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Formulation development and *in vitro* characterization of bilayer and floating-bioadhesive tablets of propranolol hydrochloride

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Abstract

The aim of the present research was to develop a bilayer and floating-bioadhesive drug delivery system exhibiting a unique combination of floatation and bioadhesion to prolong residence in the stomach using propranolol hydrochloride as a model drug. The sustained layer was compressed and granules of the floating layer were added to it then both layers were compressed using a single station rotary press. Granules and tablets were characterized using the official method. Hydroxypropyl methylcellulose (HPMC) and sodium bicarbonate were added to the floating layer and, when immersed in 0.1 mol/ l HCl, the tablet expands and rises to the surface where the drug is gradually released without interference from gas bubbles. The in vitro drug release, buoyancy lag-time, detachment force and swelling index were evaluated. The in vitro drug release from the tablet was controlled by the amount of HPMC in the sustained release layer. The floating ability of the tablets was studied. The release of propranolol hydrochloride from the tablets followed the matrix first order release model. The concentration of HPMC significantly affects the drug release rate, buoyancy lag-time, detachment force and swelling characteristics of the tablets. The tablet was buoyant for upto 8 h. This kind of tablet exhibits independent regulation of buoyancy and drug release.

Keywords: *Propranolol hydrochloride, Bilayer and floating-bioadhesive tablet, Detachment force, Hydroxypropyl methyl cellulose.*

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Introduction

Oral drug delivery has been known for decades as the most widely used route of administration among all the routes that have been explored for the systemic delivery. Oral route is the most convenient and extensively used route of drug administration. All controlled release systems have limited applications if the systems cannot remain in the vicinity of the absorption site. The controlled release drug delivery system possessing the ability of being retained in the stomach is called gastroretentive drug delivery system. They can help in optimizing the oral controlled delivery of drugs having "absorption window" continually releasing the drug prior to absorption window for prolonged period of time, thus ensuring optimal bioavailability[1]. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is, however, distinct in the two states.

Gastric emptying studies revealed that orally administered controlled release dosage forms are subjected to basically two complications: that of short gastric residence time and unpredictable gastric emptying rate[2]. Propranolol is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor agonist agents for available receptor sites. It is used as antihypertensive, antianginal, antiarrhythmic, and in treatment of migraine[3]. Propranolol is reported to be of value in cardiovascular disorders, many of which are associated with central nervous system[4].

Propranolol is highly lipophilic and almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver, and on average, only about 25% of propranolol reaches the systemic circulation. Approximately 90% of circulating propranolol is bound to plasma proteins. Propranolol is extensively metabolized with most metabolites appearing in the urine.

Peak plasma concentrations occur about 1 to 4 h after an oral dose. $t_{1/2}$ of propranolol is 3–4 h[5]. Thus, propranolol has relatively short half-life. Consecutively, for an optimum effect, the administration of propranolol hydrochloride as conventional tablets (with rapid disintegration and dissolution) must be carried out several times a day. Therapy with immediate release propranolol hydrochloride tablets typically requires 40–160 mg as daily dose given in three to four divided doses[6]. Presence of food increases the bioavailability. The secretory transporter P-glycoprotein (P-gp) located on the epithelium cells is responsible for low and variable bioavailability of various compounds such as propranolol[7]. Although P-gp appears to be distributed throughout the gastrointestinal tract (GIT), its levels are higher in more distal regions (stomach < jejunum < colon). Absorption through P-glycoprotein prolongs the drug exposure to CYP3A4.

The colocalization of P-gp and CYP3A4 in the mature enterocytes and their overlapping substrate specificity reasonably suggests that the function of these two proteins may be synergistic and appear to be coordinately regulated. Consequently, a greater proportion of drug will be metabolized since the repetitive two-way kinetics (drug exsorption from the enterocytes into the lumen via P-gp and reabsorption back into enterocyte) will simply prolong the drug exposure to CYP3A4. This mechanism not only limits the absorption of a wide variety of drugs, including peptides, but also poses a threat for potential drug interactions[7,8]. Based on previously published literature, applications of gastroretentive drug delivery system (GRDDS) may be summarized for several categories of drugs[8]as drugs for local action in stomach, e.g., 5-flurouracil, antacids; drugs

unstable in lower part of GIT, e.g., captopril; drugs insoluble in intestinal fluids (acid soluble basic drugs), e.g., propranolol, metoprolol, diazepam; drugs with variable bioavailability, e.g., sotalol hydrochloride, levo DOPA and drugs with site-specific absorption in stomach or upper parts of small intestine, e.g., atenolol, levo DOPA, salbutamol, sotalol.

