Formulation Strategy for Low Absorption Window Antihypertensive Agent

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In the present study a hydrodynamically balanced system of celiprolol hydrochloride was developed as single unit floating capsule. Various grades of low density polymers were used for formulation of this system. They were prepared by physical blending of celiprolol hydrochloride and the polymer in varying ratios. The formulation was optimized on the basis of *in vitro* buoyancy and *in vitro* release in citrate phosphate buffer at pH 3.0. Effect of various release modifiers was studied to ensure the delivery of drug from the hydrodynamically balanced system capsule over a period of 12 h. Capsule prepared with HPMC K4 M and liquid paraffin gave the best *in vitro* percentage release and was taken as optimized formulation. By fitting the data in zero order, first order and Higuchi model it could be concluded that the release followed zero order release, as the correlation coefficient was higher for zero order release. It could be concluded from R^2 value for Higuchi model and K-Peppas model that drug release followed fickian diffusion mechanism.

Key words: Hydrodynamically balanced system, celiprolol hydrochloride, *in vitro* buoyancy studies, stability studies

Drug absorption from gastrointestinal tract is a complex procedure and is subject to many variables. It has been reported that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Gastroretentive system can remain in the gastric region for several hours and therefore significantly prolong the gastric residence time of drugs. Many approaches have been reported in the literature for the formulation of gastroretentive system viz. mucoadhesion[1-2], floatation, sedimentation[3-5], expansion[6-7] and modified shape systems[8-9]. Both single and multiple systems have been reported in the literature[10]. Floating drug delivery offers a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

Celiprolol hydrochloride (CEH) is an antihypertensive agent that antagonizes the action of β_1-receptor. It has been reported that the absolute bioavailability of celiprolol when given orally is 30-70%. The biological half life of celiprolol hydrochloride is 4-6 h and the main site of absorption is proximal small intestine. A hydrodynamically balanced system (HBS) is planned for CEH, as such a system when administered would remain buoyant on the gastric fluids for a prolonged period of time and the drug would be available at the main site of its absorption i.e. proximal small intestine resulting in enhanced bioavailability.

MATERIALS AND METHODS

Celiprolol hydrochloride, different grades of the HPMC (K4M, K15M, and K100M), ethyl cellulose, and polyethylene oxide WSR 60K were obtained as gift samples from Ranbaxy Research Laboratories, New Delhi, India. Liquid paraffin was obtained from S. D. Fine Chemicals, Mumbai. All other reagents were of analytical reagent grade.

Preparation of capsules:
Single unit capsules were formulated with the help of different low density polymers, which upon administration would attain a density of less than that of the gastric fluids and therefore would float (Table 1). On the basis of floatation HPMC K4M was selected for further studies. 200 mg of celiprolol and different ratios of the polymer were accurately

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TABLE 1: FORMULAE FOR FLOATING CAPSULE

Formulation code	Content of capsule (200 mg)
A	HPMC K4M
B	HPMC K15M
C	HPMC K4M: HPMC 15M (1:1)
D	HPMCK100 M
E	Guar gum
F	Sodium carboxy methyl cellulose

weighed and were physically blended in a glass mortar and pestle and filled in a hard gelatin capsule (size 00). Total weight of capsule was kept 400 mg. The formula of various formulations is given in the Table 2.

In vitro buoyancy studies:

The capsules were immersed in 900 ml of citrate buffer pH 3, simulating the fed state of stomach, in USP paddle apparatus at 100 rpm. The time for which the capsule remained buoyant was observed and was taken as the floating time. The polymer that showed the best floating behavior was taken for *in vitro* release studies (fig. 1).
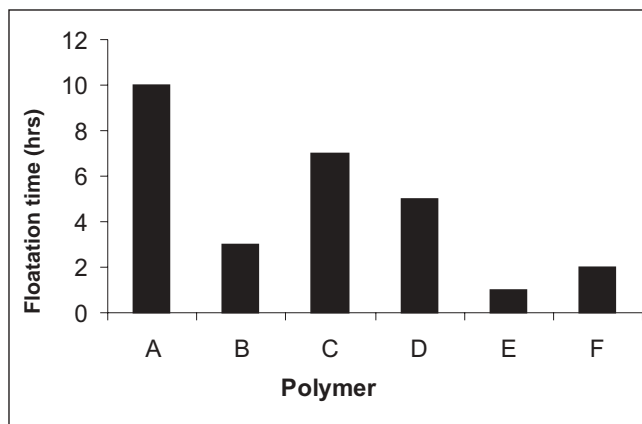
In vitro release studies:

Based on the *in vitro* buoyancy studies, formulations showing good floatation were subjected to *in vitro* release studies. *In vitro* studies were carried out by carrying out the dissolution studies in USP paddle type apparatus at 100 rpm using 900 ml of citrate buffer pH 3.0. The samples were withdrawn at regular intervals and replaced with the blank buffer. Sample were analyzed by spectrophotometrically (Shimadzu UV 1601) at 232 nm.

