IJPSR (2013), Vol. 4, Issue 12 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 02 July, 2013; received in revised form, 14 August, 2013; accepted, 16 November, 2013; published 01 December, 2013

DESIGN AND FABRICATION OF GASTRORETENTIVE BILAYER FLOATING TABLET OF PROPRONOLOL HCl USING NATURAL POLYMER

P.H. Wakde*, R.H. Kasliwal and S.B. Mane

J.L. Chaturvedi College of Pharmacy, Electronic Zone Building, MIDC, Hingna Road, Nagpur- 440 016, Maharashtra, India

Keywords:

Bilayer floating tablet, Propranolol hydrochloride, Guar gum, Pectin, Sodium bicarbonate, Citric acid

Correspondence to Author:

P.H. Wakde

J. L. Chaturvedi College of Pharmacy, Electronic Zone Building, MIDC, Hingna Road, Nagpur-440016, Maharashtra, India

E-mail: preetiwakde64@gmail.com

ABSTRACT: The purpose of this study is to prepare a bilayer gastro retentive tablet of Propranolol HCl using direct compression technology and optimize the type and concentration of polymer to give maximum retentive effect with good drug release profile. Propranolol hydrochloride, a nonselective β-adrenergic blocker having short half-life (3-4 hr) and first pass metabolism favors for sustained release dosage form. In this study, a bilayer tablet was prepared which contains an immediate release portion and a floating layer. Gaur gum, Pectin were used as gel forming agents either alone or in combination, Sodium bicarbonate and citric acid as gas generating agent, superdisintegrant sodium starch glycolate for the fast release layer. The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 14 h from the sustaining layer of tablets. The bilayer tablets were characterized by lag time, floating time, weight variation, drug content and dissolution profile. Best Formulation BFT1 [Gaur gum-Pectin (2:1)] shows lag time of 8.0min, floating time of 14 h and drug release of 98.97±0.81%. The optimized formulation was subjected to stability studies at 40^{o}C and 75% RH for period of two months. Short term stability studies showed good result.

INTRODUCTION: The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within thegastrointestinal tract (GIT) until all the drug is completely released at the desired period of time. Indeed, gastric drug retention has received significant interest in the past few decades [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(12).123-36

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.4(12).123-36

Most of the conventional oral delivery systems have shown some limitations related to fast gastric-emptying time [2]. One of the novel approaches in the area of oral sustained release drug delivery is gastroretentive drug delivery system (GRDDS).

Drugs those are having a narrow absorption window and having more solubility in gastric region are suitable candidates for GRDDS. GRDDS prolongs the retention time of dosage forms in the stomach or upper gastrointestinal tract, as to improve solubility, bioavailability and the therapeutic efficacy of the drugs. Several techniques have been proposed to increases the gastric residence time of dosage forms such as buoyancy or floating system, hydrodynamically

balanced system, expanding or swelling system, bio/mucoadhesive system, sedimentation or high density system, geometry or modified shape system may also use to increase gastric residence time.

Propranolol hydrochloride, a nonselective β-adrenergic blocker used widely in the treatment of hypertension, angina pectoris, pheochromocytoma and cardiac arrhythmias. It is almost absorbed from gastrointestinal tract but subjected to hepatic tissue binding and first pass metabolism. Conventional form available is administered orally, in doses of 40 mg to 80 mg twice a day. But due to raising problems with the conventional tablet resulting in fluctuations of drug plasma levels and also the drug has short biological half-life (3-4 hr) and first pass metabolism favors for sustained release dosage form. In recent years slow and sustained release formulation of propranolol hydrochloride has become available with claims that these formulations maintain beta adrenoreceptor blockade throughout a 24 hr period and enable the drug to be given once daily.

In the present study, we aimed to design and fabricate a quick/slow delivery dosage form as a bilayer floating tablet of Propranolol hydrochloride consisting of two layers i.e. fast releasing layer and sustain release layer (floating layer). This type of system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release floating phase to avoid repeated administration.

Bilayer floating tablets were formulated to get initial burst effect of propranolol hydrochloride to provide the loading dose followed by sustained release for 16 hr as an alternative to conventional dosage form. Proper combination of the quick and sustained release floating phases using natural polymers would allow the optimization of the fast and slow-dose fractions as a function of the drug pharmacokinetics and metabolism.

Advantages of Bilayer Floating Drug Delivery System [3]:

1. These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.
2. The fluctuations in plasma drug concentration are minimized, and concentration- dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.
3. The efficacy of the medicaments administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medicaments.
4. Complete absorption of the drug from the floating dosage form is expected even at the alkaline pH of the intestine. The dissolution of the drug in gastric fluid occurs and then the dissolved drug is available for absorption in the small intestine after emptying of the stomach contents.
5. Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
6. Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric-coated LASIX- long product (29.5%).

MATERIALS AND METHODS: Propranolol hydrochloride was obtained as a gift sample from Cipla Pharmaceuticals, Mumbai. Guar gum, Pectin, Sodium starch glycolate, Sodium bicarbonate, Citric acid and Poly vinyl pyrrolidone K30 were purchased from Loba Chemicals, Mumbai.

All the chemicals and reagents required for the present work are of analytical grade.

Preparation of Bilayer floating tablets: Bilayer floating tablet contains two layers i.e. immediate release layer and floating sustained release layer.

Formulation of the immediate release tablet: Various formulation batches of Propranolol hydrochloride were prepared and those formulations showing good results were used for the preparation of immediate release tablet. Propranolol hydrochloride and lactose was mixed properly with disintegrant in a mortar according to the composition given in **table 1**.

The resulting mixture or blend was passed through sieve (40 #). Accurately weighed 120 mg of powder blend fed manually into each die of 8 station tablet machine and compressed by using 11 mm flat faced punch by direct compression method. Compression force was kept constant for all formulations. Prior to the compression, the blends of all batches were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibililty index and Hausner's ratio [4].

Formulation of Floating Sustained Release Tablets: Accurate quantity of drug and polymers were weighed according to the formula shown in table 2 and mixed well. The mass was prepared using 5% w/v solution of PVP K30 in isopropyl alcohol as granulating fluid. Then the mass was passed through 16 # sieve and granules were allowed to dry in oven at 40ºC for 30 minutes. Dried granules were passed through 12 # sieve. Then 10% fines were added in the granules and mixed with magnesium stearate and talc for 5 min and processed for compression by using 11 mm round flat faced punches of tablet punching machine. Compression force was kept constant for all formulations. Prior to the compression, the granules of all batches were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio [5, 6].

Formulation of Bilayer Floating Tablets: Bilayer floating tablets were prepared by using optimized immediate release layer (**A2**) and floating sustained release layer (**F6**). Accurately weighted 120 mg of immediate release layer and 380 mg of floating sustained release layer individually. Bilayer floating tablets were prepared by direct compression method according to formula given in **table 3**.

