Formulation of gastroretentive floating drug delivery system using hydrophilic polymers and its \textit{in vitro} characterization

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The aim of the present research is to formulate and evaluate the gastroretentive floating drug delivery system of antihypertensive drug, propranolol HCl. Gastroretentive floating tablets (GRFT) were prepared by using a synthetic hydrophilic polymer polyethylene oxide of different grades such as PEO WSR N-12 K and PEO 18 NF as release retarding polymers and calcium carbonate as gas generating agent. The GRFT were compressed by direct compression strategy and the tablets were evaluated for physico-chemical properties, \textit{in vitro} buoyancy, swelling studies, \textit{in vitro} dissolution studies and release mechanism studies. From the dissolution and buoyancy studies, F 9 was selected as an optimized formulation. The optimized formulation followed zero order rate kinetics with non-Fickian diffusion mechanism. The optimized formulation was characterised with FTIR studies and observed no interaction between the drug and the polymers.


**INTRODUCTION**

Oral dosage forms have been developed from the past four decades due to their significant therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation (Srikanth \textit{et al.}, 2011a). Nowadays, the trend is going towards the preparation of novel controlled drug delivery systems, in which the active drug can be controlled for a longer period. However, in the controlled drug delivery, the drug absorption is inadequate and highly variable in the individuals due to its physiological variability such as gastrointestinal transit as well as gastric residence time (GRT) of the dosage forms (Srikanth \textit{et al.}, 2011a). Gastroretentive technology is an alternative to overcome this problem. Through this technology, the dosage form
can be able to remain in the gastric region for several hours and hence significantly prolonging the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines (Chawla et al., 2003).

The gastric retention of the dosage forms can be achieved by several methods such as floatation, mucoadhesion, swellable system, hydrodynamically balanced system, sedimentation, expansion modified shape systems, and so on (Streubel, Siepmann, Bodmeier, 2006). Out of the techniques, floatation is the convenient and effective method for the gastric retention. Gastroretentive floating drug delivery systems (GRFDDS) can be buoyant in the gastric medium for prolonged period of time due to its lower bulk density compared to the gastric medium. While the system is floating on the gastric contents, the drug will be released constantly at a desired rate from the dosage form and the GRT will be enhance. Due to increase in the GRT of the dosage form, more amount of the drug can be released in the gastric region, so that improves the bioavailability of the drug and also a better control of fluctuations in the plasma drug concentrations (Mayavanshi, Gajjar, 2008) is achieved.

In the present investigation propranolol HCl (PPH) was selected as a model drug for the development of gastroretentive floating drug delivery systems. PPH, a type of drug known as a beta-blocker, is used in the treatment of high blood pressure, angina pectoris (chest pain, usually caused by lack of oxygen to the heart due to clogged arteries), changes in heart rhythm, prevention of migraine headache, hereditary tremors, hypertrophic subaortic stenosis (a condition related to exertional angina), and tumors of the adrenal gland (Tripathi, 2003). C_{max} of PPH occurs about 1 to 4 h after an oral dose and its elimination half-life is 3-4 h. Due to its short half-life, conventional tablets have to be administered several times to get an optimum effect or else controlled drug delivery is the alternative. Due to the short half-life and insolubility in intestinal fluids (acid soluble basic drug), PPH has been selected as a drug candidate for developing gastro retentive dosage form (Srikanth et al., 2011b).

The objective of the present research is to prepare PPH gastroretentive floating drug delivery system with suitable release retarding agents and to evaluate its buoyancy properties. In the present work different grades of polyethylene oxides (PEO) such as PEO WSR N 12 K and PEO 18 NF were used as swelling as well as release retarding polymers. The molecular weight of PEO WSR N 12 K and PEO 18 NF is 1000 000 and 4300 000 respectively. Calcium carbonate was used as gas generating agent.

