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Development of a new single unit dosage form of propranolol HCl extended release non-effervescent floating matrix tablets: *In vitro* and *in vivo* evaluation

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ABSTRACT

The objective of the present investigation was to develop extended release non-effervescent floating matrix tablets of Propranolol Hydrochloride (PPH) to extend the gastric residence time (GRT) and prolong the drug release after oral administration. Different viscosity grades of Hydroxypropyl methylcellulose (HPMC) polymers such as HPMC K4M, HPMC K15M and HPMC K100M were used as drug release retardants. Glyceryl behinate (Compritol 888 ATO) and Glyceryl monosterate (Precirol ATO 5) were used as low density lipids in order to get the desired buoyancy over a prolonged period of time. The drug excipients compatibility study was carried out by using Differential Scanning Calorimetry (DSC). All the formulations were prepared by direct compression technique. The prepared tablets were evaluated for their physical characters, *in vitro* drug release and *in vitro* buoyancy. The release and floating property depends on the polymer type, polymer proportion, lipid type and lipid proportions. The drug release profiles of all the formulations were subjected to Zero order, First order, Higuchi and Peppas kinetic models, and the optimized formulation (F7) followed the Peppas model (R^2= 0.987) with non-Fickian diffusion mechanism(n>0.5). The optimized formulation was subjected for *in vivo* radiographic studies in healthy human volunteers (n=3). These studies revealed a mean gastric residence time of 5±1.73 h (n=3).

INTRODUCTION

The oral route remains the preferred route for the administration of therapeutic agents because of the low cost of therapy and ease of administration leading to high levels of patient compliance. Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate (Chien, 1990). An important requisite for the successful performance of oral CRDDS is that the drug should have good absorption throughout the gastrointestinal tract (GIT) to ensure continuous absorption of the released drug (Ritschel and Kearns, 1999). A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular portion of the GIT only or are absorbed to a different extent in various segments of the GIT (Harder *et al.*, 1990; Rouge *et al.*, 1996).

Such drugs are said to have an *absorption window*. Drugs having site-specific absorption are difficult to design as oral CRDDS because only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption (Drewe *et al.*, 1992). After crossing the absorption window, the released drug goes to waste with negligible or no absorption. This phenomenon drastically decreases the time available for drug absorption after its release and jeopardizes the success of the delivery system.

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In this situation, design of CRDDS is to be modified in such a way that it has more residence time in stomach to release the drug before the absorption window. This type of design is called as gastroretentive drug delivery system (GRDDS) and provides the better absorption. Garg *et al.,* 2008 classified the GRDDS into four main classes: (i) floating systems (Xiaoqiang *et al.,* 2006), (ii) expandable systems (Deshpande *et al.,* 1997), (iii) bioadhesive systems (Chavanpatil *et al.,* 2006) and (iv) high density systems (Hwang *et al.,* 1998).

Floating systems are of two types: (A) effervescent systems, depending on the generation of carbon dioxide gas upon contact with gastric fluids, and (B) non-effervescent systems. The latter systems can be further divided into four sub-types, including hydrodynamically balanced systems (Seth, 1964), microporous compartment systems (Harrigan, 1977), alginate beads (Whitehead *et al.,* 1996) and hollow microspheres or microballons (Kawashima *et al.,* 1992). In addition, super-porous hydrogels (Chen *et al.,* 2000) and magnetic systems (Gröning *et al.,* 1998) were described.

Propranolol hydrochloride (PPH), is a non-selective beta-adrenergic blocking agent, has been widely used in the treatment of hypertension, cardiac arrhythmias and many other cardiovascular disorders. Its oral bioavailability is 15% to 23% and has half-life of 3 to 6 h (Williams and Temke, 2002). So, patients were routinely asked to take PPH for several times in a day. Such frequent drug administration may reduce patient's compliance and therapeutic efficacy.

To overcome these problems it is required to deliver the single dose for a prolonged period of time. Moreover, PPH shows maximum solubility at acidic pH (Shivanand *et al.,* 2010). Thus it is a suitable candidate for the development of gastroretentive drug delivery system.