Initially sustained release granules were fed manually into the die of 11 mm round flat faced punches of tablet punching machine (8 Station D-tooling, Karnavati-Rinek Mini Press-II) and then compressed at low compression force to form uniform layer. Subsequently immediate release powder blend was added over that layer and completely compressed on tablet punching machine by using 11 mm round flat faced punch.

TABLE 1: FORMULATION OF IMMEDIATE RELEASE TABLET

Ingredients (mg/tablet)	Formulation Code	
	A1	A2
Propranolol hydrochloride	40	40
Sodium starch glycolate	10	12
Lactose	66	64
Magnesium stearate	2	2
Talc	2	2
Total weight (mg)	120	120

TABLE 2: FORMULATION OF FLOATING SUSTAINED RELEASE TABLET

Ingredients (mg/tablet)	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Propranolol hydrochloride	40	40	40	40	40	40	40	40
Guar gum	40	40	80	-	-	80	120	80
Pectin	40	-	-	40	80	40	40	40
Citric acid	25	25	25	25	25	25	25	35
Sodium bicarbonate	75	75	75	75	75	75	75	85
PVP K30	50	50	50	50	50	50	50	50
Microcrystalline cellulose	130	130	90	90	50	90	10	30
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10
Total weight (mg)	380	380	380	380	380	380	380	380

TABLE 3: FORMULATION OF BILAYER FLOATING TABLET

Ingredients (mg/tablet)	Formulation Code BFT1	
Propranolol hydrochloride	40	Immediate Release layer
Sodium starch glycolate	12	
Lactose	64	
Magnesium stearate	2	
Talc	2	
Propranolol hydrochloride	40	Sustained Release layer
Guar gum	80	
Pectin	40	
Citric acid	25	
Sodium Bicarbonate	75	
PVP K30	50	
Microcrystalline cellulose	50	
Magnesium stearate	10	
Talc	10	
Total weight (mg)		**500**

Drug Excipient compatibility study: The excipient compatibility of drug and the polymer was studied using their physical mixture in ratio 1:1. The mixtures were prepared by triturating the drug with guar gum and pectin. Mixtures were stored for a week at 40ºC temperature. FT-IR and DSC studies were done to investigate the drug-excipients interactions [7].

Precompression studies: The flow properties of immediate release blend and floating sustained release granules (before compression) were characterized in terms of loose bulk density, Tapped bulk density, Angle of repose, Carr's index & Hausner's ratio.

Loose bulk density: It is indicative of the packing of particles and as such is greatly influenced by the size of granules. Loose bulk density of tablets was determined by pouring gently 2g of the powder blend from each formula through a glass funnel into 10 ml measuring cylinder. The volumes occupied by the samples were noted. Loose bulk density was expressed in (g/ml) and calculated by using following formula:

$$LBD = \frac{\text{Weight of powder blend}}{\text{Untapped volume of the packing}}$$

Tapped bulk density: It was determined by pouring gently 2 g of the powder blend from each formula through a glass funnel into 10 ml measuring cylinder. The cylinder was tapped gently on to a hard surface from the height of 2 inches at second interval until a constant volume was obtained. Volume occupied by the sample after tapping was noted. Tapped density was expressed in (g/ml) and calculated by using following formula:

$$TBD = \frac{\text{Weight of powder blend}}{\text{Tapped volume of the packing}}$$

Angle of Repose: The angle of repose is one of the simplest techniques used to determine the flow ability of powder materials. The angle of repose was determined by the fixed height method. The height of funnel was maintained at 2 cm and the average internal diameter of the funnel stem was 6mm. Granules from each formula were poured through the funnel till the pile touches the tip of funnel. A rough circle was drawn around the pile and radius was measured. The angle of repose was expressed in (θ) and determined by using following formula:

$$\tan \theta = h/r, \text{ or } \theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose, h = height of powder cone, r = radius of the powder cone

Compressibility Index / Carr's Index: Compressibility index is a measure of flow rate of powder and measure of relative importance of inter particulate interactions. The flow ability is related to Carr's Index. It is related to the relative flow rate, cohesiveness and particle size.

Carr's Index=

$$\frac{\text{Tapped Bulk Density - Loose Bulk Density}}{\text{Tapped Bulk Density}} \times 100$$

Hausner's ratio: Hauser's ratio is indicative of flow property. It is derived property from bulk and tapped density. Lower Hausner's ratio indicates better flow whereas higher ratio indicates poor flow of granules. In Hausner's ratio the values less than 1.25 indicate good flow. Values greater than 1.25 indicates poor flow and values between 1.25 and 1.5 indicates need to be added glidant normally improves flow. Hauser's ratio is calculated by the following formula:

$$\text{Hausner's ratio} = TBD/LBD$$

Postcompression studies:

Organoleptic properties: The tablets were evaluated for their organoleptic properties such as colour, appearance and surface texture.

Weight variation: It was performed as per the method given in the Indian Pharmacopoeia (1996). 20 tablets were selected randomly from the formulation and the average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. Following are the formulas:

$$\text{Average weight of tablet} = \frac{\text{Total weight of tablet}}{\text{Number of tablet}}$$

%Deviation=

$$\frac{\text{Average Weight} - \text{Individual Weight}}{\text{Average Weight}} \times 100$$

Hardness: This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this five tablets were selected at random and the hardness of each tablet formulation and marketed tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Friability: The friability test was carried out to evaluate the hardness and stability instantly. The tablet friability was measured according to the Indian Pharmacopoeia. In this, 10 tablets were weighed initially and put in a rotating apparatus drum (Roche friabilator). Then, they are subjected to fall from 6 inches height. After completion of 100 rotations, loose dust particles were removed from the tablets after the test and the tablets were again weighed. The tablet friability was expressed in (%).

The percentage friability of the tablet formulation was calculated by using following formula is given below:

%Friability=

$$\frac{\text{Weight of Initial Tablets} - \text{Weight of Final Tablets}}{\text{Weight of Initial Tablets}} \times 100$$

Tablet Thickness and Size: Thickness and size of tablets were important for uniformity of tablet size. Thickness and size of the tablet formulation was measured using Vernier's calliper and is expressed as (mm).

***In-vitro* disintegration time:** The disintegration time for all immediate release formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The medium, simulated gastric fluid was maintained at a temperature of 37°± 2°C and time taken for the entire tablet to disintegrate completely was noted. Average of three determinations was taken [8].

Drug content uniformity: Ten tablets were finely powdered and an amount equivalent to 40 mg of propranolol hydrochloride was accurately weighed and transferred to a 100 ml volumetric flask. Then 70ml methanol was added. The flask was shaken for 10 minutes. Finally, the volume was made upto the mark with methanol. The mixture was then filtered and 1 ml of the filtrate was suitably diluted with methanol to obtain a solution containing about 40 µg ml^{-1} of propranolol hydrochloride and analyzed for Propranolol hydrochloride content at 290 nm using a double beam UV/Visible and methanol as a blank [5].

