flat faced punch. The composition of novel core-in-cup tablet is presented Table 1.

Swelling index:

Novel buccal adhesive core-in-cup tablets were weighed individually (designated as W_1) and placed separately in petridishes containing 4 ml of phosphate buffer pH 6.6. At regular intervals (0.5, 1, 2, 3, 4, 5 and 6 h), the tablets were removed from the petridishes and excess water was removed carefully by using filter paper. The swollen tablets were reweighed (W_2); the swelling index of each system was calculated using the following formula, swelling index=W_2-W_1/ W_1.

Determination of *In vitro* mucoadhesion strength:

The mucoadhesive strength of buccal adhesive core-in-cup tablets was measured using a modified two-arm balance. The porcine buccal mucosa and rabbit buccal mucosa were used as biological membranes for the studies. The porcine buccal mucosa and rabbit mucosa were obtained from the local slaughterhouse and stored in Krebs buffer at 4° from the time of collection and studies were carried out within 3 h of the procurement. The weight required to detach the tablet from the model substrate was measured using a modified two-arm balance.

In vitro drug release studies:

In vitro drug release studies were performed separately for fast release layer, sustained release layer and buccal adhesive core-in-cup tablets using a modified dissolution apparatus. The modified dissolution apparatus consists of 250 ml beaker as a receptor compartment and glass rod attached with a grounded glass disk of 2 cm diameter as a donor tube. The back layer of the buccal adhesive core-in-cup tablet or sustained release layer was attached to the glass disk with instant adhesive (superwiz). The donor tube was dipped into receptor compartment containing 150 ml of phosphate buffer pH 6.6 as a dissolution medium that was maintained at 37±2° and stirred at a constant speed using a magnetic bead. Aliquots (5 ml each) were withdrawn at preset times (0.08, 0.16, 1, 2, 3, 4, 5 and 6 h) and the same volume of phosphate buffer pH 6.6 pre warmed at 37±2° was replaced to maintain the sink condition. The drug content was estimated using an UV spectrophotometer at 290 nm.

Stability studies in buffer solutions:

Stability of PHCL was evaluated in phosphate buffer solutions pH 6.0, 6.6 and 7.0. PHCL (900 μg/ml) solutions were prepared using these buffer solutions and incubated

TABLE 1: COMPOSITION OF BUCCAL ADHESIVE CORE-IN-CUP TABLETS

Ingredients	Formulations							
	A	B	C	D	E	F	G	H
Fast release layer (mg)								
Propranolol Hcl	2	2	2	2	4	4	4	4
D-mannitol	30	30	30	30	30	30	30	30
Lactose	18	18	18	18	16	16	16	16
Sustain release layer (mg)								
Propranolol Hcl	8	8	8	8	16	16	16	16
Carbopol 934 P	30	15	10	00	30	15	10	00
HPMC K4M	00	15	20	30	00	15	20	30
Lactose	12	12	12	12	4	4	4	4
Cup layer (mg)								
Carbopol 934 P	155.5	72.5	51.83	000.0	155.5	72.5	51.83	000.0
HPMC K4M	000.0	72.5	103.66	155.5	000.0	72.5	103.66	155.5
Magnesium stearate (3 %)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Carbopol 934 P: HPMC K4M ratio	1:0	1:1	1:2	0:1	1:0	1:1	1:2	0:1

Composition of different formulations of novel buccal adhesive core-in-cup tablets of Propranolol Hydrochloride. The formulations A-D contain 10 mg and E-H contains 20 mg of PHCL respectively. The PHCL is presented in 1:4 ratio in fast and sustained release layers, respectively.

at 37±2° for 24 h under constant stirring conditions. The drug content was estimated at preset time 0, 1, 6 and 24 h using UV spectrophotometer at 290 nm.

Stability studies in human saliva:

Human saliva was collected from volunteers, filtered and tablets were immersed in 5 ml of the human saliva for 6 h. At regular intervals of time (0, 1, 2 and 6 h), the stability of buccal adhesive core-in-cup tablet in the presence of human saliva was evaluated for changes in its appearance such as color, shape and PHCL content.