MATERIALS

Propranolol HCl received as a gift sample from M/s. Aurobindo Pharma Ltd., Hyderabad, India. Hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M and HPMC K100M) were received from DOW chemical company, USA. Compritol 888 ATO and Precirol ATO 5 were received from Gattefosse, Germany. Microcrystalline cellulose, magnesium stearate and aerosil were purchased from S.D. Fine-Chem. Ltd., Mumbai, India. Hydrochloric acid is purchased from Merck specialties Pvt. Ltd., Mumbai.

METHODS

Drug-excipients compatibility study

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) experiments were carried out to find out the presence of any interaction among drug and the excipients (Vaghani *et al.,* 2010). Pure drug, 1:1 ratio of drug and polymer, and optimised formulation were subjected to the analysis. About 5-15 mg of sample to be analysed was taken in the pierced DSC aluminium pan and scanned in the temperature range of 50-300 °C. The heating rate was 10°C/min.; nitrogen served as purged gas and the system was cooled down by liquid nitrogen. The differential thermal analyser (DSC 822 e/200, Mettler Toledo, Switzerland) was used for this purpose.

Preparation of floating tablets of PPH

Floating tablets containing propranolol HCl (PPH) were prepared by direct compression technique. Polymers and floating aid ratios were taken as 1:1 and 1:3 (Table 1). PPH and all other ingredients are accurately weighed and sifted through sieve # 40. The PPH was well mixed with quantity of required polymers (HPMCK4M, HPMC K15M and HPMC K100M), floating aids (Compritol 888 ATO and Precirol ATO 5) and Avicel PH200 in geometric proportions. Then the blend was lubricated with the previously weighed and sieved magnesium stearate and aerosil. Finally about 130mg of the lubricated blend was subjected to compression by using 7mm circular standard flat faced punch on a 16 station rotary tablet punching machine (Cadmach, Ahmedabad).

Evaluation of floating tablets of PPH

Physical characteristics of the PPH floating tablets

Tablet thickness

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets of each formulation by using vernier calipers. The average thickness and standard deviation were calculated.

Weight variation

Twenty tablets from each batch were individually weighed in grams on an electronic balance (Shimadzu, AUX 220, Japan). The average weights and standard deviations were calculated and the results were expressed as compliance or non-compliance of set limits.

Table 1: Composition of Propranolol HCl floating matrix tablets (All ingredients in mg/tablet).

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	40	40	40	40	40	40	40	40	40	40	40	40
Compritol 888 ATO	30	30	30	-	-	-	15	15	15	-	-	-
Precirol ATO 5	-	-	-	30	30	30	-	-	-	15	15	15
HPMC K4M	30	-	-	30	-	-	45	-	-	45	-	-
HPMC K15M	-	30	-	-	30	-	-	45	-	-	45	-
HPMC K100M	-	-	30	-	-	30	-	-	45	-	-	45
Avicel PH 200	25.5	25.5	25.5	25.5	25.5	25.5	25.5	25.5	25.5	25.5	25.5	25.5
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium sterate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Total tablet weight	130	130	130	130	130	130	130	130	130	130	130	130

Tablet hardness

Tablet hardness was measured using a Pfizer hardness tester (Cadmach, CMTT R/1342, Ahmedabad). The crushing strength of the six tablets with known weight and thickness of all formulations were recorded in the range of 4-5 kg/cm^2 and the average hardness and standard deviation were reported.

Friability

Ten tablets were taken from each batch and weight was noted. These tablets were rotated at 25 rpm for 4 minutes in a friabilator (Electro Lab, EF2, Mumbai). The tablets were then de-dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets according to following equation.

$$\text{Percentage friability} = (W_1 - W_2) \times 100/W_1$$

Where, W1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Friability values below 1% are generally acceptable.