Propranolol has short half-life, high first-pass metabolism, presence of food increases the bioavailability, P-gp plays important role in the absorption, and the drug is acid-soluble basic drug which make it suitable for GRDDS. Till today, no floating-bioadhesive drug delivery system has yet developed for propranolol. So, it was decided to formulate propranolol floating-bioadhesive tablets of propranolol.

Materials and Method

Materials

Propranolol hydrochloride was obtained as gift sample from Cipla Pharmaceuticals, Goa. Methocel K100M, starch 1500, and maize starch were gifts from Emcure Research Center (Pune, India). Dicalcium phosphate and sodium bicarbonate were purchased from Nulife Pharmaceuticals (Pune, India). All solvents used were of analytical grade.

Preparation of bilayer and floating-bioadhesive tablets of propranolol hydrochloride

Propranolol hydrochloride bilayer tablets contained two layers *i.e.* a floating layer and a sustained release (SR) layer. All ingredients were passed through a sieve (60#) and mixed well in a mortar. Granules of the floating layer were prepared using a 5% (w/v) PVP ethanolic solution. Weighed quantities of the SR layer equivalent to 450 mg were subjected to mild compression. Weighed granules of the floating layer equivalent to 330 mg were added to the compressed SR layer and both the layers were then compressed in a single station rotary press (Rimek Mini Press II).

Characterization of granules

The characteristic parameters of the granules were evaluated. The angle of repose and flow rate was determined by the funnel method. The bulk density and tapped density were determined by the cylinder method and Carr's index was calculated using the following equation 1.

$$\text{Carr's index} = \frac{Df - D0}{Df} X\ 100 \qquad (1)$$

Where, D_f =Poured bulk or bulk density, D_0= Tapped or consolidated bulk density

Characterization of tablets

Drug content and physical evaluation

The drug content of the tablets was determined using 0.1 mol/l HCl as a solvent, and the samples were analyzed spectrophotometrically (JASCO, V-530, Japan) at 290 nm. Tablets were also examined with regard to their weight variation (n = 10), friability (n = 10) and hardness (n = 6) [9].

Buoyancy lag-time studies

The buoyancy lag-time of the tablets was studied at 37 ± 0.5°C, in 100 ml 0.1 mol/l HCl (pH 1.2). The time required for the tablet to rise to the surface and fl oat was taken as the buoyancy lag-time.

Dissolution studies

The release rate of propranolol hydrochloride from floating tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml 0.1 mol/l HCl, at 37 ± 0.5°C and 50r/min. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 24 h, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman filter paper and the absorbance of these solutions was measured at 290 nm. The cumulative percentage drug release was calculated using 'PCP Disso v2.08' Software.

Detachment stress

The mucoadhesive forces of the bilayer tablets were determined by the measuring device shown in Fig. 1.

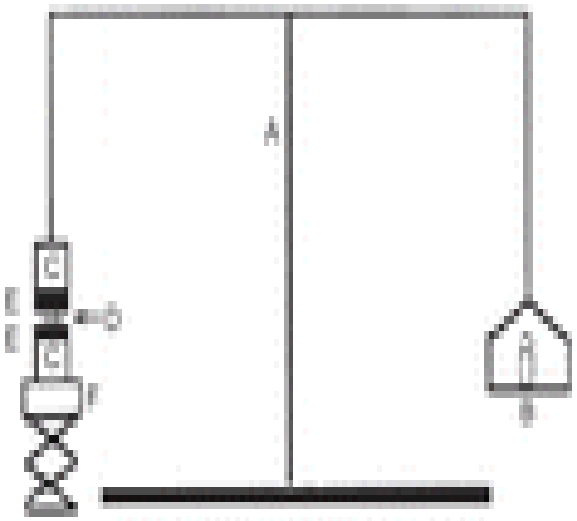

Fig. 1(a) Detachment stress measuring device

Fig. 1(b) Detachment stress measuring device

Pieces of sheep fundus tissue were stored frozen in saline solution and thawed to room temperature immediately before use. At the time of testing a section of tissue (E) was transferred, keeping the mucosal side out, to the upper glass vial (C) using a rubber band and an aluminum cap. The diameter of each exposed mucosal membrane was 1.1 cm. The vials with the fundus tissue were stored at 37°C for 10 min. Next, one vial with a section of tissue (E) was connected to the balance (A) and the other vial was fixed on a height-adjustable pan (F). A bilayer tablet (D) was applied to the lower vial with the help of two pieces of adhesive tape. The height of the vial was adjusted so that the tablet could adhere to the mucosal tissues in the vial. A constant weight (10 g) was placed on the upper vial and applied for 2 min, after which it was removed and the upper vial was then connected to the balance. Weights (B) were added at a constant rate to the pan on the other side of the modified balance of the device until the two vials were separated. The bioadhesive force, expressed as the detachment stress in dyne/cm was determined from the minimum weight required to detached the two vials using the following equation 2^{10}.

