

Formulation Design, Development of Gastro Retentive Floating Tablets of Propranolol

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Abstract

Aim: The present research work was carried out by formulate and evaluate the gastro-retentive floating tablets of propranolol. **Materials and Methods:** Propranolol HCl is an antihypertensive agent. It is mainly used in the treatment of acute myocardial infarctions. Consequently, the current exploration was to design a gastro-retentive drug delivery system of propranolol using swelling polymer through wet granulation method. All the formulations were evaluated for weight variation, hardness, friability, drug content, and *in-vitro* dissolution. In this gastro-retentive dosage form using hydroxypropylmethylcellulose-K4M (HPMC-K4M) was prepared to develop a sustain release tablets, which could retain in the stomach for longer periods of time delivering the drug to the site of action that is in the stomach. **Statistical Analysis used:** Fourier-transform infrared signifying compatibility of the drug and polymers in the tablet composition. **Results:** Pre- and Post-compression parameters of all the formulations were within the pharmacopoeial limits and *in-vitro* drug release of F2 formulation was found to be 99.14% in 12 h. **Conclusion:** Dissolution studies of the composition, it was concluded that the formulation F2 which is containing 50 mg of HPMC-K4M, 25 mg of sodium bicarbonate, 25 mg of polyvinylpyrrolidone K30, 1.5 mg of magnesium stearate, and 1.5 mg of Talc is the best formulation. F2 possessed quick buoyancy lag time of 40 s and good total floating time of 12 h. As the consequence of this study, it may accomplish that the floating tablets using HPMC-K4M are a hydrophilic polymer increases the gross register tonnage of the dissolution fluid in the stomach to deliver the drug in a sustained manner.

Key words: Gastro retentive drug delivery system, hydroxypropylmethylcellulose-K4M, propranolol, wet granulation

INTRODUCTION

Gastric retention provides advantages, for instance, the delivery of drugs with narrow absorption windows in the small intestinal region. In addition, the longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine. Furthermore, improved bioavailability is expected for drugs that are readily absorbed on release in the gastrointestinal tract. These drugs can be delivered ideally by slow release from the stomach.

Propranolol, a nonselective beta-adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. It is highly lipophilic and is almost completely absorbed after oral administration. Although, much of the drug is metabolized by the liver during its first passage through the portal circulation; on an

average, only about 25% reaches the systemic circulation, its elimination half-life is also relatively short (about 2–6 h).^[1-3]

MATERIALS AND METHODS

Propranolol, hydroxypropylmethylcellulose K4M (HPMC-K4M), HPMC K15 M, xanthan gum, sodium bicarbonate, magnesium stearate, talc, and microcrystalline cellulose.

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Received: 28-05-2018

Revised: 12-06-2018

Accepted: 17-06-2018

Methodology

Preformulation studies

Standardization of propranolol by ultraviolet (UV)-visible spectrophotometer

In 0.1 N HCl solution

Preparation of stock solution Stock: solution 100 µg/ml of propranolol was prepared in 0.1N HCl solution. This solution was approximately diluted with 0.1N HCl to obtain a concentration of 10 µg/ml. The resultant solution was scanned in the range of 200–400 nm using UV double beam spectrophotometer (Lab India UV-3000+).

Standard calibration of propranolol in 0.1N HCl: A total of 100 mg of propranolol was accurately weighed and dissolved in 100 ml of 0.1N HCl to obtain a concentration of 1000 µg/ml. From the above, 10 ml was withdrawn and diluted to 100 ml to obtain a concentration of 100 µg/ml. From this stock solution aliquots of 0.2 ml, 1 ml, 1.5 ml, 2 ml, and 2.5 ml were diluted in 10 ml volumetric flask with phosphate buffer to give concentrations in the range of 2–25 µg/ml, respectively, absorbance was measured at 284 nm.

Precompression parameters

Bulk density (D_b)

It is the ratio of the total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder, and initial weight was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$D_b = M/V_b$$

Where M is the mass of powder, V_b is the bulk volume of the powder.

Tapped density (D_t)

It is the ratio of the total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times, and the tapped volume was noted if the difference between these two volumes is <2%. If it is more than 2%, tapping is continued for 1250 times, and tapped volume was noted. Tapping was continued until the difference between successive volumes is <2% (in a bulk density apparatus). It is expressed in g/ml and is given by

$$D_t = M/V_t$$

Where M is the mass of powder, V_t is the tapped volume of the powder.