Estimation of Drug Content

The formulated PPH floating tablets were assayed for drug contents. From each batch of prepared tablets, six tablets (n=6) were taken randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred into a 100 ml volumetric flask, to this 100 ml of 0.1N HCl was added and then the solution was subjected to sonication for about 2 hours. The solution was filtered and suitable dilutions were prepared with 0.1N HCl. The absorbance of the samples was estimated using double beam UV-Visible spectrophotometer (Elico, SL210, Hyderabad) at 290 nm. The drug content was estimated using calibration curve of the drug.

In vitro buoyancy study

The in vitro buoyancy was determined by as per the reported method (Rosa *et al.,* 1994). Here, the tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT). And total duration of time for the dosage form to remain buoyant is called total floating time (TFT).

In vitro dissolution study

The release of PPH from the tablets was studied using USP 29 dissolution apparatus II. About 900 ml of 0.1N HCl (pH1.2) was used as dissolution medium. The temperature was maintained at 37±0.5 ^{0}C.

The rotation speed was 100 rpm. About 5 ml of aliquot was withdrawn at predetermined time intervals of for every 1 h up to 10 h. The medium was replenished with 5ml of fresh medium each time. Samples were analyzed by using double beam UV/visible spectrophotometer (Elico, SL210, Hyderabad) at 290 nm. The cumulative percentage of drug release was calculated by using standard calibration curve of PPH.

Mechanism of drug release and kinetics

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release the dissolution data was fitted into Zero-order (Chen and Hao, 1998), First order (Wagner, 1969), Higuchi (Higuchi, 1963), and Peppas release model (Korsmeyer et al,1983). The dissolution data obtained was plotted as cumulative percent drug release versus square root of time as per Higuchi equation as follow:

$$F = kt^{1/2}$$

Where 'F' is the fraction of drug released, 'k' is the release rate constant and t is the time.

The release data was further treated by the Peppas equation as follow:

$$F = kt^n$$

The equation was treated logarithmically to determine the value of release exponent, *n*; the value of *n* is indicative of mechanism of drug release. If 'n' is equal to 1, the release is zero order. The value of n is less than or equal to 0.5 then the release is best explained by Fickian diffusion, and is between 0.5 and 1 then the release is through anomalous diffusion or non-Fickian diffusion (Swellable & Cylindrical Matrix).

***In vivo* confirmation of buoyancy by using radiographic studies**

In vivo gastric retention time (GRT) was determined by X-ray technique in healthy human volunteers (n=3). The protocol of the radiographic studies on healthy human volunteers was approved by the Institutional Ethics Committee, KLR College of pharmacy, Paloncha, Khammam, India. For in vivo study, barium sulphate containing floating tablets were prepared by the same method as described in the formulation. In this study, half of the amount of PPH was replaced with barium sulphate ($BaSO_4$) and all other ingredients remained same. For in vivo retention study, the volunteers of 25-29 years age and 60-72 kg weight were used. The tablet was administered orally with a glass of water after overnight fasting. During the study they were not allowed to eat but the water was available *ad libitum.* X-ray photographs were taken at different time intervals such as 0.5, 3 and 6 h. The mean gastric residence time was calculated.

RESULTS AND DISCUSION

Drug-excipients compatibility study

The Drug excipients compatibility study was carried out by using DSC. The thermal properties of the drug and the mixture of drug and excipients are of important interest since this can help to assess the interaction among different components of the formulations. The DSC curve of pure drug (Figure 1a) showed a sharp endothermic peak at 167.9 ^{o}C. The mixture of drug, HPMC and Compritol 888 ATO showed a sharp endothermic peak at 166.2 ^{o}C (Figure 1b).