Accelerated stability studies:

The buccal adhesive core-in-cup tablets were packed in aluminum foil and kept at 40±2° for 70 days. Tablets were withdrawn on day 0, 15, 45 and 70 and evaluated for weight loss, hardness, friability, mucoadhesion strength and drug content.

***In vivo* evaluation of placebo buccal adhesive core-in-cup tablets:**

Institutional Ethics Committee clearance was obtained to conduct the study on ten healthy human male volunteers (aged 18-55 y). Informed consent was obtained from the volunteers before the study. Food was prohibited from 0.5 h before till the end of the study but water was provided whenever required. They were instructed to press the placebo buccal adhesive core-in-cup tablet against the buccal mucosa for 1 min. The volunteers were asked to record the time of insertion and time and circumstances of end of the adhesion (erosion or dislodgment of tablets). The questionnaire was given to score criteria's like irritancy, comfort, taste, dry mouth, salivation and dislodgment of the tablet during the study period and heaviness of the tablets at the place of attachment.

RESULTS AND DISCUSSION

It is essential to investigate the permeation of the drug molecules through the appropriate buccal mucosa before a buccal adhesive system is developed. The structure of the oral mucosa suggests two possible drug transport routes, the paracellular route and transcellular route. According to the pH-partition hypothesis, only the lipophilic drugs are able to cross-lipoidal membranes in significant amount. Whether buccal drug transport is by transcellular route or paracellular route is still uncertain. It is noteworthy that a similar correlation between permeability co-efficient and distribution co-efficient has been found in the corneal penetration of β-blocking agents. In these experiments a plateau has been found for lipophilic drugs at log distribution co-efficient. It is likely that there will be a plateau for drugs with a higher lipophilicity. The important role of the lipophilicity is also shown by the amount of drug remaining in the tissue after experiments, which is probably due to binding of drug in lipophilic parts of the epithelium. *In vitro* permeation studies of PHCL through porcine buccal mucosa and supportive data of Brun *et al.* clearly indicated that the mechanism of PHCL absorption is by passive diffusion[7-8].

The swelling index of buccal adhesive core-in-cup tablets for a period of 6 h is shown fig. 2. Tablets containing carbopol 934 P and HPMC K4 M at the ratio of 1:0, 1:1, 1:2 and 0:1 showed swelling rate in the order 0:1>1:2>1:1>1:0 (fig. 2). The hygroscopic nature of the polymers is one of important properties that affect the onset of swelling. Faster swelling has been observed for tablets containing carbopol 934P:HPMC K4M at the 0:1 ratio when compared to other formulations. Maximum swelling was attained in 5 h, after which polymer started eroding slowly in the swelling medium. High amount of water uptake may be due to quick hydration of the HPMC K4M and swelling rate of the tablets increases with increase in the concentration of HPMC K4M in tablets. Tablets containing carbopol 934 P alone (A and E) have shown lesser swelling index when compared to other formulations may be due to lesser uptake of water by the polymer for a period of 6 h[9].

Mucoadhesion is defined as the adhesion between a polymer and mucus. In general, mucoadhesion is considered to occur in three major stages, wetting, interpenetration, and mechanical interlocking between mucus and polymer. The mucoadhesion strength depends on a number of parameters such as molecular weight of the polymers, contact time with mucus, swelling rate of the polymer and biological membranes used for the study. The porcine buccal mucosa and rabbit buccal mucosa were used as biological membranes to investigate the effect of different biological membranes on the mucoadhesion strength. The maximum mucoadhesive strength has been observed for core-in-cup tablets containing carbopol 934 P and HPMC K4M at the ratio of 1:1 (formulations B and F) followed by ratios of 1:2 (C and G), 0:1(D and H) and 1:0 (A and E) (Table 3). The low mucoadhesion strength of the tablets containing carbopol alone may be due to loss of hydrogen bonding with the mucus. The mucoadhesion strength of the carbopol depends upon the pH of the medium. The pH of the buffer used in the present study was kept at 6.6, which presumably could have decreased the mucoadhesion strength of the buccal adhesive core-in-cup tablets which may be due to a change in the ionization property of carboxylic group present in the polymer (formulation A and E). Mucoadhesion strength of the tablets also varied when different biological membranes (porcine and rabbit) were used and this may be due to different amounts of keratin present in the individual buccal mucosa. Maximum mucoadhesion strength has been observed in case of porcine buccal mucosa when compared to rabbit buccal mucosa due to lesser amount of keratin[10].