Detachment stress (dyne/cm) = $m \cdot g/A$ (2)

Swelling characteristics

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml 0.1 mol/l HCl at 37 ± 0.5°C. The tablets were removed periodically from the dissolution medium and, after removing free water, the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU %) according to the equation[11] 3.

$$WU\% = \frac{\text{Weight of swollen tablet} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100 \quad (3)$$

Stability studies

The stability studies were carried out according to ICH and WHO guidelines to assess the drug and formulation stability. Optimized B5 formulations were sealed in aluminum packaging having a polyethylene coating on the inside. Samples were kept in a humidity chamber maintained at 45°C and 75% RH for 3 months. At the end of the study period, samples were analyzed for drug content, buoyancy lag-time, buoyancy time and detachment stress.

Results and discussion

All formulations were prepared as two-layered tablets. The first layer contains a mixture of sodium bicarbonate, starch 1500 and HPMC K100M, with the HPMC K100M being used as a matrix material to retain the air bubbles. The first layer allowed the tablets to float. Sodium bicarbonate was added as a gas-generating agent. The ideal amount of both, effervescent mixture and polymer, for the floating layer was estimated by determining the onset time of floating. In an attempt to shorten the onset time by increasing the concentration of effervescent mixture, it was found that tablets were dispersed; on the other hand, a lower concentration prolongs this. The SR layer provided controlled release of active material and contains the drug, with HPMC K100M as a hydrophilic matrix material (Table 1). Hence, the unique combination of floating and bioadhesion is highly likely to prolong the gastric retention time of propranolol hydrochloride, resulting in high aqueous solubility and restricting GI absorption to the upper part of the small intestine. The prepared granules of the floating layer were characterized with respect to the angle of repose, flow rate, bulk density, tap density and Carr's index (Table 2). The angle of repose was less than 25º for all the batches of granules indicating satisfactory flow behavior. Other granule parameters were also determined and found to be within acceptable limits. Table 2 shows that, as the concentration of HPMC increases, the angle of repose and Carr's index increase while the flow rate decreases.

Physical evaluation

The weight variation, friability, hardness and content uniformity were found to be within acceptable limits (Table 2). Thus, all the physical properties of these tablets were satisfactory as specified in the Indian Pharmacopoeia.

Buoyancy lag-time studies

All tablet formulations exhibited satisfactory floatation ability and remained buoyant for more than 24 h in dissolution medium subjected to rotation. The buoyancy lag-time of tablets depends on the amount of sodium bicarbonate involved in CO_2 formation. For a floating system, the ideal matrix or coating material should be highly permeable to dissolution media in order to initiate rapid generation of CO_2 to promote floating. Both the layers contain HPMC K100M, which leads to a reduced buoyancy lag-time. Formulations B1 to B5 showed buoyancy lag-times ranging from 6.89 ± 1.19 to 12.89 ± 1.54 min (Table 3). These results indicate that the buoyancy lag-time was satisfactory when using sodium bicarbonate.

Detachment force

The values given in Table 3 indicate that the bioadhesive force increased significantly as the concentration of mucoadhesive polymer increased. All bilayer formulations showed mucoadhesive force in the range of 79.21 to 122.93 dynes/cm. Bioadhesion is a surface phenomenon in which a material of natural or synthetic origin adheres or sticks to a biological surface, usually mucus membrane. Many hydrophilic polymers adhere to mucosal surfaces as they attract water from the mucus gel layer adhereing to the epithelial surface. This is the simplest mechanism of adhesion and it has been defined as "adhesion by hydration". There are various kinds of adhesive force, *e.g.* hydrogen bonding between the adherent polymer and the substrate, *i.e.* mucus, which are involved in mucoadhesion at the molecular level[13]. So, as the concentration of polymer increases, the detachment force also increases.