MATERIAL AND METHODS

Material

Propranolol HCl was provided by Dr Reddy’s Laboratories Ltd (Hyderabad, India). PEO grades, calcium carbonate and magnesium stearate were obtained as gift samples from UniChem Laboratories Ltd (Goa, India). All other reagents and chemicals were of analytical grade.

Preparation of gastroretentive floating tablets (GRFT) of propranolol HCl

All the ingredients sufficient for a batch of 100 tablets according to the formulae shown in Table I were accurately weighed and passed through the sieve #40. PPH was geometrically mixed with PEO until a homogeneous blend was achieved. Calcium carbonate was added to the above mixture and mixed for 5 min in a polybag. Blend was lubricated with presifted magnesium stearate (sieve # 60) for 3 min. The lubricated blend was evaluated for flow properties. The final blend was directly compressed into tablets on a 16-station rotary tablet punching machine (M/s. Cadmach Machinery Co. Pvt., Ltd., India) using 8 mm round plain punches at the hardness of 4-6 kg/cm².

Determination of flow properties of lubricated blend

Angle of repose method

Angle of repose was determined by fixed funnel and free standing cone method. A funnel with the end of the stem cut perpendicular to its axis of symmetry was fixed at a given height (h) above the graph paper placed on a flat horizontal surface. The gum powder was carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius of the base (r) of the pile was determined and the tangent angle of the repose (θ) was calculated by following equation (Banker, Anderson, 1991).

\[\tan \theta = \frac{h}{r}\]

Determination of compressibility index, Hausner’s ratio

Compressibility index (C.I) and Hausner’s ratio of the lubricated blend was determined by measuring the Bulk density (BD) and Tapped density (TD) of a powder.
The BD was determined by three tap method. An amount of powder equivalent to 10 g was accurately weighed, placed in a 100 mL measuring cylinder without compaction. The volume occupied was measured and the initial bulk density was calculated by the following equation (Carr, 1965).

\[
\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}}
\]

Tapped density (TD) of a powder is the ratio of the mass of the powder to the volume occupied by the powder after a fixed number of taps. The tapped density of the powder represents its random dense packing (Carr, 1965).

An amount of powder equivalent to 10 g was accurately weighed, transferred into a 100 mL measuring cylinder and placed on to the tapped density tester (model C-TDA2, Campbell Electronics, Mumbai, India) and subjected to USP-II method i.e., 250 drops per minute with a drop height of 3 mm±10%. The volume of the powder bed was measured after each increment of 250 drops until the difference between succeeding measurements is less than 2%. The final volume was recorded and the tapped density was calculated by the following equation.

\[
\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped volume of the powder}}
\]

Hausner’s ratio was determined by dividing the tapped density (TD) by bulk density (BD), and Carr’s compressibility index (CI) was determined using the following equation (Carr, 1965).

\[
\text{CI} (%) = \left( \frac{\text{TD} - \text{BD}}{\text{TD}} \right) \times 100
\]

### Evaluation of the tablets

The floating tablets were evaluated for physicochemical parameters like weight variation, hardness, friability & assay, buoyancy characteristics, swelling studies, in vitro dissolution studies and release mechanism studies.

#### Weight variation

Twenty tablets were selected at random and weighed individually for the determination of weight variation of tablets. The mean and standard deviation were determined (Indian Pharmacopoeia, 2007).

#### Hardness test

Five tablets were selected at random and the hardness of each tablet was measured on Monsanto hardness tester.

