

## **Design and *in vitro* evaluation of effervescent gastric floating drug delivery systems of propranolol HCl.**

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**Keywords:** effervescent, floating system, propranolol HCl, polyethylene oxide, *in vitro* buoyancy.

**Abstract.** The purpose of this research was to develop and evaluate effervescent gastric floating tablets of propranolol HCl. The oral delivery of antihypertensive propranolol HCl was facilitated by preparing an effervescent floating dosage form which could increase its absorption in the stomach by increasing the drug's gastric residence time. In the present work, effervescent floating tablets were prepared with a hydrophilic carrier such as polyethylene oxide (PEO WSR N 60K and PEO WSR 303) as a release retarding agent and sodium bicarbonate as a gas generating agent. The prepared tablets were evaluated for all their physicochemical properties, *in vitro* buoyancy, drug release and rate order kinetics. From the results, P9 was selected as an optimized formulation based on their 12 h drug release, minimal floating lag time and maximum total floating time. The optimized formulation followed first order rate kinetics with erosion mechanism. The optimized formulation was characterized with FTIR studies and no interaction between the drug and the polymers were observed.

## **Diseño y evaluación in vitro de sistemas de administración de tabletas flotantes gástricas efervescentes de HCl propranolol.**

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**Palabras clave:** efervescentes, sistemas flotantes, propranolol HCl, óxido de polietileno, flotación *in vitro*.

**Resumen.** El propósito de la presente investigación fue desarrollar y evaluar tabletas flotantes, efervescentes de HCL propranolol. La administración oral del antihipertensivo HCL propranolol se facilitó mediante la preparación de una forma de dosificación flotante y efervescente que permitiría su absorción en el estómago, mediante el aumento del tiempo de residencia gástrico de la droga. En el presente trabajo, las tabletas flotantes efervescentes fueron preparadas con un portador hidrofílico, tal como el óxido de polietileno (PEO WSR N 60K and PEO WSR 303), como agente retardador y bicarbonato de sodio como un agente generador de gas. Se evaluaron todas las propiedades fisicoquímicas de las tabletas preparadas, su flotación *in vitro* y su tasa de orden cinético. Se seleccionó el P9 a partir de los resultados obtenidos, como una fórmula óptima, basados en la liberación de la droga a las 12 h, tiempo mínimo de retraso para flotación y máximo tiempo total de flotación. La formulación optimizada siguió una tasa cinética de primer orden con mecanismo de erosión. Esta fórmula óptima se caracterizó mediante estudios FITR y no se observó ninguna interacción entre la droga y los polímeros utilizados.

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### **INTRODUCTION**

The oral route is the predominant and most preferable route for drug delivery; but drug absorption could be inadequate and highly variable in individuals due to physiological variabilities such as gastrointestinal transit as well as the gastric residence time (GRT) of the dosage forms (1,2). GRT of the oral controlled release system is always less than 12 h (3). These aspects lead to development of a drug delivery system which will remain in the stomach for a prolonged and predictable time. Gastroretentive drug delivery system is the feasible approach to overcome such problems and will provide us with new and important therapeutic options.

Gastroretentive drug delivery is an approach to prolong GRT, thereby targeting

site specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion-modified shape systems or by the simultaneous administration of a pharmacological agent, that delays gastric emptying. Even though lot of technologies are available for gastric retention, the floating approach is most effective due to its additional advantages like random gastric emptying, site specific drug delivery, better bioavailability, less irritation, fewer side effects, etc. (4, 5). Floating systems can be developed by two approaches. First is the effervescent system, which needs a gas generating agent that may alkalize the microenvironment of the

stomach and whose buoyancy would be dependent on the gas generating agent, unlike the second which is a non-effervescent approach.