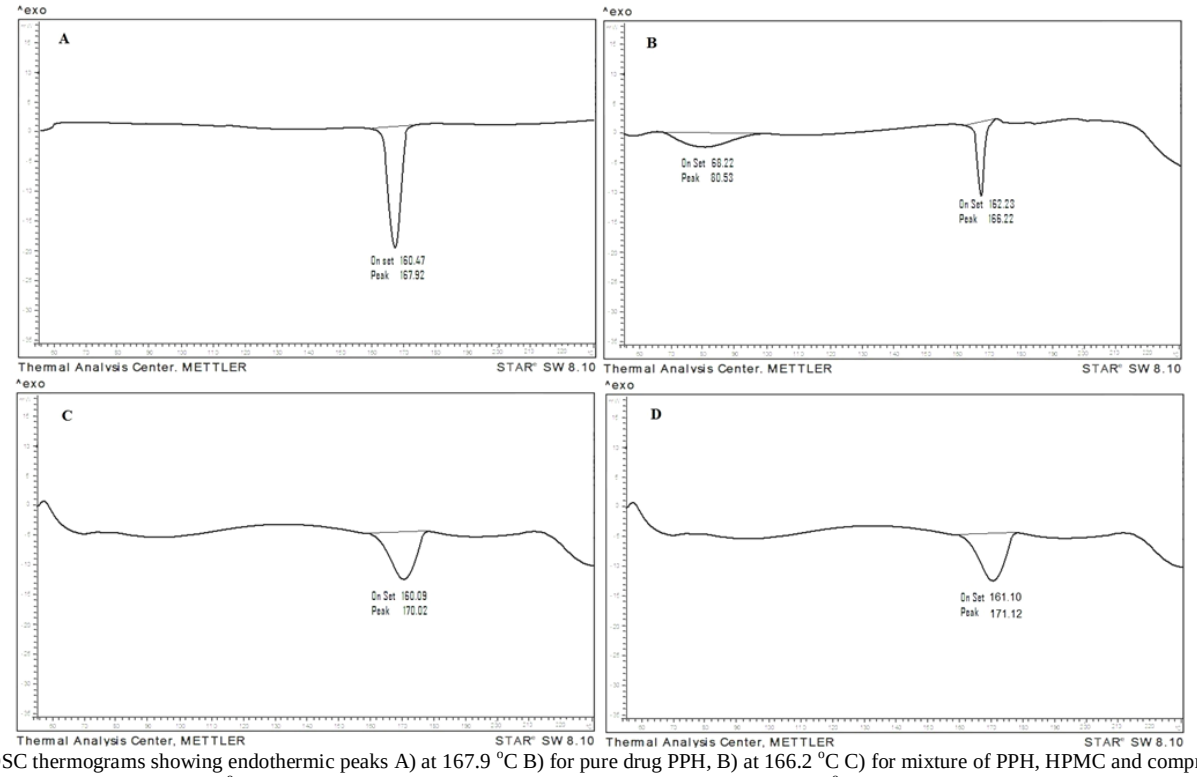

Fig. 1: DSC thermograms showing endothermic peaks A) at 167.9 ^{o}C B) for pure drug PPH, B) at 166.2 ^{o}C C) for mixture of PPH, HPMC and compritol ATO 888, C) at 170.0 ^{o}C D) for mixture of PPH, HPMC and precirol ATO 5 and D) at 171.1 ^{o}C for optimized formulation F7).

Table 2: Physical characters of prepared Propranolol HCl floating matrix tablets.

Formulation code	Thickness (mm) n = 10	Weight variation (mg), n = 20	Friability (%) n = 10	Hardness (kg/cm^2) n = 6	Drug content (%) n = 6	Floating time (h) n = 3	Matrix integrity
F1	3.16±0.19	129.4±1.6	0.26	5.1±0.5	97.3±0.3	>12	Good
F2	3.27±0.15	130.3±0.7	0.23	5.5±0.3	97.0±1.5	>12	Very good
F3	3.18±0.25	128.6±1.1	0.48	4.8±0.5	98.2±1.8	>12	Excellent
F4	3.12±0.34	129.5±0.5	0.51	5.0±0.2	98.1±1.6	>12	Good
F5	3.22±0.26	130.3±0.6	0.42	4.8±0.3	99.1±0.9	>12	Very good
F6	3.26±0.25	128.7±1.0	0.34	5.0±0.5	98.2±0.8	>12	Excellent
F7	3.22±0.25	130.8±0.7	0.52	5.2±0.4	99.1±0.5	>12	Good
F8	3.26±0.28	129.0±1.2	0.49	4.8±0.7	101.3±0.5	>12	Very good
F9	3.28±0.32	130.2±0.6	0.36	4.9±0.5	99.9±1.5	>12	Excellent
F10	3.18±0.22	129.8±0.8	0.39	5.0±0.4	99.2±0.5	>12	Good
F11	3.22±0.12	129.8±0.9	0.49	4.8±0.2	100.7±0.5	>12	Very good
F12	3.03±0.14	130.1±1.2	0.36	5.2±0.4	99.9±1.4	>12	Excellent