#### Friability test

The friability test was carried out in Roche Friabilator. Twenty tablets were weighed (X₀) initially and put in a rotating drum. They were subjected to 100 falls of 6 inches height (25 rpm for four minutes). After complete rotations the tablets were dedusted by using camel hairbrush and weighed (X). The percent loss in weight or friability (f) was calculated by the formula given in the following equation: (Carr, 1965)

\[
f = \left(1 - \frac{X}{X_0}\right) \times 100
\]

#### Assay

From each batch, 10 tablets were randomly collected and powdered in a glass mortar. Accurately weighed 80mg of the powder was transferred into a 100 mL volumetric flask. The drug was extracted with 50 mL of 0.1 N HCl with vigorous shaking on a mechanical shaker for 1 h and filtered into a 100 mL volumetric flask through 0.45 µm Millipore nylon filter disc and the filtrate was made up to the mark with 0.1 N HCl. Further appropriate dilutions were made and the absorbance was measured at 289 nm against blank (0.1 N HCl).
Floating characteristics

All the formulated floating tablets were subjected to floating studies and for each batch 5 tablets were used. The *in vitro* buoyancy was determined by floating lag time, as per the method described by Srikanth *et al.* (2011c). The tablets were placed in a 900 mL beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as total floating time (Srikanth *et al.*, 2011c).

Swelling studies

The swelling ability of the GRFT was determined in 900 mL of acidic medium (0.1 N HCl) at room temperature. Weighed tablet was immersed in the medium and it was removed periodically from the medium. After draining the free water, the tablets were measured for weight gain. Swelling index (% SI) was expressed by the following equation (Debajyoti, Amresh, 2010).

\[
\% \text{ SI} = \left( \frac{\text{Weight of the swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \right) \times 100
\]

*In vitro* dissolution studies

The release of propranolol HCl from floating tablets was determined by using Dissolution Tester USP XXIII (LABINDIA, Disso 200). The dissolution test was performed using 900 mL 0.1 N HCl solution at 37 ± 0.5 °C and the paddles were rotated at 50 rpm. At appropriate time interval, 5 mL of aliquot was withdrawn from the dissolution medium and it was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to suitable concentrations with 0.1 N HCl. The absorbance of the solutions were measured at 289 nm for propranolol HCl with a UV-Visible double beam spectrophotometer (Elico SL210, India). Cumulative percentage drug release was calculated using an equation obtained from standard curve. The dissolution experiments were done in triplicate.

Release kinetics

There are number of kinetic models are available to describe the overall release of drug from the dosage forms. The dissolution profiles of all the batches were fitted to zero order, first order, Higuchi, Hixon-Crowell (erosion) and Korsmeyer-Peppas to ascertain the kinetic modelling of drug release (Lazarus, Cooper, 1961; Wagner, 1969; Higuchi, 1963; Korsmeyer, Gurny, Peppas, 1983; Hixson, Crowell, 1931).

<table>
<thead>
<tr>
<th>Model</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero-order</td>
<td>( Q_t = Q_0 + k_0 t )</td>
</tr>
<tr>
<td>First-order</td>
<td>( \ln Q_t = \ln Q_0 - k_1 t )</td>
</tr>
<tr>
<td>Higuchi</td>
<td>( Q_t = k_H \sqrt{t} )</td>
</tr>
<tr>
<td>Hixon-Crowell</td>
<td>( Q_0^{1/3} - Q_t^{1/3} = k_s t )</td>
</tr>
<tr>
<td>Korsmeyer-Peppas</td>
<td>( Q_t/Q_\infty = k_t^n )</td>
</tr>
</tbody>
</table>

\( Q_t \): amount of drug released in time t, \( Q_0 \): initial amount of drug in the Tablet, \( Q_\infty \): fraction of drug released at time t, \( k_0 \); \( k_1 \); \( k_H \); \( k_s \); \( k_t \): release rate constants, \( n \): the release exponent indicative of the mechanism of drug release.

The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi or erosion equation. The ‘n’ value is obtained as a slope for different batches of matrix tablets by plotting log percent drug dissolved against log time. If the value of \( n = 0.45 \) indicates Fickian (case I) release; \( >0.45 \) but \(<0.89 \) for non-Fickian (anomalous) release; and \( >0.89 \) indicates super case II transport. Case II generally refers to the erosion of the polymeric chain and non-Fickian diffusion refers to a combination of both diffusion and erosion mechanism from the controlled drug release tablets.