In the present investigation propranolol HCl was selected as a model drug for the development of effervescent floating drug delivery systems. Propranolol hydrochloride was the first beta adreno receptor blocking drug to achieve wide therapeutic use in angina and hipertensión (6, 7). It is a secondary amine compound, and its structure is shown in Fig. 1. Peak plasma concentrations occur about 1 to 4 h after an oral dose. T<sub>1/2</sub> of propranolol HCl is 3-4 h. Thus, propranolol has a relatively short half-life. Consequently, for an optimum effect, the administration of propranolol hydrochloride as conventional tablets (with rapid disintegration and dissolution) must be carried out several times a day. Therapy with immediate release propranolol hydrochloride tablets typically requires a daily dose of 40-160 mg given in three to four divided doses. The presence of food increases its bioavailability. The secretory transporter P-glycoprotein (P-gp) located on the epithelium cells is responsible for low and variable bioavailability of various compounds such as propranolol. Due to its short half life and insolubility in intestinal fluids (acid soluble basic drug), propranolol HCl has been selected as a drug candidate for developing a gastro retentive dosage form.

In the present investigation gastric effervescent floating tablets (GEFT) of propranolol were formulated to be retained in the stomach and deliver the drug in about 12 h. In the present work different grades of polyethylene oxides (PEO), such as PEO WSR N 60K and PEO WSR 303, were used as swelling, as well as release retarding polymers. The molecular weights of PEO WSR N 60K and PEO WSR 303 are 2000000 and 7000000 respectively. Sodium bicarbonate was used as gas generating agent.

## MATERIALS AND METHODS

### Materials

Propranolol HCl was provided by Dr Reddy's Laboratories Ltd (Hyderabad, India). PEO grades, sodium bicarbonate, microcrystalline cellulose 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 GEFT of propranolol HCl

All the ingredients sufficient for a batch of 50 tablets, according to the formulae shown in Table I, were accurately weighed and passed through the sieve #40. Propranolol HCl was geometrically mixed with PEO until a homogeneous blend was achieved. Sodium bicarbonate and microcrystalline cellulose (Avicel PH 200) were

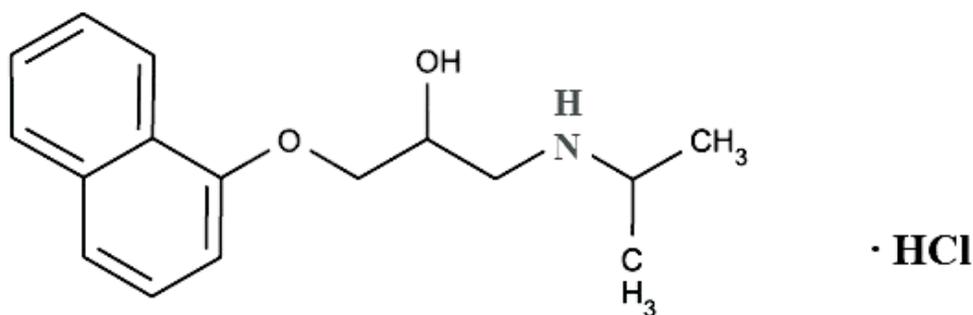


Fig. 1. Structure of propranolol HCl.

**TABLE I**  
FORMULAE OF PROPRANOLOL HCl FLOATING TABLETS

| Ingredients                | P 1  | P 2 | P 3 | P 4 | P 5 | P 6 | P 7 | P 8 | P 9 | P10 |
|----------------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Propranolol HCl            | 80   | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  | 80  |
| PEO WSR N- 60 K            | 40   | 80  | 160 | 240 | 320 |     |     |     |     |     |
| PEO WSR 303                |      |     |     |     |     | 10  | 20  | 40  | 60  | 80  |
| NaHCO <sub>3</sub>         | 13.5 | 18  | 27  | 36  | 45  | 21  | 21  | 21  | 21  | 21  |
| Microcrystalline cellulose |      |     |     |     |     | 97  | 87  | 67  | 47  | 27  |
| Mg stearate                | 1.5  | 2   | 3   | 4   | 5   | 2   | 2   | 2   | 2   | 2   |
| Tablet weight (mg)         | 135  | 180 | 270 | 360 | 450 | 210 | 210 | 210 | 210 | 210 |

added to the above mixture and mixed for 5 min in a polybag. The blend was lubricated with presifted magnesium stearate (sieve # 60) for 3 min. The flow product of 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 & 9 mm round plain punches according to the tablet weight.