Angle of repose (θ)

The friction forces in a loose powder can be measured by the angle of repose. It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$$\tan(\theta) = h/r$$

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

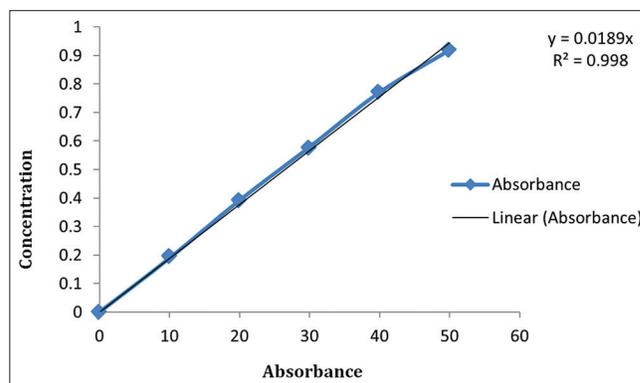


Figure 1: Concentration and absorbance obtained for calibration curve of propranolol hydrochloride in 0.1N HCl

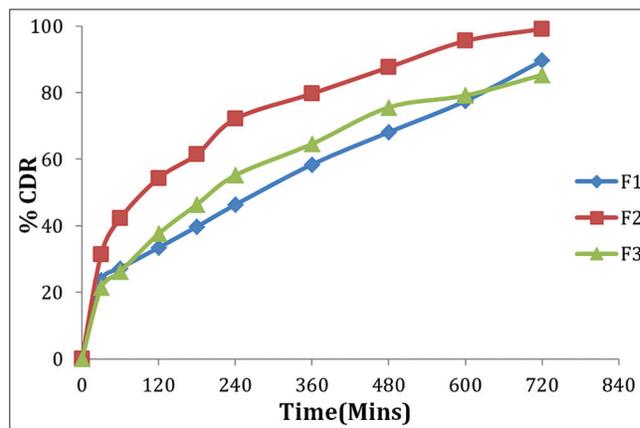


Figure 2: Dissolution profiles of formulations F1-F3

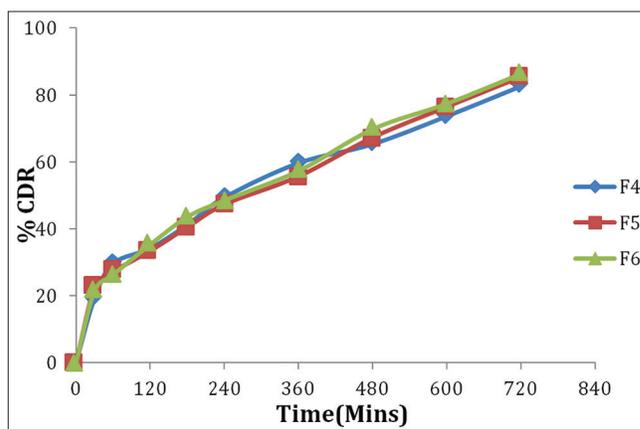


Figure 3: Dissolution profiles of formulations F4-F6

Where; θ is the angle of repose.
h is the height in cm, r is the radius in cm.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of the powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel.

Carr's index (or) % compressibility

It indicates powder flow properties. It is expressed in percentage and is given by

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = \frac{D_t}{D_b}$$

Where, D_t is the tapped density, D_b is the bulk density.
Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).^[4-6]

Preparation of tablets

The tablets were prepared by wet granulation method. All the powders were passed throughout 80 mesh. Requisite quantities of all ingredients were mixed thoroughly, and a sufficient volume of the granulating agent was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 40°C for 12 h. Once, dry the granules retained on 44 mesh were mixed with 10% of fine granules that passed through 44 mesh. Talc and magnesium stearate were added as glidant and lubricant.

Evaluation of tablets

Physical properties such as weight variation, hardness, thickness, friability, and drug content of tablet performed and results are evaluated.

Weight variation

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu), and the test was performed according to the official method.

Hardness

The resistance of tablets to shipping or breakage, under conditions of storage, transportation, and handling before usage depend on its hardness. The hardness of tablet of each formulation was measured using Monsanto hardness tester. The hardness was measured regarding kg/cm².

Thickness

The thickness of tablets was determined using Vernier caliper. Three tablets from each batch

were used, and average values were calculated.

Friability

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.

Drug content

Twenty tablets were crushed and powder equivalent to weight of tablet dissolved in 0.1 N HCl. Then, suitable dilutions were made and absorbance at 284-nm wavelength was taken by using a UV spectrophotometer. Drug content was calculated using absorbance at wavelength 284 nm.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Table 1: Composition of propranolol hydrochloride

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Propranolol	40	40	40	40	40	40
HPMC-K4M	40	50	-	-	-	-
HPMC-K15M	-	-	40	50	-	-
Xanthan gum	-	-	-	-	40	50
PVP-K30	25	25	25	25	25	25
Sodium bicarbonate	25	25	25	25	25	25
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5
MCC	42	32	42	32	42	32

Total weight of tablet 175 mg. HPMC-K4M:
Hydroxypropylmethylcellulose-K4M, PVP-K30:
Polyvinylpyrrolidone K30