Characterization of the optimized formulation

Formulations were optimized based on the 12 h drug retarding property, minimal polymer quantity and well buoyancy properties. Optimized formulation was further characterized with Fourier transformation-infrared spectroscopy (FTIR) for interaction studies.

Fourier transformation-infrared spectroscopy (FTIR)

FTIR was used to identify if there is any drug excipient interaction. FTIR studies were performed on drug, polymer and optimized formulation. Samples were analyzed by potassium bromide pellet method in an IR spectrophotometer (Shimadzu, FTIR 8700) in the region between 3500-500 cm\(^{-1}\).

RESULTS AND DISCUSSION

Pre-compression studies

Direct compression technique was used for the preparation of the floating tablets. Flow characteristics of
the material being compressed are important parameters and hence studies were undertaken for the evaluation of flow characteristics of the lubricated blend used in the present study. The results of flow properties of the prepared lubricated blends are shown in Table II. The angle of repose values were within the range of 30-34° and 29-34° for PEO WSR N-12 K and 18 NF based formulations respectively indicating good flow properties. The compressibility index and Hausner’s ration of all the formulations were in the range of 12-14 and 1.11 to 1.15 respectively indicating that flow properties of the blends were good.

**Tableting properties**

The results of the weight uniformity, hardness, friability as well as drug content are presented in Table III. It was observed all the formulations of PPH prepared using selected polymers PEO WSR N-12 K and PEO 18 NF complied with compendia standard for uniformity of weight. The hardness for all the formulations was found to be in the range of 4-6 kg/cm². The assay of the drug was >99%. The percentage weight loss in the friability test was found to be <0.5%. Thus, all the formulations were found to be of good quality fulfilling all the official requirements.

**In vitro buoyancy studies**

All the formulations were evaluated for in vitro buoyancy properties and results are mentioned in Table III. Floating lag time of PEO WSR N 12 K and PEO 18 NF based formulations were found to be in the range of 8-12 min and 1-6 min respectively. Total floating times of same based formulations were in the range of 4-12 h and 4-14 h respectively. From the buoyancy properties, it was observed that calcium carbonate is essential for the floating. Calcium carbonate liberates carbon dioxide, when it contact with acidic medium. The gas generated is trapped and protected within the gel formed by hydration of the PEO, thus decreasing the density of the tablet below 1 g/mL, and the tablet becomes buoyant (Srikanth et al., 2012a). Both grades of PEO are readily swellable polymers; this made the tablets buoyant in less time. PEO WSR 18 NF based formulations floated rapidly than PEO WSR N-12 K.

**Table II - Flow properties of lubricated blend**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Angle of repose (°)</th>
<th>Compressibility Index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 1</td>
<td>30</td>
<td>12</td>
<td>1.12</td>
</tr>
<tr>
<td>F 2</td>
<td>31</td>
<td>12</td>
<td>1.14</td>
</tr>
<tr>
<td>F 3</td>
<td>32</td>
<td>13</td>
<td>1.14</td>
</tr>
<tr>
<td>F 4</td>
<td>33</td>
<td>12</td>
<td>1.12</td>
</tr>
<tr>
<td>F 5</td>
<td>34</td>
<td>14</td>
<td>1.15</td>
</tr>
<tr>
<td>F 6</td>
<td>30</td>
<td>14</td>
<td>1.12</td>
</tr>
<tr>
<td>F 7</td>
<td>34</td>
<td>14</td>
<td>1.13</td>
</tr>
<tr>
<td>F 8</td>
<td>33</td>
<td>13</td>
<td>1.11</td>
</tr>
<tr>
<td>F 9</td>
<td>30</td>
<td>12</td>
<td>1.12</td>
</tr>
<tr>
<td>F 10</td>
<td>29</td>
<td>13</td>
<td>1.14</td>
</tr>
</tbody>
</table>

x: mean ± s.d. (n=20); y: mean ± s.d. (n=10); * n=5; ** n= 20 FLT: floating lag time; TFT: total floating time; PEO: polyethylene oxide.
Swelling studies

The swelling studies of the floating tablets were conducted for 12 h. Swelling index of the all formulations was exhibited in the range of 74-102 %. From the swelling results, it is confirmed that swelling index is depended upon the quantity of the polymer and exposure time of the tablet to the medium. The swelling of the floating tablet has been increased gradually along with the time and it reached to saturation at particular time depends upon the quantity of the polymer it has (Swarna et al., 2012). Results showed that the swelling index increases with increased in concentration of PEO (Figure 1).