Effect of release modifiers:

Ethylcellulose (EC), Polyethylene oxide (PEO) WSR 60K and liquid paraffin were used at different concentration as shown in Table 2. For addition of ethyl cellulose (5-25%) to the formulation corresponding solution of ethyl cellulose was made in

TABLE 2: WORKING FORMULAE FOR FLOATING CAPSULES

Formulation Code	Celiprolol HCl (mg)	HPMC K4M (mg)	Ethyl cellulose (mg)	Polyethylene Oxide (mg)	Liquid Paraffin (mg)
L1	200	198	-	-	2
L2	200	197	-	-	3
L3	200	196	-	-	4
P1	200	180	-	20	-
P2	200	176	-	24	-
J1	200	190	10	-	-
J2	200	176	24	-	-
J3	200	150	50	-	-

Fig. 1: Floatation behavior of various polymers

acetone and granulated with weighed drug content and HPMC K4 M and were allowed to dry at 30°. The granules were passed through sieve no 44 and 400 mg of granules equivalent to 200 mg of the drug were filled in capsule. PEO was added in dry form. Liquid paraffin (1%, 1.5% and 2%) was added by making a solution in isopropanol, granules were prepared, dried and passed through the sieve no 25 mesh and filled in to capsules.

Analysis of *in vitro* drug release:

To analyze the mechanism of drug release from the capsules, the *in vitro* dissolution data was fitted to zero order, first order[11], Higuchi release model[12] and Korsemeyer and Peppas model[13-14].

Stability studies:

Stability studies were carried out according to ICH guidelines by storing the optimized formulation at 40°C/75±5% RH for a period of three months. The samples were withdrawn at 30, 60 and 90 d and analyzed for drug content and dissolution study as given in *in vitro* release studies by an HPLC method. The chromatographic column used was C_{18}. Mobile phase used was acetonitrile:phosphate buffer pH 3.0 (30:70), with 0.1% triethylamine, a stability indicating method. Flow rate was kept at 0.8 ml/min[15].

RESULTS AND DISCUSSION

The *in vitro* release studies revealed that the formulation remained buoyant but probably because of the high aqueous solubility of (CEH), the release could not be sustained. Only formulation containing HPMC K4M could sustained the drug release up to 9 h therefore it is decided to add release modifier to

these formulations (Table 2) so as to aid the sustained release of the drug from the formulation.

It was observed that best result was obtained with formulation set I, (L2) containing HPMC K4M, CEH and liquid paraffin at 1.5% level as the drug release could be sustained for 12 h (fig. 2). But the formulation set II (P1, P2) containing polyethylene oxide 10%, 12% were able to sustain the release only for up to 9 h (fig. 3). Formulation set III (J1, J2, J3) containing ethyl cellulose 5%, 10% and 25% could not sustain the drug release for up to 12 h (fig. 4). HPMC K4 M formed a firm matrix and could control the drug release for a longer duration time. Liquid paraffin has only been used as an inert material for enhancing the buoyancy of the formulation[16]. However based on release profile we can conclude that besides imparting the buoyancy to the formulation it also modify the release significantly. Among the release modifiers used to control the release of celiprolol from the formulation, formulation containing liquid paraffin (1.5%) gave the best *in vitro* release as it could control the release for 12 h and hence it was the optimized formulation.

The *in vitro* release pattern of the optimized formulation was analyzed by fitting the dissolution data in to various kinetics models. It was observed that R^2 value was higher when fitted to zero order equation (fig. 5), Table 3, followed by Higuchi model (fig. 6), as compared to first order equation (fig. 7), which indicated a zero order release from the optimized HBS capsule for celiprolol hydrochloride. As the n value for the k-Peppas model was found to

Fig. 3: Release of celiprolol hydrochloride from floating capsules containing PEO as release modifier
Release of celiproplol from floating capsules containing 10% polyethylene oxide P1 (—♦—) and 12%, P2 (—■—).

Fig. 4: Release of celiprolol hydrochloride from floating capsule containing ethyl cellulose as release modifier
Release of celiprolol hydrochloride from floating capsules containing ethyl cellusose as release modifier. Formulations J1 (—♦—), J2 (—■—) and J3 (—▲—) contain ethyl cellulose 5%, 10% and 25%, respectively.

be less than 0.5 (0.438) it suggests that release from the optimized formulation follows fickian diffusion mechanism (fig. 8).