***In Vitro* Buoyancy studies:** The *in vitro* buoyancy was determined by the floating lag time. The tablets from each formulation (F1 to F8) were placed in 250-ml beaker containing 200ml of 0.1 N HCl. The time required for the tablet to rise to the surface for floating were determined as the floating lag time and further floating duration of all tablets were determined by visual observation[9].

Floating lag time : The tablet was placed in 250ml beaker and the time taken to float on the 200ml of 0.1 N HCl was noted.

Floating time: The tablet was placed in 250ml beaker and the total time duration of the tablet to float on the 200ml of 0.1 N HCl was noted.

***In-vitro* drug release study of Bilayer Floating Tablet:** *In-vitro* drug release of propranolol HCl was determined using a USP, 8 stage dissolution rate test apparatus II (Paddle method) (Veego

Scientific) at 50 rpm. The dissolution rate was studied using 900 ml of 0.1 N hydrochloric acid (pH 1.2). The temperature was maintained at 37±0.2ºC. The sample (5 ml) was withdrawn at different time intervals, i.e. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 60, 120, 180, 240, 300, 360, 420, 480, 540, 600, 660, 720, 780 and 840 minutes, filtered through Whatmann filter paper and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for propranolol hydrochloride content at 290 nm [10, 11, 12, 13].

Kinetics of *In-vitro* Drug Release: To study the release kinetics of *In-vitro* drug release of propranolol HCl, data was applied to kinetic models such as zero order, first order, Higuchi, Hixon–crowell and Korsemeyer-Peppas. The drug release data was evaluated by model - dependent (curve fitting) using PCP Disso v3 software and model with the higher correlation coefficient was considered to be best model. In order to know the drug release mechanism the data was further analyzed by Korsmeyer Peppas equation and the value of 'n' i.e. release exponent was calculated. The n value is used to interpret the release mechanism[14].

i) Zero order pattern:

$$C = K_0 t \quad \rightarrow \text{eq}^n (1)$$

Where, K_0 is the zero order rate constant (concentration/time) and t is the time (hrs).

ii) First order pattern:

$$\text{Log } C = \text{Log } C_0 - Kt / 2.303 \quad \rightarrow \text{eq}^n (2)$$

Where, C_0 is the initial concentration of drug, t is the time (hrs) and K represents first order rate constant.

iii) Higuchi model:

$$Qt = Kt^{1/2} \quad \rightarrow \text{eq}^n (3)$$

Where, Qt is the amount of released drug in time 't' and K is kinetic constant.

iv) Korsemeyer – Peppas model:

$$Mt / M\infty = Kt^n \quad \rightarrow \text{eq}^n (4)$$

Where, Mt is the amount of released drug at time 't', M∞ is the overall amount of the drug (whole dose) released after 12 hrs, K represents diffusional characteristic of drug/ polymer system constant and n is the diffusional or release exponent that characterizes the mechanism of release of drug.

The value of 'n' for a tablet, n = 0.5 for Fickian diffusion, n = 0.5 to <1 for Anomalous transport, n = 1.0 for Case II transport and n = Higher than 1.0 for Supercase II transport.

Accelerated Stability Study: In the present study, accelerated stability studies were carried out at 40°C and 75±5% relative humidity for a specific time period of 2 months for Optimized formulation BFT1.

For the accelerated stability study, the tablets were sealed in aluminiun packaging coated inside with polyethylene. These sample containers were placed in desiccators maintained at 40°C temperature and 75±5% relative humidity.

Note: Saturated solution of sodium chloride at 40°C yields 75% relative humidity.

The samples were withdrawn at the end of 15, 30, 45 and 60 days interval and evaluated for physical parameters, drug content and *in vitro* drug release [15].

RESULTS AND DISCUSSION:

Drug- Excipient compatibility study: FT-IR and DSC studies of pure drug, polymers and drug-polymer mixture were done separately to investigate the drug-excipients interactions.

FT-IR spectrum: The FT-IR spectrum was measured in the solid state as potassium bromide dispersion. The FT-IR spectrum of pure propranolol HCl and the mixture of propranolol HCl, guar gum and pectin are presented in **fig. 1 and fig. 2** respectively.

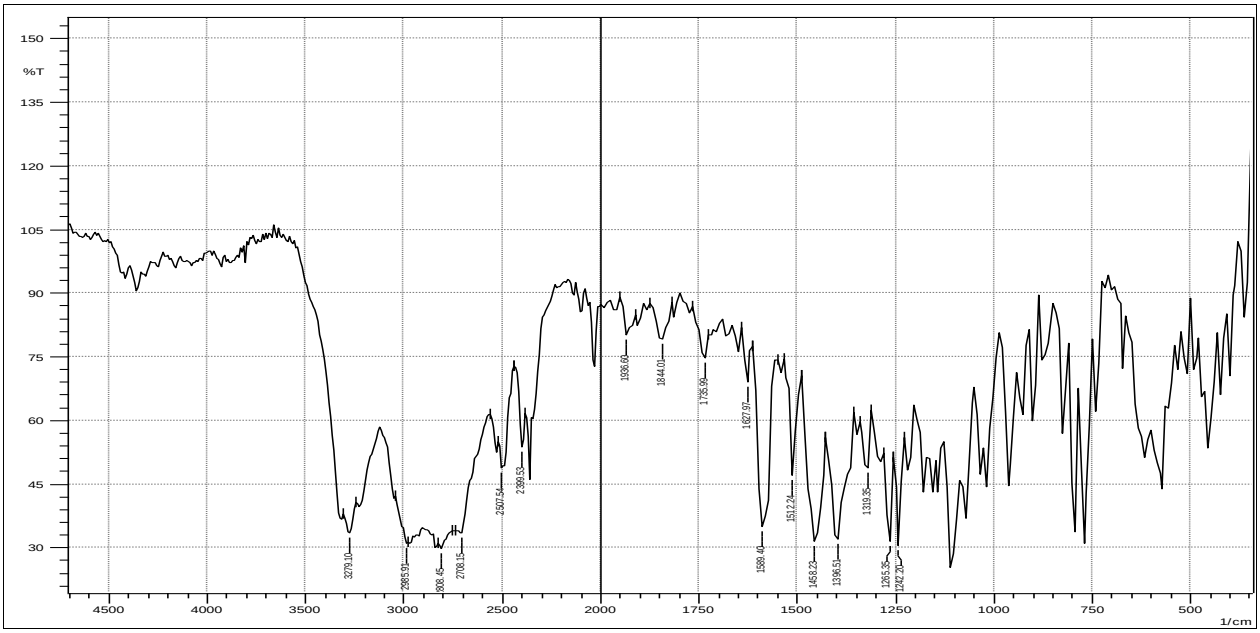

FIG. 1: FT-IR SPECTRUM OF PROPRANOLOL HCl

TABLE 4: INTERPRETATION OF IR SPECTRUM OF PROPRANOLOL HCl

Peak observed (cm^{-1})	Interpretation
3279.1	Secondary amine –NH stretching
2985	C–H stretching
1589	Aryl C ¼ C stretching
1242	Aryl O–CH2 asymmetric stretching
1030	Aryl O–CH2 symmetric stretching
798	Peak due to alpha-substituted naphathalene