In vitro dissolution studies

The results of dissolution studies of formulation F 1-F 5 and F 6-F 10 containing increased concentrations of PEO WSR N-12 K and PEO 18 NF respectively were shown in Figures 2 and 3, respectively. PEO WSR N-12 K based formulations (F 1-5) containing drug to polymer ratios 1:1, 1:2, 1:3, 1:3.5 and 1:4 released 29.44, 22.13, 19.74, 17.32 and 14.56 % of the active drug at the end of 1 h and retarded the drug up to 6, 8, 10, 12 and 14 h respectively. Another grade PEO polymer PEO 18 NF, having high molecular weight, was used for the gastric retention of the active drug. As the concentration of 18 NF increased, the drug retardation is also increased. The formulations F6, F7, F8, F9 and F10 showed maximum drug release at 6, 8, 10, 12 and 14 h respectively. The formulation F 9 showed excellent buoyancy properties and retarding properties than all other formulations.

From all the above results it was concluded that the drug retardation is mainly depends up on the concentration of the polymer as well as swelling property of the polymer. Molecular weight of the polymer was also played a major role in the drug retardation (Srikanth et al., 2012b). It was observed that polymer with high molecular weight

![FIGURE 1 - Swelling index of propranolol HCl GRFT. PEO: polyethylene oxide.](image1)

![FIGURE 2 - Dissolution profile of propranolol HCl GRFT by PEO WSR N-12K. PEO: polyethylene oxide.](image2)
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A retarded drug efficiently than the polymer with lower molecular weight. The order of the drug retarding capacity of the polymer and their drug-polymer ratio was as follows PEO NF (1:1.5) > PEO WSR N-12 K (1:3.5). Even though positive results were obtained by F 4 formulated with PEO WSR N 12 K, F 9 formulated with PEO 18 NF was selected as an optimized formulation as the same desired results were obtained with less quantity of the polymer besides its good buoyancy properties.

Release kinetics

All the formulations made with PEO WSR N-12 K followed zero order kinetics with erosion mechanism. All PEO WSR 18 NF based formulations followed zero order rate kinetics except the F 6 formulation which followed first order rate kinetics. Formulations F 6 and F 7 followed erosion mechanism with higher regression values of 0.9970 and 0.9853 respectively and remaining all formulations followed non Fickian diffusion mechanism. From the results, it was observed that as the concentration of the polymer increases, the release mechanism changed from erosion to diffusion. (Table IV).

Optimization

Based on the low polymer concentration, good buoyancy properties and drug retardation property up to 12 h, the formulation F 9 was selected as an optimized. PEO 18 NF was selected as a suitable polymer for the development of gastro retentive floating drug delivery system of propranolol HCl.

Fourier transformation-infrared spectroscopy (FTIR)

The FTIR spectrum of PPH, PEO 18 NF and F 9 was shown in the Figure 4. The drug PPH showed characteristic