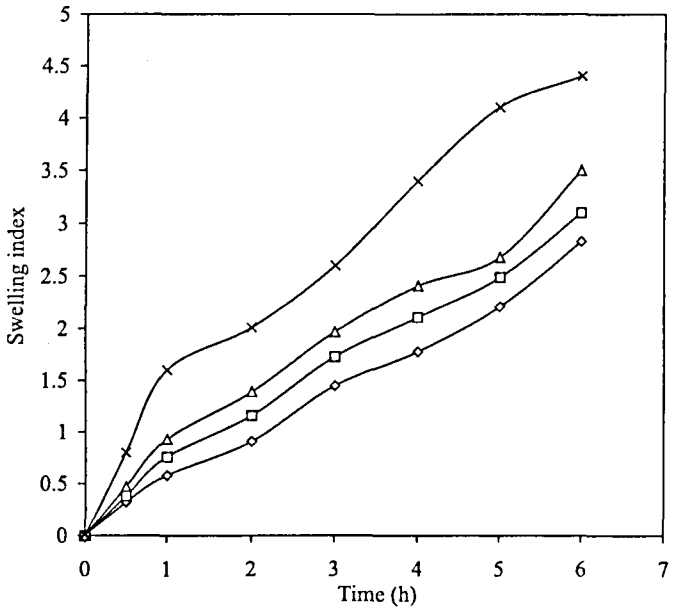

Fig. 1: Swelling index profile of buccal adhesive core-in-cup tablets.

Swelling index profile of novel buccal adhesive core-in-cup tablets of Propranolol Hydrochloride of formulations A-D containing 10 mg of PHCL, carbopol 934 P and HPMC K4M in the ratio of 1:0 (×), 1:1 (△), 1:2 (◇), and 0:1 (□) representing formulations A, B, C and D, respectively.

TABLE 2. MUCOADHESIVE STRENGTH OF CORE-IN-CUP TABLETS

Formulation code	C934P: HPMCK4M	Porcine buccal mucosa	Rabbit buccal mucosa
A	1:0	22.22	15.59
B	1:1	44.76	34.59
C	1:2	39.76	25.52
D	0:1	23.29	18.80

Mucoadhesive strength of novel core-in-cup tablets of propranolol hydrochloride of formulations A-D containing 10 mg of PHCL, carbopol 934 P and HPMC K4M in the ratio of 1:0, 1:1, 1:2 and 0:1. The mucoadhesive strength was measured by using porcine buccal mucosa and rabbit buccal mucosa.

An ideal controlled release system should release the drug immediately to attain the required therapeutic level at a faster rate and maintain the therapeutic level for longer period of time. Usually, a buccal drug delivery system such as a matrix system contains only sustained release layer. The core-in-cup tablet system developed in the present investigation has both i.e., fast release layer and sustained release layer to fulfill the above requirement. The release of PHCL from novel buccal adhesive core-in-cup tablets varied with the type and ratios of polymers used. The release behaviour of PHCL from core-in-cup tablets containing carbopol 934 P and HPMC K4M at different ratios followed in the decreasing order 0:1>1:0>1:2>1:1. However, when the concentration of the drug increases in the tablets, the release behaviour of PHCL also increases. Tablets containing HPMC K4M alone (formulation D and H) showed maximum cumulative drug release from core-in-cup tablets when compared to other formulations which might be due to a higher uptake of water by HPMC K4M as evidenced from the swelling studies. It was observed that there was increase in the drug diffusion from the polymer matrix with increase in the water uptake. This high uptake of water leads to considerable swelling of the polymer matrix that causes the drug to diffuse out from polymer matrix at a faster rate. Tablets containing carbopol 934 P alone (formulation A and E) showed higher drug release when compared to formulations B, C, F and G may be due to ionization of carbopol 934 P at pH 6.6, a pH environment higher than its pKa 6. Ionization of carbopol leads to the development of negative charges along the backbone of the polymer. Repulsion of like charges uncoils the polymer into an extended structure leading to slightly higher uptake of water that increases the drug release from the polymer matrix systems[11]. Combination of carbopol 934 P and HPMC K4M at the ratio of 1:1 and 1:2 has been effective in controlling the release of PHCL for longer period of time. Incorporation of loading dose (fast release layer) along with sustained release layer into the buccal adhesive tablets help in attaining the therapeutic drug level at faster rate and maintains it for longer period of time (fig.3). The mechanism of drug release was studied using the Korsemeyer and Peppas equation, $M_t/M_\infty=Kt^n$, where, M_t/M_∞ is fractional release of the drug, 't' denotes the release time, K represents a constant incorporating structural and geometrical characteristics of the device, and n is the diffusional exponent and characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the n value falls between 0.5 and 1.0, while in case of Fickian diffusion, n=0.5; for zero order release (case II transport), n=1, and for supercase II transport, n>1[11].