The Figure 1c suggested that mixture of drug, HPMC and precirol ATO 5 is having endothermic peak at 170.0°C which was well preserved with slight change in terms of broadening of peak towards the higher temperature. This minor change in the endotherm of drug could be due to the mixing of drug and polymer, which lowered the purity of each component in the mixture and may not necessarily indicate potential incompatibility. The DSC thermogram of optimized formulation F7 (Figure 1d) showed an endothermic peak of drug at 171.1°C which was well preserved with slight change in terms of broadening. From the results it was concluded that the drug was compatible with polymers and other excipients used in the formulation.

Physical characterization of the prepared PPH floating tablets

Post compression properties of prepared PPH floating tablets were shown in Table 2. The hardness of all the formulations was found to be in the range of 4.8±0.2 (F11) to 5.5±0.3 (F2) kg/cm^2. Tablet hardness imparts the compactness to the tablet.

The Thickness of all the formulations ranged from 3.03±0.14 (F12) to 3.28±0.32 mm (F9). Another measurement of tablet strength was friability, percentage weight loss in the friability test was found to be less than 1% in all the formulations. Percentage friability and weight variation passes the test as per standard pharmacopoeial limits.

The drug content of all the floating tablets contain PPH ranged from 97.0±1.5 (F2) to 101.3±0.5% (F12) indicating uniformity of drug content. All the physical properties like weight variation, thickness, hardness and friability of all formulations were complied with pharmacopoeial limits, so all the formulations were with the acceptable limits.

In vitro buoyancy studies

In order to develop the desired non-effervescent floating tablets of PPH, it was necessary to optimize both the floating properties and release rate of the drug, The compritol 888 ATO and precirol ATO 5 were used as low density lipid agents, which slow down the water diffusion inside the dosage form and provide a prolonged drug release which results floating of dosage form over a predetermined period of time. Floating lag time of all the formulations remains zero.

Because in all the formulations, we used only the low density lipid agents such as compritol 888 ATO and precirol ATO 5 as floating agents. Formulations F1 to F6 prepared with different grades of HPMC polymers and low density lipid agents in the ratio of 1:1. Further formulations F7 to 12 contain HPMC polymers and floating aids in the ratio of 3:1. Due to the low density the tablet remained buoyant. All the formulations remain buoyant for more than 12 h in dissolution medium. The in vitro buoyancy of formulations F2 and F7 were shown in Fig.2 and Fig.3 respectively.

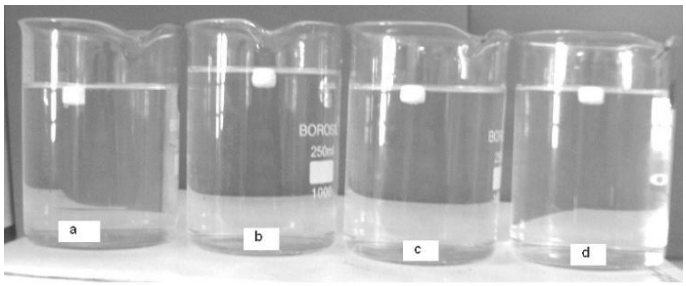

Fig. 2: In-vitro buoyancy of formulation F2 in 0.1 N HCl a) at 1 h b) at 4 h c) at 8 h and d) at 12 h.