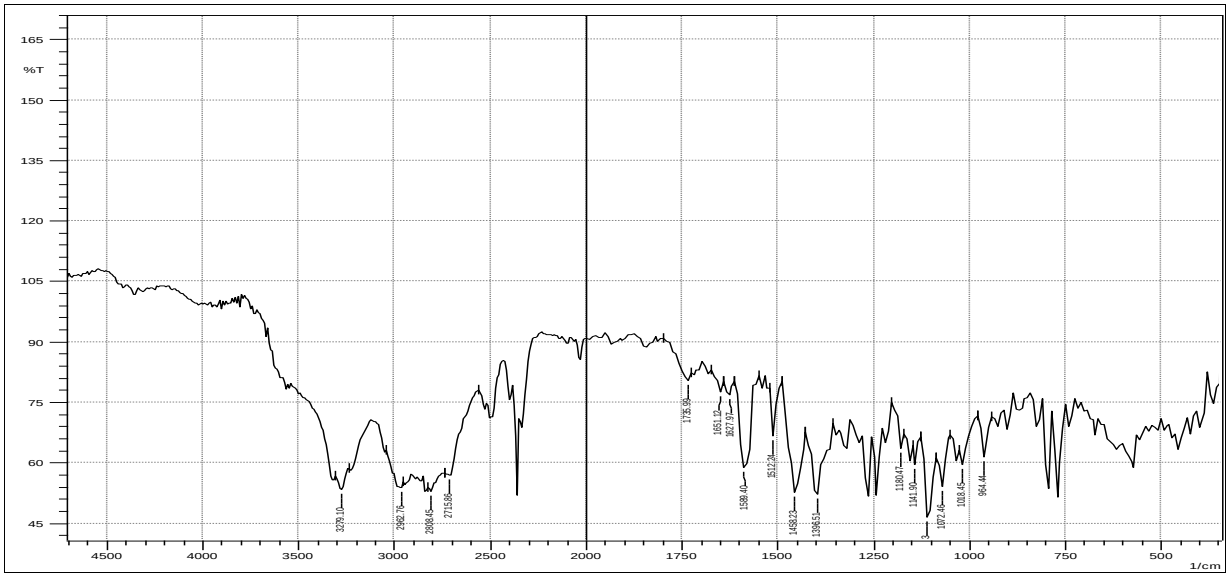

FIG. 2: FT-IR SPECTRUM OF PROPRANOLOL HCl + PECTIN + GUAR GUM

The FT-IR spectrum of drug and polymers revealed that, the major frequencies of functional groups of pure drug remain intact in the mixture containing different polymers. Hence, there is no interaction between the drug and polymers used in the study.

Differential Scanning Calorimetry (DSC): DSC thermogram of pure Propranolol Hydro-chloride and the mixture of propranolol HCl, guar gum and pectin were recorded on a Shimadzu TA60 thermal analyzer. The DSC thermogram of propranolol HCl and the mixture of propranolol HCl, guar gum and pectin are presented in **fig. 3 and fig. 4** respectively.