Swelling characteristics

The percentage water uptake of the formulations (B1– B5) ranged from 143.89 to 272.10 %. The

percentage water uptake was found to be increased on increasing the concentration of HPMC K100M in the formulations and, hence, the water uptake capacity increases. Drug diffusion depends significantly on the water content of the tablet. This may be because the mobility of the polymer chains is very dependent on the water content of the system. In the case of high water content, polymer chain relaxation takes place with volume expansion resulting in marked swelling of the system. Also, higher water content could lead to greater penetration of the gastric fluid into the tablet leading to faster carbon dioxide gas generation, thereby reducing the floating lag-time. Consequently, faster and greater swelling of the tablet would lead to an increase in the dimensions of the tablet leading to an increasing in the diffusion pathways and, thus, a reduction in diffusion rate. So, the drug release was found to be high initially and then gradually decreased [14].

In vitro dissolution studies

The release data were evaluated by the model-dependent (Curve fitting) method using 'PCP Disso v2.08' software. The release rate kinetic data for all formulations are shown in Table 4. In present study, the matrix first order model describing drug release from polymeric systems was used. The matrix first order models takes into account the fact that the drug release mechanism often deviates from Fick's law and exhibits anomalous behavior described by the following equation 4,

$$Mt / M\infty = k \times t^{n} \qquad (4)$$

Where *M*, is the quantity of drug released at infinite time, *k* is the kinetic constant and *n* is the release exponent. There are various release behaviors according to the geometric shapes of the drug delivery device. A tablet exhibits slab geometry and, if *n* takes the value 0.5, this means diffusion controlled drug release and the value 1.0 indicates swelling controlled drug release. A value of *n* between 0.5 and 1.0 can be regarded as an indicator of both phenomena (anomalous transport). The value of *n* for all the formulations is shown in Table 4. The value of *n* was found to range from 0.342 to 0.767 which increases as the concentration of polymer increases, showing that the release mechanism shifted in the direction of anomalous transport. The results of the *in vitro* release studies are shown in Fig. 2. Formulation B1, B2, B3, B4 and B5 exhibited a release of 84.12, 80.12, 65.06, 58.12 and 43.20%, respectively, in 9 h. The concentration of HPMC K100M in the release layer was the key factor governing drug release. In the bilayer tablet, the drug release layer included the gelling agent forming a gelatinous barrier which controls the drug release without interference from gas bubbles generated in the floating layer. It has been found that bilayer tablets exhibit reproducible release. The time taken to release 50% (t_{50}) and 70% (t_{70}) of the drug from different tablets was determined (Table 4). As the concentration of HPMC K100M increases in the formulation the release rate was found to decrease.

Table 1. Formulations of bilayer and floating- bioadhesive tablets[a]

Ingredients	Floating Layer	Sustained release layer				
		B1	B2	B3	B4	B5
Propranolol Hydrochloride		80	80	80	80	80
HPMC K100 M	100	40	80	120	160	200
Starch 1500	130	130	100	110	70	50
Maize starch		80	90	100	110	80
Sodium bicarbonate	100					
Dicalcium phosphate		120	100	40	30	40

Table 2. Characterization of granules and tablets of propranolol hydrochloride*

Preparations	Parameters	B1	B2	B3	B4	B5
\ Granules	Angle of repose (^{o})	16±1.4	18±0.6	19±2.6	22±3.4	24±1.9
	Flow rate (g/min)	1.18±0.4	1.18±0.8	0.98±0.6	0.97±0.5	0.92±0.8
	Bulk density (g/ml)	0.596	0.595	0.604	0.630	0.639
	Tap density (g/ml)	0.732	0.762	0.781	0.839	0.912
	Carr's index	17.71±2.2	23.47±3.7	24.85±1.5	25.41±2.4	31.32±1.8
Tablets	Weight variation (%)	±2.0	±5.0	±3.0	±2.0	±2.0
	Friability (%)	0.34	0.28	0.12	0.19	0.18
	Hardness (kg/cm^2)	7.1±0.3	8.4±0.5	7.7±0.3	7.4±0.4	8.1±0.3
	Content uniformity (%)	98.8±1.7	98.7±2.4	97.5±2.6	97.5±1.3	98.8±1.5

***Each sample was analyzed in triplicate (n=3)**

Table 3. Evaluation of bilayer and floating-bioadhesive tablets of propranolol hydrochloride[#]

Formulations	Buoyancy lag time (min)	Detachment force (dynes/cm^2)	Swelling characteristics
B1	12.89±1.54	79.21	143.89
B2	10.5±1.23	85.21	165.43
B3	8.1±2.65	91.10	221.89
B4	7.2±1.92	112.12	255.93
B5	6.89±1.19	122.93	272.1