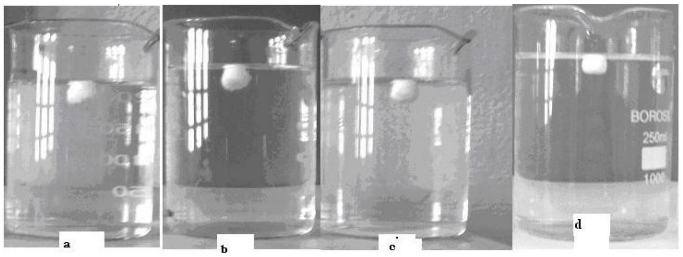

Fig. 3: In-vitro buoyancy of optimized formulation F7 in 0.1 N HCl a) at 1 h b) at 4 h c) at 8 h and d) at 12 h.

In vitro dissolution studies

The in-vitro dissolution testing was performed in 0.1N HCl and the results of the formulations were showed in Figure 4 and Figure 5. Polymer and floating lipid aid ratios were taken as 1:1 (F1 to F6) and 3:1 (F7 to F12).

Formulations F1-F6 prepared by using 1:1 ratio of HPMC polymer and floating aids. The cumulative drug release of formulation F1 was about 101±1.7 % in 8 h. The formulation F4 released about 102±2.1% of drug in 9 h. Further, formulations F7-F12 were prepared with HPMC and floating aid in the ratio of 3:1. The cumulative drug release was found to be in the range of 63.8±1.3 (F9) to 101±2.2% (F7).

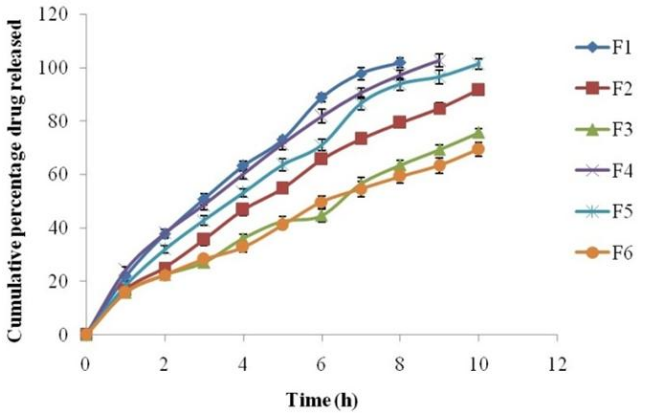

Fig. 4: Cumulative percentage release of PPH from floating matrix tablets containing 1:1 ratio of floating aids and different HPMC grade polymers (n=3, Mean±SD).)

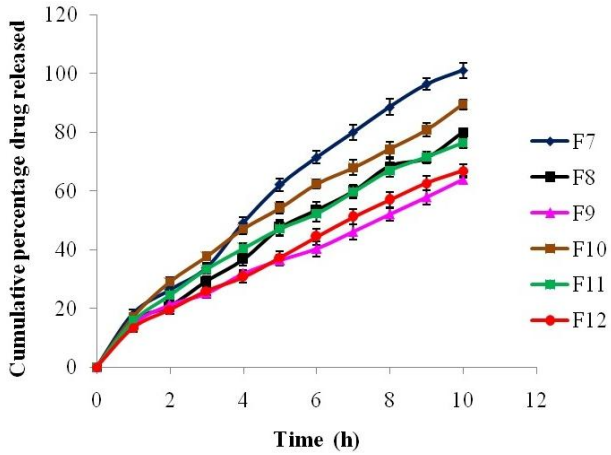

Fig. 5: Cumulative percentage release of PPH from floating matrix tablets containing 1:3 ratio of floating aids and different HPMC grade polymers (n=3, Mean±SD).

When floating tablets were exposed to dissolution medium, the medium penetrated into the free spaces, hydrated the polymer and lipid aid and get swells and it forms a gel consistency. Then from this the drug released slowly for the prolonged period of time. The cumulative percentage drug releases was shows in Figure 4 and Figure 5. The results obtained from the study, the most promising formulation was F7, because it released about 98.42±1.89% of the drug in 10h.