Table 2: Standard graph of propranolol hydrochloride in 0.1N HCl

Concentration	Absorbance
0	0
10	0.189
20	0.392
30	0.579
40	0.771
50	0.919

Table 3: Pre compression parameters

F. Code	Bulk density	Tapped density	Hausner's ratio	Compressibility index (%)	Angle of repose
F1	0.415±0.05	0.573±0.05	1.11	12.4	27.1±0.34
F2	0.436±0.03	0.542±0.07	1.10	14.5	28.3±0.43
F3	0.427±0.02	0.526±0.02	1.08	10.3	25.4±0.25
F4	0.449±0.09	0.517±0.01	1.09	9.7	27.1±0.69
F5	0.473±0.06	0.529±0.03	1.12	13.5	29.3±0.24
F6	0.413±0.04	0.516±0.04	1.10	11.2	26.5±0.47

Table 4: Post compression parameters

F. Code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm ²)	Friability (%)	Drug content (%)
F1	150±0.16	3.41	3.9±0.3	0.67	100.8
F2	149±0.39	3.75	3.4±0.2	0.58	99.7
F3	148±0.11	3.17	4.1±0.6	0.62	101.2
F4	149±0.38	3.52	3.8±0.3	0.55	99.9
F5	150±0.57	3.31	4.2±0.9	0.68	100.2
F6	150±0.25	3.83	3.9±0.2	0.54	99.8

Table 5: *In-vitro* dissolution studies

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	23.61	31.36	21.34	19.32	22.35	21.52
60	27.24	42.27	26.25	29.59	27.16	26.27
120	33.46	54.35	37.61	34.16	33.39	35.24
180	39.76	61.53	46.43	41.17	40.45	43.53
240	46.34	72.16	55.18	49.34	47.26	48.46
360	58.42	79.73	64.63	59.62	55.65	57.27
480	68.15	87.62	75.59	65.27	67.27	69.74
600	77.54	95.54	79.16	73.62	76.45	77.35
720	89.62	99.14	85.34	82.59	85.36	86.29

Determination of swelling index

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of distilled water at 37.5°C paddle rotated at 50 rpm. The tablets were removed periodically from dissolution medium. After draining free from water by blotting paper, these were measured for weight gain. Swelling characteristics were expressed regarding percentage water uptake (WU %) according to the equation shows the relationship between swelling index and time.

$$\text{WU \%} = \frac{\text{Weight of swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

Buoyancy determination

The time between introduction of the dosage form and its buoyancy on the simulated gastric fluid and the time during

which the dosage form remained buoyant were measured. The time taken for the dosage form to emerge on the surface of a medium called floating lag time or buoyancy lag time (BLT) and total duration of floatation, i.e. as long the dosage form remains buoyant is called total floating time (TFT). The buoyancy test of the tablet was studied by placing them in 500 ml beaker containing 0.1 N HCl, then tablet from same batches were placed in dissolution test apparatus containing 900 ml 0.1N HCl, maintained at $37 \pm 0.5^\circ\text{C}$ and agitated at 50 rpm. The floating-onset time (period between placing tablet in the medium and buoyancy beginning) and floating duration of the tablet was determined by visual observation.

In vitro release studies

The *in vitro* dissolution test was performed using USP Type-II dissolution test apparatus [Figures 1-3]. *In-vitro* dissolution studies of the prepared drug were carried out in 900 ml of 0.1 N HCl as a medium using USP Type 2 test apparatus with three replicates. The paddle rotation speed was 75 rpm, and a temperature of 37.5°C was maintained. In all experiments, 5 ml of dissolution sample was withdrawn at 5 min interval, filtered using a 0.45-mm Whatman filter, and replaced with an equal volume of fresh medium to maintain a constant total volume. Samples were analyzed on UV/visible spectrophotometer at 284 nm.^[7-10]

RESULTS AND DISCUSSION

Standard curve of propranolol

Propranolol HCl has the λ_{max} at 284 nm. Standard graph of propranolol HCl in 0.1N HCl was plotted, and a good correlation was obtained with R² value of 0.998.

Physical characteristics of blends and tablets

The blends of altered compositions were evaluated for angle of repose, Carr's compressibility index, etc., the results of Angle of repose and Carr's compressibility Index (%) ranged from 25.4 ± 0.25 to 29.3 ± 0.24 and $9.7-14.5$, respectively, which showed that blends from all the formulations having good flow property. The hardness and percentage friability ranged from 3.4 ± 0.2 to 4.2 ± 0.9 kg/cm² and $0.54-0.68\%$, respectively [Tables 1-5].

CONCLUSION

It was concluded that based on *in-vitro* dissolution studies of the formulation F2, i.e. the formulation-containing 50 mg of HPMC-K4M, 25 mg of sodium bicarbonate, 25 mg of polyvinylpyrrolidone K30, 1.5 mg of magnesium stearate, and 1.5 mg of talc is the best formulation. F2 possessed quick BLT of 40 s and good TFT of 12 h.

ACKNOWLEDGMENT

The authors are thankful for the management of Unity College of Pharmacy, Raigir (V), Bhongir (M), Yadadri Bhongir (Dist), Telangana state, India.

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Source of Support: Nil. **Conflict of Interest:** None declared.