[#] Each sample was analyzed in triplicate (n=3)

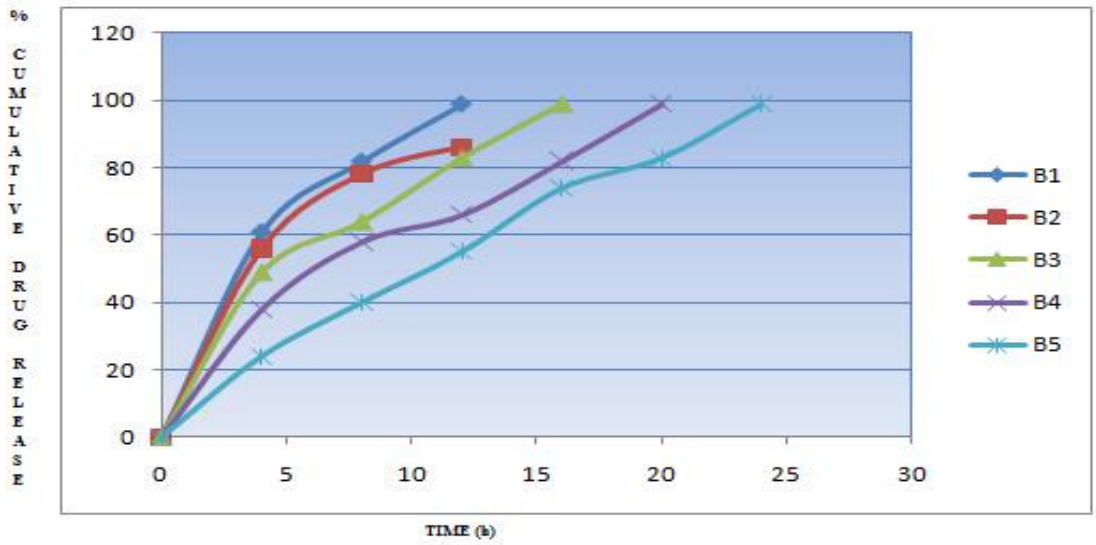

Fig. 2 Drug release profile from floating-bioadhesive tablets

Table 4. Drug release kinetics and dissolution parameters of propranolol hydrochloride[+]

Formulations	Best fit model	R	n	k	$T_{50\%}$ (h)	$T_{70\%}$ (h)
B1	Matrix	0.979	0.342	40.878	2.43	5.43
B2	First order	0.992	0.411	28.767	3.41	5.78
B3	Matrix	0.989	0.499	29.345	4.13	7.23
B4	Matrix	0.987	0.555	19.286	5.47	>9
B5	First order	0.988	0.767	8.243	>9	>9

[+]Each sample was analyzed in triplicate (n=3)

Table 5. Characteristics of optimized B5 formulation before (0 d) and after storage

Time (d)	Drug content (%)	BLT (min)	Buoyancy time (h)	Detachment force (dynes/cm^2)
0	**99.88±1.4**	**7±2.6**	**>12 h**	**127.324**
7	**99.59±1.8**	**8±3.2**	**>12 h**	**118.165**
15	**99.21±2.1**	**14±2.8**	**>12 h**	**110.768**
30	**99.71±1.6**	**16±2.2**	**>12 h**	**101.963**
60	**98.76±1.3**	**19±3.5**	**>12 h**	**96.432**
90	**98.65±1.6**	**21±4.2**	**>12 h**	**89.821**

***Storage at 40°C and 75% RH for three month (n=6)**

Stability study

The stability studies were carried out on the optimized formulation *i.e.* F3. The formulations were stored at 40 ± 2°C/75 ± 5% RH for 3 months to assess their long- term stability. The protocol of the stability studies conformed to WHO guidelines for stability testing of protocols intended for the

global market. After an interval of 7, 15, 30, 60 and 90 days, samples were withdrawn and retested for drug content, buoyancy lag-time, buoyancy time and detachment stress (Table 5). The results indicated that, irrespective of the concentration of polymer, these formulations remained stable for three months.

Conclusion

In the present study, we successfully developed optimized bilayer and floating-bioadhesive dosage forms which exhibit a unique combination of floatation and adhesion for prolonged residence in the stomach. The optimized B5 tablet formulation showed a satisfactory dissolution profile, detachment stress and floating characteristics. The tablets remained floating in the stomach for up to 8 h.

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