Stability studies revealed that the drug content in HBS capsule degraded by 0.76% in a period of 90 d. (fig. 9). Hence a shelf life of 1.9 years could be assigned to the above formulation. Dissolution profile for stability sample showed that there was no significant change in the release rate of the drug from optimized capsule kept on stability studies (fig. 10).
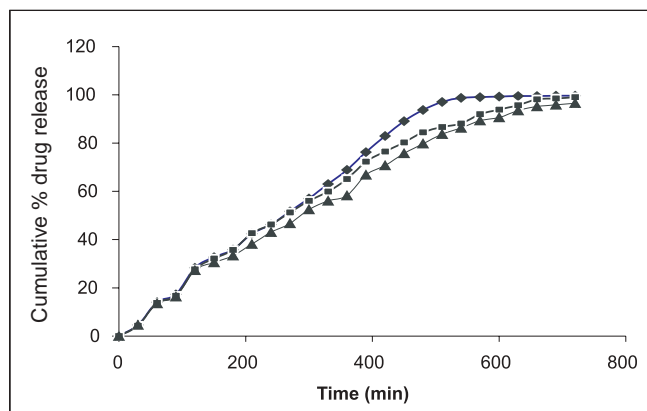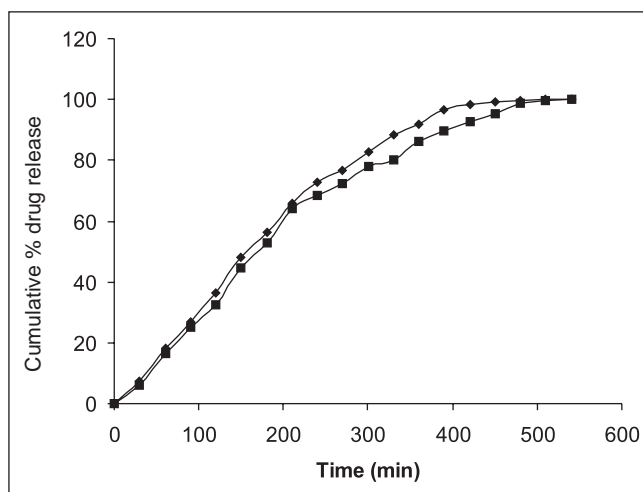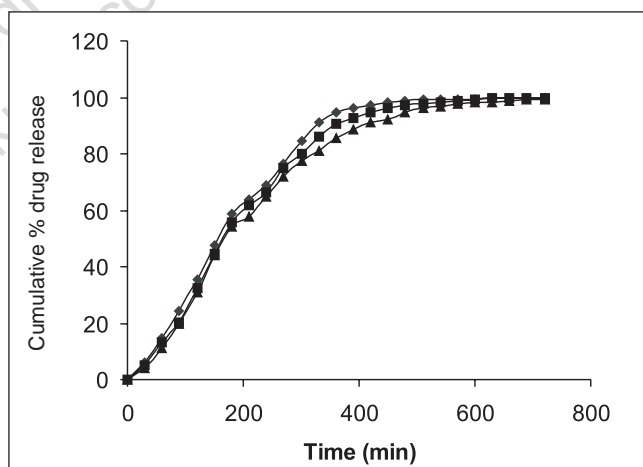
Fig. 2: Release of celiprolol hydrochloride from floating capsules containing liquid paraffin as release modifier
Release of celiprolol from floating capsules containing liquid paraffin at 1.0%, L1 (—♦—), 1.5% L2 (—■—) and 2.0% L3 (—▲—)

TABLE 3: RELEASE OF CELIPROLOL HYDROCHLORIDE FROM OPTIMIZED FLOATING CAPSULE

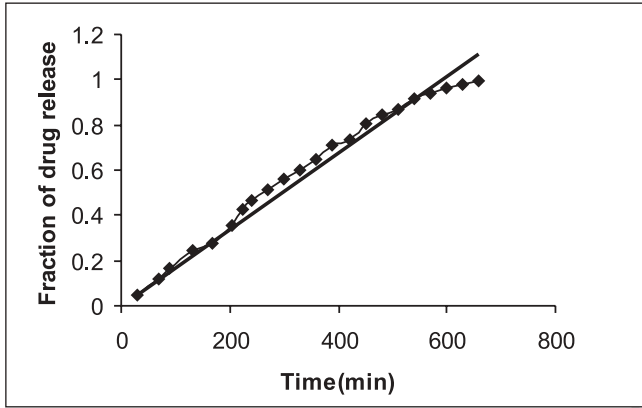| Release order/model	R (Coefficient of correlation)
Zero-order release model	0.976
First -order release model	0.841
Higuchi model	0.886