#### Evaluation of the tablets

The floating tablets were evaluated for floating characteristics, *in vitro* dissolution studies and other physico chemical parameters like weight variation, hardness, friability and assay.

#### Weight variation

According to I.P. twenty tablets were selected at random, weighed individually for the determination of weight variation of tablets. The mean and standard deviation were determined (8).

#### Hardness test

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

#### Friability test

The friability test was carried out in a Roche Friabilator (8). Twenty tablets were

weighed initially ( $X_0$ ) 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 a camel hairbrush and weighed ( $X$ ). The percentage loss in weight or friability ( $f$ ) was calculated by the formula given in equation 1

$$F = \left( 1 - \frac{X}{X_0} \right) \times 100$$

#### Assay

From each batch, 10 tablets were randomly collected and powdered in a glass mortar. 80 mg of the powder were accurately weighed and transferred into a 100 mL volumetric flask. The drug was extracted with 50 mL of 0.1 N HCl by vigorous shaking on a mechanical shaker for 1h, and filtered into a 100 mL volumetric flask through a 0.45  $\mu$ m 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 a blank (0.1 N HCl).

#### Floating characteristics

All the formulated floating tablets were subjected to floating studies and 5 tablets were used for each batch. The *in vi-*

tro buoyancy was determined by the floating lag time, as per the method described by Srikanth *et al.* (9). The tablets were placed in a 900 mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as the floating lag time. The duration that the dosage form remained constantly on the surface of medium was determined as the total floating time.

### *In vitro* dissolution studies

The release of propranolol HCl from floating tablets was determined by using a Dissolution Tester USP XXIII (LABINDIA, Disso 200). The dissolution test was performed using 900 mL 0.1N HCl solution at  $37 \pm 0.5^\circ\text{C}$  and the paddles were rotated at 50 rpm. At the appropriate time interval, a 5 mL 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 absorbances of the solutions were measured at 289nm for propranolol HCl with a UV-Visible double beam spectrophotometer (Elico SL210, India). The cumulative percentage of drug release was calculated using an equation obtained from a standard curve. The dissolution experiments were done in triplicate.

### Release kinetics

There are a number of kinetic models 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 modeling of drug release (10-14). Mathematical equations of the above models are mentioned in Table II.

The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mecha-

**TABLE II**  
MATHEMATICAL MODELS

| Model            | Equation                        |
|------------------|---------------------------------|
| Zero-order       | $Q_t = Q_o + k_o t$             |
| First-order      | $\ln Q_t = \ln Q_o - k_1 t$     |
| Higuchi          | $Q_t = k_H \sqrt{t}$            |
| Hixon-Crowell    | $Q_o^{1/3} - Q_t^{1/3} = k_s t$ |
| Korsmeyer-Peppas | $Q_t / Q_\infty = k_k t^n$      |

$Q_t$ : amount of drug released in time  $t$ ,  $Q_o$ : initial amount of drug in the Tablet,  $Q_t/Q_o$ : fraction of drug released at times  $t$ ,  $k_o$ ;  $k_1$ ;  $k_H$ ;  $k_k$ ;  $k_s$ : release rate constants,  $n$ : the release exponent indicative of the mechanism of drug release.

nism of drug release from matrix systems was studied by using the Higuchi or erosion equations. The 'n' value was obtained as a slope for different batches of matrix tablets by plotting the log percent of drug dissolved against log time. A 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

Formulation was optimized based on the drug retarding properties, polymer quantity and 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 the potassium bromide pellet method in an IR spectrophotometer (Shimadzu, FTIR 8700) in the region between 3500-500  $\text{cm}^{-1}$ .