Mechanism of drug release and kinetics

The drug release data of PPH floating tablets were fitted into different kinetic models representing Zero order, First order, Higuchi and Peppas model to know the release mechanism. Formulations F1-F3, F5, F8 and F12 followed Zero order, whereas F4 and F10 Higuchi. Further F6, F7, F9 and F11 followed Peppas model. In all the formulations, the diffusion exponent value is greater than 0.5. The optimized formulation (F7) followed the Peppas model (R^2=0.987) with non-fickian mechanism. The correlation coefficients (R^2) of all the formulations were shown in Table 3.

Table 3: Results of correlation coefficients (R^2) and diffusion exponent (n) of release data of floating tablets of propranolol HCl by curve fitting method.

Formulation code	R^2				n
	Zero order	First order	Higuchi	Peppas	
F1	0.979	0.639	0.968	0.834	0.562
F2	0.984	0.710	0.965	0.956	0.539
F3	0.988	0.697	0.950	0.968	0.581
F4	0.971	0.635	0.982	0.882	0.613
F5	0.976	0.693	0.968	0.887	0.594
F6	0.980	0.684	0.970	0.992	0.589
F7	0.966	0.716	0.952	0.987	0.625
F8	0.989	0.715	0.956	0.952	0.522
F9	0.982	0.679	0.966	0.983	0.619
F10	0.978	0.682	0.979	0.950	0.599
F11	0.979	0.689	0.978	0.991	0.601
F12	0.991	0.719	0.957	0.989	0.584

In vivo radiographic studies

In vivo radiographic studies were conducted on 3 healthy male human volunteers to find out the gastric residence time (GRT) of the tablets. The tablets prepared with combination of HPMC K100 M and compritol 888 ATO (F7) was tested for the in vivo gastric residence time. The tablets were prepared with same compression force. All the physical properties were within the range.

The tablets were given to the volunteers with a glass of water and standard diet was provided. X-rays were taken at different time intervals such as 0.5, 3 and 6 h. The X-ray images showing the tablets remained in stomach for about 6 hours in two volunteers and 3 hours in one volunteer indicating the good floating property (Fig. 6). These studies revealed that the mean GRT was found to be 5 ± 1.73 h.

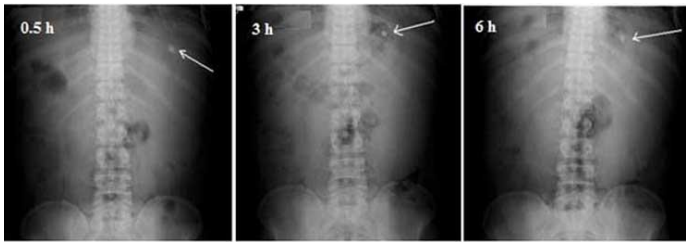

Fig. 6: X – ray image showing the presence of BaSO4 loaded Propranolol HCl floating tablets prepared with HPMC K100 M and Compritol at A) 0.5 h, B) 3 h and C) 6 h (The tablet position in the stomach is indicated with an arrow).

CONCLUSION

The non-effervescent floating tablets of PPH were developed by using HPMC K4M, HPMC K15M and HPMC K100M as release retardants. The compritol 888 ATO and precirol ATO 5 were used as floating aids. The results obtained from the drug-excipient compatibility study, there was no interaction between drug and excipients used in the formulations. The optimized formulations F7 was selected based on its good physical characteristics, in vitro buoyancy and sustained drug release. Further, the formulation F7 followed Peppas model with non-Fickian diffusion release mechanism. The radiological study of formulation F7 on healthy human volunteers revealed a mean gastric residence time of 5±1.73h. The results obtained from the study, it was concluded that the formulation retained in the stomach for a longer period of time and sustained the drug release. Hence, this dosage form was helpful in improving absorption of PPH.

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