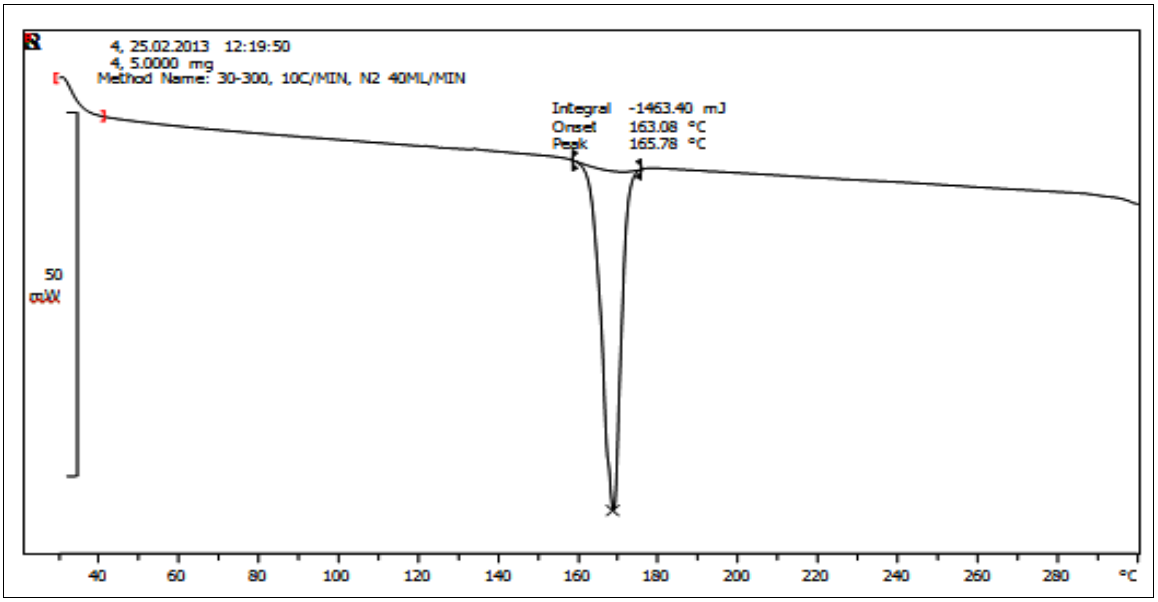

FIG. 3: DSC THERMOGRAM OF PROPRANOLOL HCl

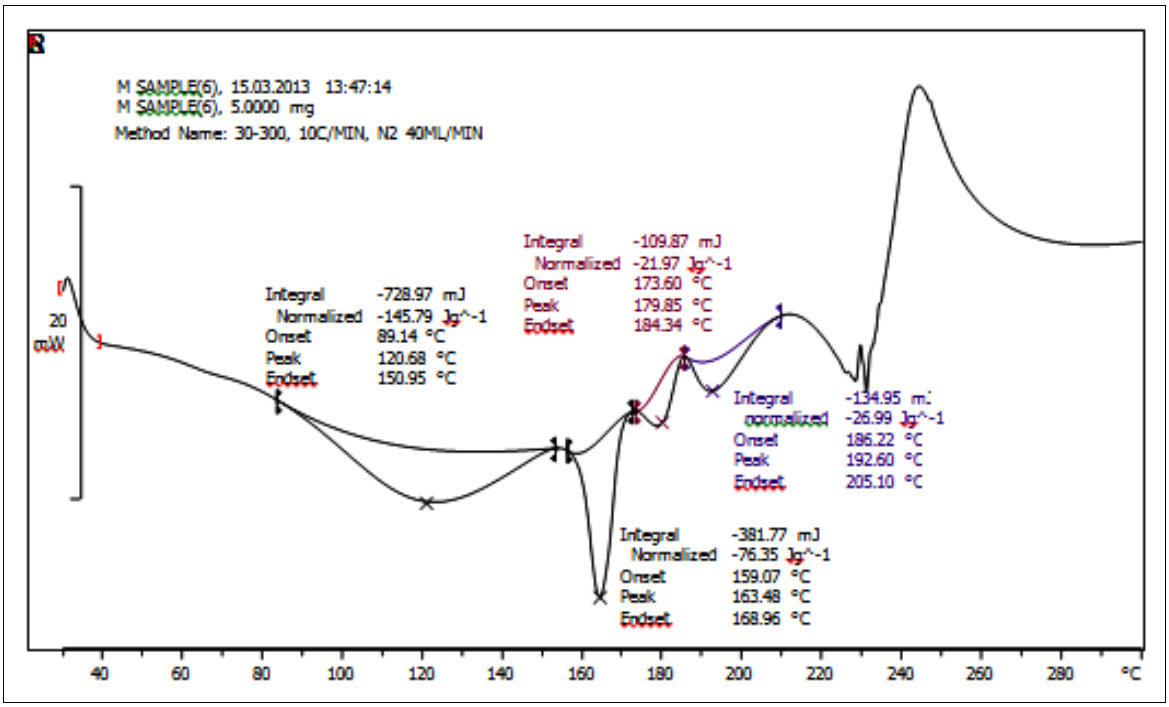

FIG. 4: DSC THERMOGRAM OF PROPRANOLOL HCL + PECTIN + GUAR GUM

DSC thermogram showed endothermic peak at 165.78^{o}C which corresponds to melting point of propranolol hydrochloride.

DSC thermograms of propranolol HCl shows sharp endothermic peak at 165.78^{0}C, indicating the melting point of stable crystalline drug. However, the DSC thermograms of mixture of propranolol HCl with pectin and guar gum shows sharp endothermic peak at 163.48^{o}C.

These thermograms indicated that no significant change in peak shape, area and no shift of peak were found. Therefore, this study revealed that there were no interaction between the drug and polymer or little interaction because pectin and guar gum are hydrocolloids and they do not melt and not give the sharp peak.

Pre compression parameters for Immediate Release Powder Blend: The immediate release powder blend shows good flowing property. Results are shown in **Table 5**.

TABLE 5: PRE COMPRESSION PARAMETERS FOR IMMEDIATE RELEASE POWDER BLEND (Mean±S.D., n=3)

Parameters	Formulation Code	
	A1	A2
Angle of repose(º)	32.46±1.26	31.31±1.18
Bulk density (g/ml)	0.549±0.0053	0.551±0.0072
Tapped density (g/ml)	0.750±0.010	0.760±0.014
% Compressibility	26.755±0.4038	27.520±0.3956
Hausner´s ratio	1.363±0.0085	1.137±0.0069

Post compression parameters for Immediate Release Tablet: Prepared immediate release tablets were evaluated for post compression parameters. Results are shown in **Table 6**.

TABLE 6: POST COMPRESSION PARAMETERS FOR IMMEDIATE RELEASE TABLET (Mean±S.D., n=3)

Parameters	Formulation Code	
	A1	A2
Weight Variation (mg) (Mean ± SD, n=20)	120 ± 1.9	120 ± 2.1
Thickness (mm) (Mean ± SD, n=5)	1.41±0.018	1.39±0.014
Hardness (Kg/cm^2) (Mean± SD, n=4)	3.25 ± 0.263	3.10 ± 0.210
Friability (%)	0.260 ± 0.006	0.254 ± 0.0059
Disintegration Time (sec)	49 ± 2	44 ± 1
% Drug content	99.71 ± 0.180	99.83 ± 0.128

All the batches pass the pharmacopoeial limits.

Precompression parameters of sustained release granules: The results for precompression parameters of sustained release granules are shown in **Table 7**.

TABLE 7: PRE COMPRESSION PARAMETERS FOR SUSTAINED RELEASE GRANULES (MEAN±S.D., N=3)

Formulation Code	Parameters				
	Angle of Repose (º)	Bulk Density (g/ml)	Tapped Density (g/ml)	% Compressibility	Hausner´s ratio
F1	27.64±0.34	0.51± 0.15	0.63± 0.16	18.51±0.28	1.22±0.02
F2	26.89±0.28	0.53±0.17	0.61±0.09	13.11±0.15	1.15±0.04
F3	26.56±0.26	0.55±0.19	0.66±0.06	16.66±0.52	1.20±0.05
F4	26.78±0.25	0.50±0.13	0.62±0.07	14.51±0.34	1.24±0.03
F5	23.14±0.11	0.46±0.12	0.54±0.22	14.81±0.39	1.17±0.08
F6	21.70±0.09	0.48± 0.11	0.56± 0.18	14.28±0.12	1.16±0.07
F7	24.53±0.16	0.44± 0.11	0.51± 0.30	13.72 ± 0.18	1.15±0.02
F8	25.72±0.15	0.48± 0.15	0.56± 0.13	14.83 ± 0.41	1.16±0.01

Precompression parameters of sustained release granules of Propranolol HCl showed good compressibility and flow property. (Angle of repose between 21 to 27 indicates very good flow property).

Post compression parameters of sustained release tablets: Prepared floating sustained release tablets were evaluated for post compression parameters. Results are shown in **Table 8**.

Buoyancy study of floating sustained release tablets: Buoyancy studies of all the formulation batches were done to determine the floating behaviour of the floating sustained release tablets. Results are shown in **Table 9**.

Floating lag time and further floating duration of all tablets was determined by visual observation. In **F6** formulation the floating lag time achieved at 110 sec. and total duration floating time more than 14 hrs were observed.

***In-vitro* drug release study of immediate release tablet:** *In-vitro* drug release data shown in **Table 10 and Fig. 5**.