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Hixson-Crowell</th>
<th>Korsmeyer-Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$K_0$</td>
<td>$r$</td>
<td>$K_1$</td>
<td>$r$</td>
<td>$r$</td>
</tr>
<tr>
<td>F 1</td>
<td>16.348</td>
<td>0.9875</td>
<td>0.7038</td>
<td>0.9568</td>
<td>0.9839</td>
</tr>
<tr>
<td>F 2</td>
<td>10.111</td>
<td>0.9847</td>
<td>0.3220</td>
<td>0.9655</td>
<td>0.9896</td>
</tr>
<tr>
<td>F 3</td>
<td>8.3879</td>
<td>0.9863</td>
<td>0.2946</td>
<td>0.9341</td>
<td>0.9803</td>
</tr>
<tr>
<td>F 4</td>
<td>7.8399</td>
<td>0.9952</td>
<td>0.1614</td>
<td>0.9762</td>
<td>0.9787</td>
</tr>
<tr>
<td>F 5</td>
<td>7.0801</td>
<td>0.9983</td>
<td>0.1257</td>
<td>0.9712</td>
<td>0.9855</td>
</tr>
<tr>
<td>F 6</td>
<td>17.1</td>
<td>0.9839</td>
<td>0.4535</td>
<td>0.9898</td>
<td>0.9790</td>
</tr>
<tr>
<td>F 7</td>
<td>12.837</td>
<td>0.9912</td>
<td>0.3496</td>
<td>0.9635</td>
<td>0.9740</td>
</tr>
<tr>
<td>F 8</td>
<td>8.902</td>
<td>0.9926</td>
<td>0.2437</td>
<td>0.9515</td>
<td>0.9859</td>
</tr>
<tr>
<td>F 9</td>
<td>7.9968</td>
<td>0.9942</td>
<td>0.1911</td>
<td>0.9736</td>
<td>0.9862</td>
</tr>
<tr>
<td>F 10</td>
<td>6.4698</td>
<td>0.9945</td>
<td>0.1225</td>
<td>0.9648</td>
<td>0.9996</td>
</tr>
</tbody>
</table>
secondary amine –N–H stretching at 3278 cm$^{-1}$, C-H stretching at 2959 cm$^{-1}$, Aryl C=C stretching at 1584 cm$^{-1}$, Aryl O-CH$_2$ asymmetric stretching at 1236 cm$^{-1}$, Aryl O-CH$_2$ symmetric stretching at 1034 cm$^{-1}$ and the peak at 794 cm$^{-1}$ due to \( \alpha \)-substituted naphthalene (Venkata Srikanth et al., 2012) (Figure 4). The FTIR spectrum of PEO 18 NF showed the characteristic alcoholic –OH stretching at 3431 cm$^{-1}$, -C-O-C asymmetric stretching at 1251 cm$^{-1}$ and -C-O-C symmetric stretching at 1048 cm$^{-1}$.

Optimized PEO 18 NF based formulation (F 9) showed all the characteristic peaks of PPH with minor shifts in its FTIR spectrum. This spectrum showed secondary amine –N–H stretching at 3274 cm$^{-1}$, C-H stretching at 2952 cm$^{-1}$, Aryl C=C stretching at 1577 cm$^{-1}$, Aryl O-CH$_2$ asymmetric stretching at 1241 cm$^{-1}$, Aryl O-CH$_2$ symmetric stretching at 1028 cm$^{-1}$ and the peak at 797 cm$^{-1}$ due to \( \alpha \)-substituted naphthalene (Figure 4).

The results showed no significant change in the spectrum, indicating no interaction between the polymer and drug.

**CONCLUSION**

The gastroretentive floating drug delivery is a promising approach to achieve \textit{in vitro} buoyancy by using hydrophilic polymers of polyethylene oxide grades such as PEO WSR N 12 K, PEO 18 NF and gas-generating agent calcium carbonate. The results concluded that PEO WSR N-12 K and PEO 18 NF based formulations at the drug: polymer ratio 1:4 and 1:1.5 respectively retarded the drug release promptly than all other formulations. High molecular weight PEO grade exhibited higher retarding property and good buoyancy properties. The optimized formulation gives the best result in terms of the required floating lag time and total floating time. Optimized formulation (F 9) when characterized with FTIR studies showed no interactions between drug and polymer. Hence, it can be concluded that, PEO is a suitable polymer for the development of gastroretentive floating drug delivery systems.

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