The values of n were estimated by linear regression of log (M_t/M_∞) versus log (t) for different formulations and n values lie between 0.5 to 1.0 indicates that the release of PHCL is by both diffusion and polymer chain relaxation mechanisms. The order of drug release from all the formulations was confirmed by plotting log % cumulative retained versus time and it followed first order kinetics.

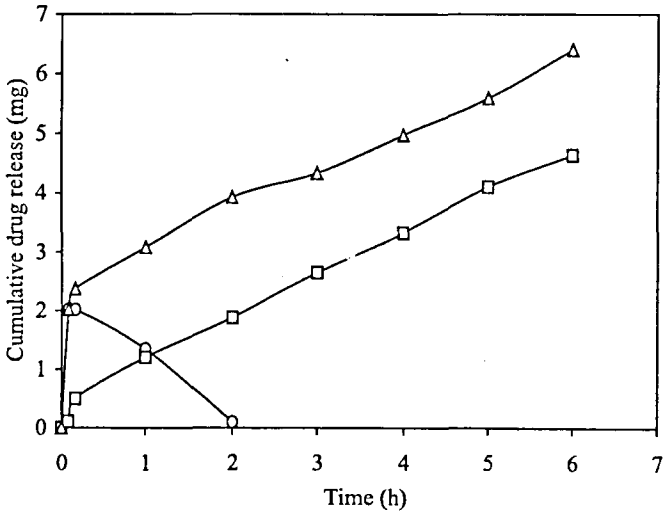

Fig. 2: *In vitro* release of PHCL from different layers of core-in-cup tablet.

***In vitro* release of PHCL from only fast release layer (o), only sustained release layer (□) and core-in-cup tablet (△) of Propranolol Hydrochloride of formulation D containing 10 mg of PHCL.**

PHCL found to be stable in phosphate buffer solutions having pH 6.0, 6.6 and 7.0 with no significant drug loss in all these buffer solutions. Stability studies in normal human saliva showed no change in the color of buccal adhesive core-in-cup tablets, which would have happened if drug was unstable in human saliva. The thickness and diameter of core-in-cup tablets increased due to swelling of the polymers in human saliva but tablets did not collapse till the end of studies indicating the satisfactory stability of shape of the tablets. Accelerated stability studies revealed no significant changes in the physical properties of the tablets, drug content and mucoadhesion strength after 70 d at 40° except slight loss in the weight of tablets due to evaporation of the moisture that was present in polymer matrix.

Placebo core-in-cup tablets containing carbopol 934 P and HPMC K4M at the ratio of 1:1 were used for *in vivo* acceptability studies on ten healthy human male volunteers. The placebo tablets did not cause any irritation to buccal mucosa and was not dislodged from the site of adhesion till the end of the study. Most of the volunteers felt that taste was normal and the tablet was not heavy at the site of attachment. Tablet was comfortable in the oral cavity and salivary secretion varied during the study among volunteers.

ACKNOWLEDGEMENTS

The authors are thankful to J. S. S. Mahavidyapeetha, Mysore for providing the necessary facilities to carry out this research work..

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