TABLE 8: POST COMPRESSION PARAMETERS FOR FLOATING SUSTAINED RELEASE TABLETS (Mean±S.D., n=3)

	Parameters

Formulation Code	Weight Variation (mg) (Mean±SD, n=20)	Thickness (mm) (Mean±SD, n=5)	Hardness (kg/cm^2) (Mean±SD, n=4)	Friability (%)	%Drug content
F1	378.85±3.42	4.52±0.11	4.75±0.11	0.36±0.08	98.27±0.76
F2	377.52±3.51	4.57±0.21	4.83±0.14	0.37±0.07	97.11±0.56
F3	378.03±3.21	4.51±0.13	4.83±0.14	0.37±0.07	98.57±0.63
F4	379.21±3.0	4.56±0.21	5.0±0.10	0.36±0.08	97.96±0.95
F5	378.12±2.4	4.49±0.2	5.19±0.19	0.35±0.05	97.89±0.94
F6	380.2±2.34	4.33±0.2	5.2±0.21	0.29±0.05	99.73±0.18
F7	381.35±2.52	4.16±0.2	5.13±0.19	0.32±0.06	98.84±0.53
F8	379.50±2.38	4.53±0.1	5.25±0.26	0.33±0.07	98.73±0.81

TABLE 9: BUOYANCY STUDY FOR FLOATING SUSTAINED RELEASE TABLETS (Mean±S.D., n=3)

Formulation Code	Parameters	
	Floating lag time (min: sec)	Total floating time (Hrs)
F1	2.15±0.08	8
F2	2.12±0.04	9
F3	2.04±0.03	8
F4	2.10±0.06	10
F5	2±0.04	11
F6	1.50±0.05	14
F7	1.53±0.04	12
F8	1.43±0.06	11

TABLE 10: *IN-VITRO* % DRUG RELEASE PROFILE OF IMMEDIATE RELEASE TABLET

Time (min)	% drug release	
	A1	A2
0	0	0
2	19.33±0.32	25.03±0.57
4	31.86±0.38	35.91±0.81
6	42.56±0.72	46.19±0.79
8	64.63±0.81	68.72±0.62
10	77.86±0.58	80.74±0.65
12	97.43±0.73	99.88±0.09
14	89.34±0.75	90.24±0.63
16	81.66±0.69	87.71±0.48
18	80.42±0.23	87.85±0.84
20	84.32±0.92	92.35±0.91

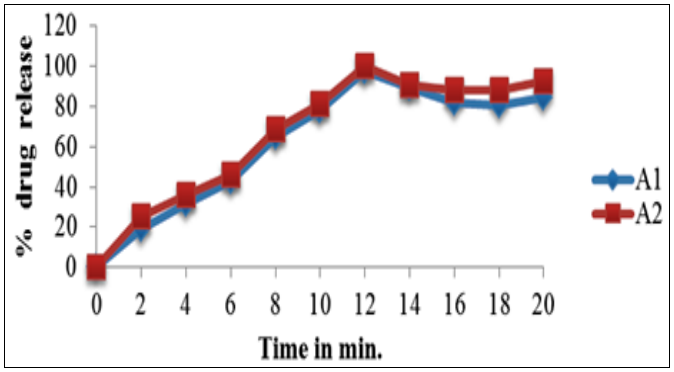

FIG. 5: *IN-VITRO* % DRUG RELEASE PROFILE OF IMMEDIATE RELEASE TABLET

Optimized formulation of immediate release layer A2 shows disintegration time of 44±1 seconds and complete drug release (99.88±0.01 %) in 12 minutes. Disintegrating agent sodium starch glycolate disintegrates the immediate release layer.

***In-vitro* drug release study of floating sustained release tablets:** *In-vitro* drug release data shown in **Table 11 and Fig. 6, 7 and 8**.

Fig. 6 shows effect of concentration of guar gum in batches F1 and F3 on % drug release i.e. 95.54% and 93.24% within 4 and 6 hrs respectively.

Similarly it shows effect of concentration of pectin in batches F2 and F4 on % drug release i.e. 93.77% and 92.63% within 7 and 8 hrs respectively. **Fig. 7** shows the release profile of floating sustained release tablets containing propranolol HCl and the polymers guar gum and pectin in different concentration ratios. Initially, the tablets containing low concentration of guar gum and pectin (1:1 ratio) in batch F5 shows the drug release in quite a short time i.e. in 10 hrs.

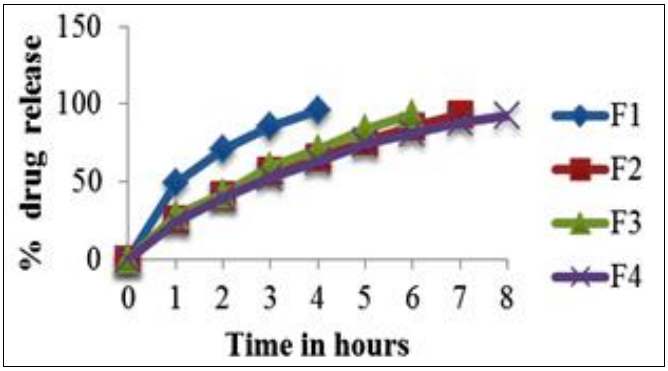

FIG. 6: COMPARISON OF THE RELEASE PROFILES OF FLOATING SUSTAINED RELEASE TABLETS OF BATCHES F1 TO F4

TABLE 11: *IN-VITRO* % DRUG RELEASE PROFILE OF FLOATING SUSTAINED RELEASE TABLETS

Time (Hrs)	% drug release							
	F1	F2	F3	F4	F5	F6	F7	F8

0	0	0	0	0	0	0	0	0
1	48.81±0.61	24.25±0.35	28.35±0.61	25.25±0.69	15.04±0.42	12.44±0.97	10.99±0.76	13.98±0.69
2	71.11±0.52	41.27±0.26	41.89±0.48	39.73±0.82	25.84±0.54	23.78±0.54	17.62±0.41	29.42±0.76
3	85.34±0.63	56.87±0.85	59.63±0.43	52.25±0.44	33.67±0.72	37.74±0.38	27.96±0.57	39.32±0.68
4	95.54±0.54	65.38±0.49	71.22±0.52	63.29±0.75	41.54±0.45	41.54±0.58	38.36±0.56	48.25±0.91
5	-	75.98±0.54	84.18±0.63	80.95±0.66	52.01±0.59	49.45±0.39	43.19±0.72	55.17±0.84
6	-	85.62±0.63	93.24±0.54	88.06±0.61	61.52±0.43	54.33±0.43	53.16±0.86	61.11±0.53
7	-	93.77±0.34	-	92.63±0.64	71.08±0.97	59.24±0.84	59.08±0.49	68.62±0.58
8	-	-	-	-	78.13±0.25	64.17±0.76	66.07±0.62	77.70±0.81
9	-	-	-	-	86.75±0.16	66.57±0.31	76.16±0.52	85.29±0.68
10	-	-	-	-	91.83±0.96	72.57±0.37	80.67±0.63	88.83±0.56
11	-	-	-	-	-	77.57±0.62	88.79±0.65	97.50±0.23
12	-	-	-	-	-	84.64±0.84	98.49±0.20	-
13	-	-	-	-	-	92.27±0.72	-	-
14	-	-	-	-	-	96.86±0.73	-	-

On the other hand, the tablets containing higher of concentration of guar gum and pectin (2:1 and 3:1 ratio) were able to sustain the release of drug over a longer period of time i.e. 12 hrs and more than 12 hrs.