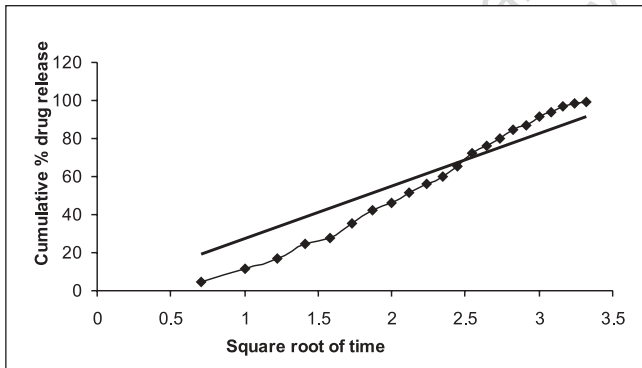**Fig. 5: Release of celiprolol hydrochloride from optimized floating capsule by zero order release model**

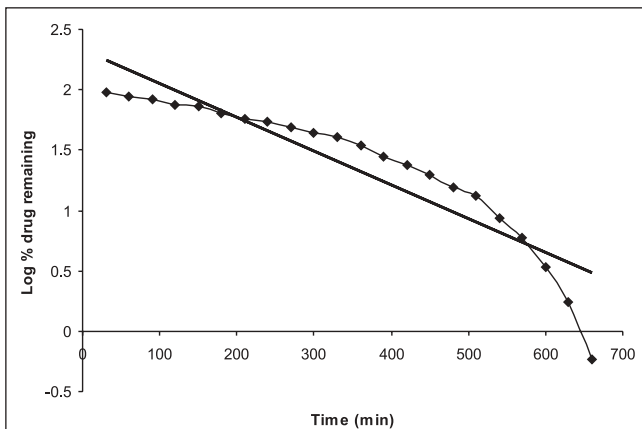**Fig. 6: Release of celiprolol hydrochloride from optimized floating capsule by Higuchi release model**

Fig. 7: Release of celiprolol hydrochloride from optimized capsule by first order release model
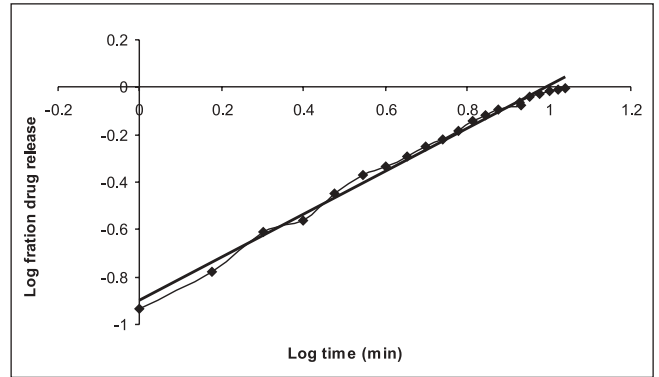

Fig. 8: Release of celiprolol hydrochloride from optimized floating capsule by K-Peppas model
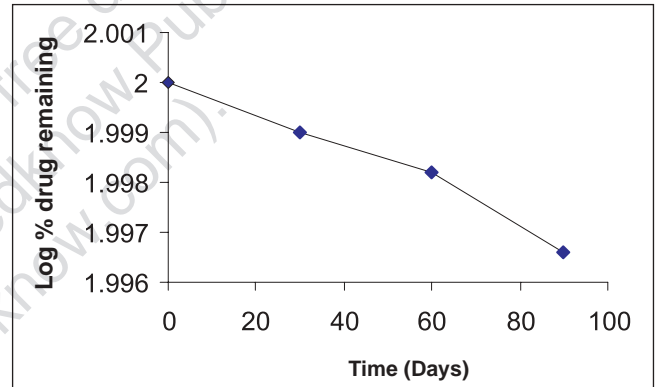

Fig. 9: Degradation kinetics of celiprolol hydrochloride in optimized formulation
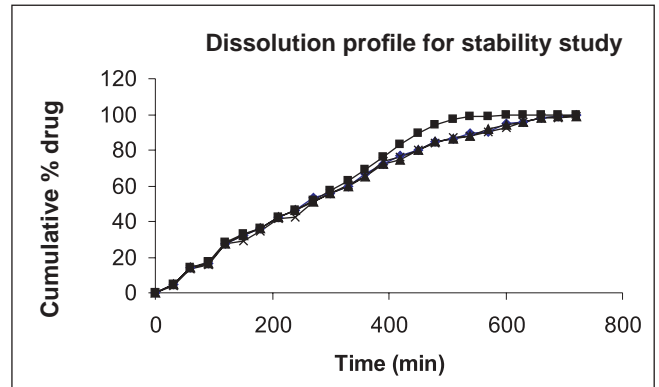

Fig. 10: Dissolution profile of celiprolol hydrochloride from stability study samples
Dissolution of celiprolol hydrochloride from stability samples kept for 0 days (—♦—), 30 days (—■—), 60 days (—▲—) and 90 days (—×—)

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