## RESULTS AND DISCUSSION

The results of weight uniformity, hardness, friability as well as drug content are presented in Table III. It was observed that all the formulations of propranolol HCl prepared using selected polymers PEO WSR N-60K and PEO WSR 303 complied with compendia standard for uniformity of weight. The hardness for all the formulations was found to be in the range of 4-6  $\text{kg}/\text{cm}^2$ . 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

Formulations were evaluated for *in vitro* buoyancy properties and results are

mentioned in Table III. It was observed that the floating lag times of PEO WSR N 60K and PEO WSR 303 based formulations were in the range of 4-9 min and 0-3 min respectively. Total floating times of same based formulations were in the range of 5-15 h and 4-14 h respectively. Floating lag times were found to be significantly controlled by sodium hydrogen carbonate content. The sodium bicarbonate induces  $\text{CO}_2$  generation in the presence of 0.1 N HCl. 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  $\text{gm}/\text{mL}$ , and the tablet becomes buoyant (15). From the results, generally as the concentration of polymer increased floating lag time decreased and total floating lag time increased at constant sodium bicarbonate ratio (10%w/w). Both grades of PEO are readily swellable polymers; this made the tablets buoyant in less time. PEO WSR 303 based formulations floated more rapidly than PEO WSR N 60K, may be due to its high swelling property.

TABLE III  
TABLETTING AND BOUYANCY CHARACTERISTICS OF PROPANOLOL HCl FLOATING TABLETS

| Formulation | Weight (mg)    | Assay (%)         | Hardness ( $\text{Kg}/\text{cm}^2$ ) | Friability (%) | Floating lag time (min) | Total Floating time (h) |
|-------------|----------------|-------------------|--------------------------------------|----------------|-------------------------|-------------------------|
| P 1         | 135 $\pm$ 1.66 | 99.12 $\pm$ 1.12  | 4 - 6                                | 0.31           | 8-9                     | > 5                     |
| P 2         | 180 $\pm$ 1.11 | 99.45 $\pm$ 1.01  | 4 - 6                                | 0.12           | 7-8                     | > 6                     |
| P 3         | 270 $\pm$ 1.02 | 98.92 $\pm$ 1.08  | 4 - 6                                | 0.45           | 6-7                     | > 12                    |
| P 4         | 360 $\pm$ 1.19 | 99.99 $\pm$ 1.23  | 4 - 6                                | 0.35           | 5-6                     | > 12                    |
| P 5         | 450 $\pm$ 1.54 | 98.12 $\pm$ 1.98  | 4 - 6                                | 0.39           | 4-5                     | > 15                    |
| P 6         | 210 $\pm$ 1.68 | 100.12 $\pm$ 1.11 | 4 - 6                                | 0.46           | 2-3                     | > 4                     |
| P 7         | 210 $\pm$ 1.43 | 101.55 $\pm$ 1.91 | 4 - 6                                | 0.41           | 1-2                     | > 8                     |
| P 8         | 210 $\pm$ 1.29 | 100.12 $\pm$ 1.85 | 4 - 6                                | 0.39           | 0.5-1                   | > 10                    |
| P 9         | 210 $\pm$ 1.12 | 100.62 $\pm$ 1.23 | 4 - 6                                | 0.38           | 0-0.5                   | > 12                    |
| P10         | 210 $\pm$ 1.20 | 100.45 $\pm$ 1.07 | 4 - 6                                | 0.37           | 0-0.2                   | > 14                    |

x: mean  $\pm$  s.d. (n=20); y: mean  $\pm$  s.d. (n=10).

### *In vitro* dissolution studies

The results of dissolution studies of formulations P1 to P5 and P6 to P10 containing increasing concentrations of PEO WSR N-60K and PEO WSR 303 respectively are shown in Figs. 2 and 3, respectively.

In batch P1, propranolol HCl tablets were prepared using PEO WSR N 60K at 1:0.5 ratio of drug: polymer. The tablet failed to float continuously and did not re-

main intact; moreover, 45% of the drug was released within 1 hour at this low concentration of PEO WSR N 60K. Hence the concentration of polymer was increased by using the drug: polymer ratio of 1:1 for batch P2, which showed matrix integrity, but the release of drug was too rapid. In batches P3 to P5, the concentration of polymer was increased in order to get the desired floating behaviour as well as retarding properties.