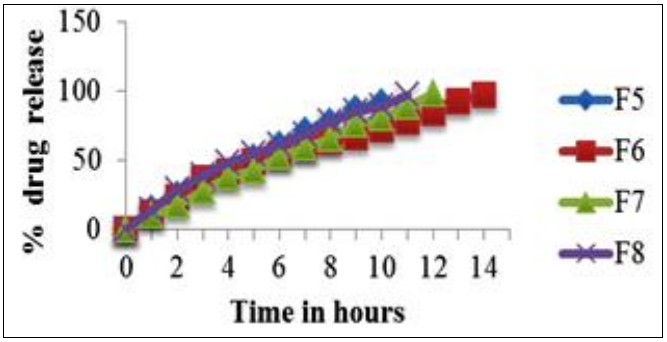

FIG. 7: COMPARISON OF THE RELEASE PROFILES OF FLOATING SUSTAINED RELEASE TABLETS OF BATCHES F5 TO F8

The tablets containing guar gum and pectin (2:1 ratio) in the batch **F6** extends the drug release upto 14 hrs and there is fair uniform drug release throughout the dissolution period. A different behaviour was observed for the tablets containing guar gum and pectin (3:1 ratio) in the batch F7.

The formulation exhibited slightly greater drug release (98.49%) than that of batch F6 within 12 hrs. The rate of drug release from the tablet also depends on the concentration of the gas generating agent used in the formulation. In batch F8, the tablets containing guar gum and pectin (2:1 ratio) and some higher concentration of the gas generating agent than the batch F6, the drug release was quite faster than batch f6 and complete drug release was observed within 11 hrs (**fig. 8**).

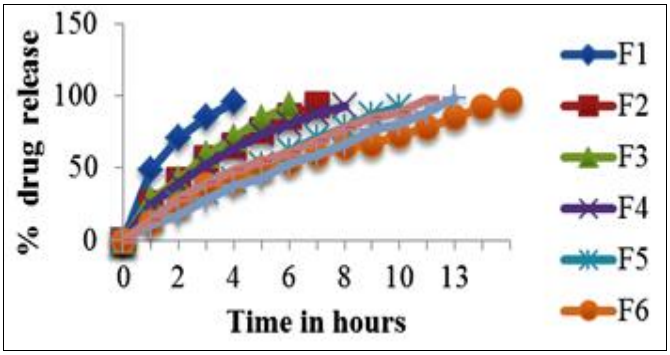

FIG. 8: COMPARISON OF THE RELEASE PROFILES OF FLOATING SUSTAINED RELEASE TABLETS OF BATCHES F1 TO F8

***In-vitro* drug release study of Bilayer floating tablet:** *In-vitro* drug release data shown in **Table 12 and Fig. 9**.

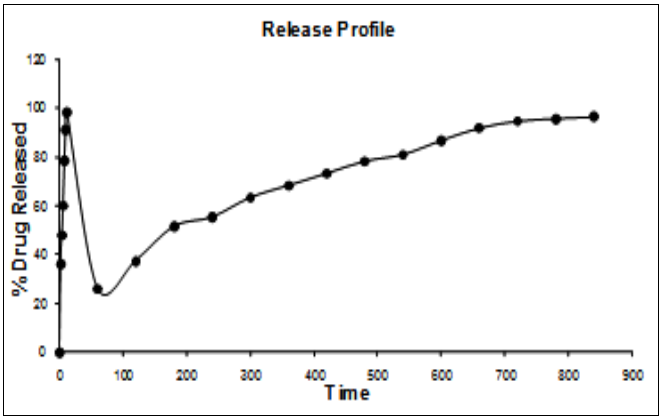

FIG. 9: RELEASE PROFILE OF BILAYER FLOATING TABLET OF BATCH BFT1

TABLE 12: *IN-VITRO* % DRUG RELEASE PROFILE OF BILAYER FLOATING TABLETS

Time (min)	% drug release of BFT1	Time (min)	% drug release of BFT1
0	0	300	63.43 ± 0.59
2	36.19 ± 0.81	360	68.37 ± 0.71
4	48.17 ± 0.78	420	73.34 ± 0.64
6	60.22 ± 0.73	480	78.34 ± 0.59
8	78.48 ± 0.68	540	81.06 ± 0.74
10	91.21 ± 0.54	600	86.86 ± 0.81
12	98.37 ± 0.21	660	91.93 ± 0.46
60	26.14 ± 0.57	720	94.71 ± 0.29
120	37.56 ± 0.78	780	95.72 ± 0.38
180	51.59 ± 0.51	840	96.47 ± 0.25
240	55.45 ± 0.65		

Fig. 9 shows the drug release profile of Bilayer floating tablet. Bilayer floating tablet prepared with optimized formulation of immediate release layer A2 shows disintegration time of 48±2 seconds and complete drug release (98.97±0.81%) in 12 minutes. Disintegrating agent sodium starch glycolate disintegrates the immediate release layer. The disintegrating agent disintegrates the immediate release layer only and leaves the floating sustained release layer intact.

The floating sustained release layer of Bilayer floating tablet shows that, the polymers guar gum and pectin (2:1 ratio) can release the drug in sustained manner for upto 14 hrs for batch F6.

Evaluation of Bilayer Floating Tablets: Prepared bilayer floating tablets were evaluated for post compression parameters. Results are shown in **Table 13**.

TABLE 13: EVALUATION PARAMETERS OF BILAYER FLOATING TABLETS (Mean±S.D., n=3)

Sr. No.	Evaluation parameters of batch BFT1	Results
1.	Physical appearance	Smooth, White-pink colour
2.	Weight Variation (mg) (Mean±SD, n=20)	500±2.18
3.	Thickness (mm), (Mean± SD, n=5)	5.05 ±0.02
4.	Hardness (Kg/cm^2), (Mean± SD, n=4)	6.2±0.32
5.	Friability (%)	0.37±0.07
6.	Disintegration Time (sec)	48±2
7.	% Drug content	98.97±0.81
8.	Floating lag time (min: sec)	8±1
9.	Total floating time (Hrs)	More than 14 hrs.

All the parameters were found to be within the pharmacopoeial limits.

Drug release kinetic profile of Floating Sustained Release Tablets: The curve fitting results of the release rate profiles for the designed formulations were subjected for data analysis using PCP Disso v3 software. It was found that the optimized formulation **F6** was fitted into Korsemeyer-Peppas model which is the best fitted model. From the Korsemeyer-Peppas equation, diffusion coefficient (n) was calculated. The results indicated that the propranolol hydrochloride formulation presented dissolution behavior followed by anomalous transport.

TABLE 14: CURVE FITTING DATA OF THE RELEASE RATE PROFILE OF FORMULATION F1 TO F8

Model		Formulation Code							
		F1	F2	F3	F4	F5	F6	F7	F8
Zero order	R^2	0.9156	0.9606	0.9044	0.9440	0.9916	0.9591	0.9969	0.9745
First order	R^2	0.9867	0.9674	0.9718	0.9871	0.9536	0.9102	0.9388	0.9072
Higuchi	R^2	0.9992	0.9894	0.9980	0.9926	0.9600	0.9802	0.9447	0.9764
Hixson-Crowell	R^2	0.9962	0.9947	0.9892	0.9989	0.9859	0.9720	0.9432	0.9759
Korsemeyer-Peppas	n	0.4880	0.6727	0.4560	0.6372	0.8008	0.7245	0.9097	0.7692
	R^2	0.9977	0.9986	0.9954	0.9987	0.9986	0.9918	0.9987	0.9947
Best fit model		Higuchi	Peppas	Higuchi	Hix-Cr	Peppas	Peppas	Peppas	Peppas

Accelerated Stability Study of optimized formulation: (40°C/75%RH): After storage, the formulation was analyzed for various physical parameters. Results are shown in **Table 15**.

TABLE 15: EVALUATION PARAMETERS OF OPTIMIZED FORMULATION BFT1 (Mean±S.D. n=3)

Sr. No.	Evaluation parameters of batch BFT1	Before stability storage	After 15 Days storage	After 30 Days storage	After 45 Days storage	After 60 Days storage
.	Physical Appearance	Smooth, White-Pink color	Smooth, White-Pink color	Smooth, White-pink color	Smooth, White-Pink color	Smooth, White-Pink color
2.	Weight Variation (mg), (Mean±SD, n=20)	500±2.18	500±2.18	499±2.17	499±2.18	500±2.20
3.	Thickness (mm), (Mean± SD, n=5)	5.05 ±0.02	5.05 ±0.02	5.04±0.03	5.04±0.02	5.03±0.03
4.	Hardness(Kg/cm^2) (Mean± SD, n=4)	6.2±0.32	6.2±0.32	6.2±0.32	6.1±0.31	6.1±0.31
5.	Friability (%)	0.37±0.07	0.37±0.07	0.38±0.09	0.39±0.0	0.41±0.1
6.	Disintegration Time (sec)	48±2	48±2	49±4	50±3	51±5
7.	% Drug content	98.97±0.81	98.97±0.81	98.68±0.75	98.45±0.56	98.06±0.48
8.	Floating lag time (min: sec)	8.00±0.45	8.00±0.45	8.15±0.36	8.24±0.46	8.45±0.42
9.	Total floating time (Hrs)	More than 14 hrs.	More than 14 hrs.	More than 14 hrs.	More than 14 hrs.	More than 14 hrs.

When the stability studies of optimized batch BFT1 were done, no major difference was found between evaluated parameters before and after storage and all parameters are in acceptable limits.

CONCLUSION: The research was undertaken with the aim to formulate and evaluate the bilayer floating tablets of Propranolol HCl using Gaur gum and Pectin as polymers.

From results obtained, it was concluded that the formulation of bilayer floating tablet of Propranolol HCl containing Gaur gum and Pectin as polymer was taken as ideal or optimized formulation for 14 hrs release as it fulfils all the requirement of sustained release dosage form.

ACKNOWLEDGEMENT: The authors are thankful to the Principal, J.L. Chaturvedi College of Pharmacy, Nagpur for providing necessary facilities for research work. They are also grateful to Cipla Ltd. Mumbai for giving gift samples of pure drug.

REFERENCES:

1. Tadros MI: Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and *in vitro–in vivo* evaluation in healthy human volunteers. Eur J Pharm and Biopharm 2010; 74:332–339.
2. Londhe S, Gattani S, Surana: Development of floating drug delivery system with biphasic release for verapamil hydrochloride: *In vitro* and *in vivo* evaluation. J Pharm Sci Tech 2010; 2(11):361-367.
3. Divya A, Kavitha K, Rupes Kumar M, Dakshayani S, Jagadeesh Singh: SD Journal of applied Pharmaceutical Science 2011; 01(08):43-47.
4. Patra Ch. Niranjan *et al.*: Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride. Acta Pharm 2007; 57:479-489.
5. Chaturvedi K, Umadevi S, Vaghani S: Floating Matrix Dosage Form for Propranolol Hydrochloride Based on Gas Formation Technique: Development and *in vitro* Evaluation. Sci Pharm 2010; 78:927–939.
6. Jagdale SC, Agavekar AJ, Pandya SV, Kuchekar BS and Chabukswar AR: Formulation and Evaluation of Gastroretentive Drug Delivery System of Propranolol Hydrochloride. AAPS Pharm Sci. Tech 2009; Vol.10, no.3:1071-1079.
7. Mujtaba SA: Development and evaluation of Bilayered tablet of Propranolol hydrochloride. M. Pharm Thesis, R.T.M. Nagpur University, Nagpur 2010; 33-34.
8. Mohsin AA, Nimbalkar NE, Aejaz A: Formulation and evaluation of mouth dissolving tablets of Amitryptyline hydrochloride by direct compression technique. Int J Pharm Sci 2010; 2(1):204-210.
9. Kavita K, Puneeth KP, Tamizh MT: Development and evaluation of Rosiglitazone Maleate Floating Tablets Using Natural Gums. International Journal of Pharm Tech Research 2010; 2(3):1662-1669.
10. Pharmacopoeia of India, Ministry of Health and Family welfare, Govt. of India 1996; Vol. II: 634.
11. Bodea A, Lucuta SE: Optimization of propranolol hydrochloride sustained release pellets using factorial design. Int J Pharm 1997; 154:49-54.
12. Huang YB, Tsai YH, Yang YC, and Chang JS: Influence of formulation variables and manufacturing process on propranolol extended release profile from HPMC matrices tablets. J Appl Polymer Sci 2004; 93(4):1886-90.
13. Huang YB, Tsai YH, Yang YC, and Chang JS: Optimization of sustained release propranolol dosage

form using factorial design and response surface methodology. Biol Pharm Bull 2004; 27(10):1626-29.
14. Peppas NA: Analysis of Fickian and non Fickian drug release from polymers. Pharm. Acta Helv 1985; 60:110-111.
15. Rahman Z, Ali M and Khar RK: Design and evaluation of bilayer floating tablet of Captopril. Acta Pharma 2006; 56:49-57.

How to cite this article:
Wakde PH, Kasliwal RH and Mane SB: Design and fabrication of Gastroretentive Bilayer Floating Tablet of Propronolol HCl using Natural polymer. *Int J Pharm Sci Res* 2013; 4(12): 123-36. doi: 10.13040/IJPSR. 0975-8232.4(12).123-36