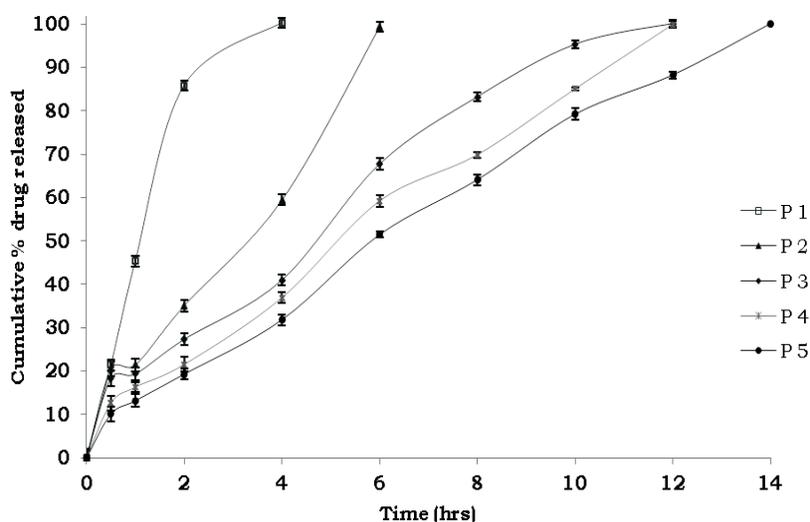


Fig. 2. Dissolution profile of propranolol HCl floating tablets prepared by using various concentrations of PEO WSR N-60K.

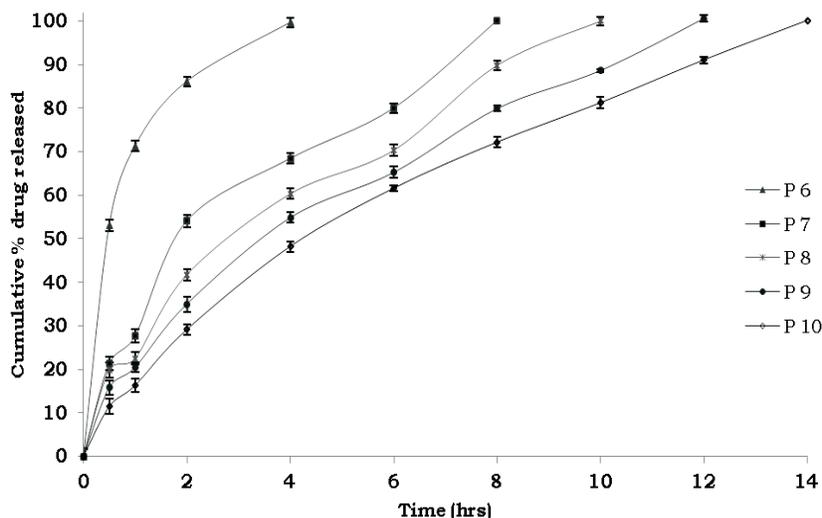


Fig. 3. Dissolution profile of propranolol HCl floating tablets prepared by using various concentrations of PEO WSR 303.

Formulation P4 gave the best results in terms of floating behaviour (lag time 5-6 minutes, duration 12 h), and drug release was in accordance with the USP specification (16). Formulations P3, P4 and P5 exhibited the 100% drug release in 11, 12 and 14 h respectively.

Another grade PEO polymer PEO WSR 303, having high molecular weight, was tried for floating controlled release. In these formulations diluent i.e. microcrystalline cellulose was included to make up the bulk volume of the tablet. The formula P6 showed a burst release pattern, and more than 70% of the drug was released in 1 h, may be due to the low concentration of the polymer and high concentration of microcrystalline cellulose. Microcrystalline cellulose may act as a disintegrant hence the matrix tablet was disintegrated in quick time and lost its integrity. The concentration of PEO WSR 303 was further increased in order to get the desired release profile. The formulations P7, P8, P9 and P10 showed maximum drug release at 8, 10, 12 and 14 h respectively. The formulation P9 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 (15). It was observed that polymer with high molecular weight 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 WSR 303 (1:0.75) > PEO WSR N 60 K (1:3). Even though positive results were obtained by P4 formulated with PEO WSR N 60K, P9 formulated with PEO WSR 303 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

PEO WSR N 60 K based formulations P1 and P2 followed first order rate kinetics with higher regression values of 0.9914, 0.9894 respectively. Formulations P3, P4 and P5 followed zero order rate kinetics. All the above formulations followed erosion mechanism. From the results observed that the rate order kinetics is depends upon the concentration of the polymer, as it increases rate order changed from first order to zero order.

PEO WSR 303 based formulations followed first order rate kinetics except P1 which followed zero order rate kinetics. Formulations P1, P2 and P3 followed a non fickian diffusion mechanism and others followed erosion mechanism. From the results it is observed that, as the concentration of polymer increases, the mechanism of drug release changed from diffusion to erosion (Table IV).

#### Optimization

Based on the low polymer concentration, buoyancy properties and best dissolution profile, P9 was selected as an optimized formulation. PEO WSR 303 was selected as a suitable polymer for the development of gastric effervescent floating tablets of propranolol HCl with low polymer concentration.

#### Fourier transformation-infrared spectroscopy (FTIR)

The FTIR spectrum of propranolol HCl showed characteristic secondary amine -N-H stretch at  $3280\text{ cm}^{-1}$ , C-H stretch at  $2964\text{ cm}^{-1}$ , Aryl C=C stretch at  $1579\text{ cm}^{-1}$ , Aryl O-CH<sub>2</sub> asymmetric stretch at  $1240\text{ cm}^{-1}$ , Aryl O-CH<sub>2</sub> symmetric stretch at  $1030\text{ cm}^{-1}$  and the peak at  $798\text{ cm}^{-1}$  due

TABLE IV  
CORRELATION COEFFICIENT VALUES AND RELEASE KINETICS

| Formulation | Zero order |        | 1st order |        | Higuchi | Hixson<br>Crowell | Peppas |        |
|-------------|------------|--------|-----------|--------|---------|-------------------|--------|--------|
|             | $K_0$      | r      | $K_i$     | R      | r       | r                 | n      | r      |
| P 1         | 23.978     | 0.9333 | 1.1745    | 0.9914 | 0.9721  | 0.9943            | 0.5734 | 0.9436 |
| P 2         | 15.51      | 0.9876 | 0.2124    | 0.9894 | 0.9516  | 0.9867            | 0.8429 | 0.9916 |
| P 3         | 8.3052     | 0.9850 | 0.2713    | 0.9555 | 0.9828  | 0.9835            | 0.7093 | 0.9910 |
| P 4         | 7.9787     | 0.9958 | 0.1732    | 0.9790 | 0.9781  | 0.9855            | 0.7607 | 0.9917 |
| P 5         | 7.0537     | 0.9963 | 0.1639    | 0.9775 | 0.9791  | 0.9919            | 0.8008 | 0.9979 |
| P 6         | 10.906     | 0.9512 | 0.2158    | 0.9492 | 0.9841  | 0.9431            | 0.5648 | 0.9632 |
| P 7         | 10.869     | 0.9516 | 0.2190    | 0.9627 | 0.9858  | 0.9496            | 0.5505 | 0.9657 |
| P 8         | 9.3062     | 0.9762 | 0.2538    | 0.9778 | 0.9953  | 0.9883            | 0.6225 | 0.9924 |
| P 9         | 7.85       | 0.9790 | 0.2047    | 0.9934 | 0.9964  | 0.9971            | 0.6247 | 0.9974 |
| P 10        | 6.8803     | 0.9811 | 0.1829    | 0.9888 | 0.9959  | 0.9978            | 0.6745 | 0.9967 |

to  $\alpha$ -substituted naphthalene (17) (Fig. 4). The FTIR spectrum of PEO WSR 303 showed the characteristic alcoholic -OH stretch at  $3433\text{ cm}^{-1}$ , -C-O-C asymmetric stretch at  $1260\text{ cm}^{-1}$  and -C-O-C symmetric stretch at  $1060\text{ cm}^{-1}$ .

Optimized PEO WSR 303 based formulation (P9) showed all the characteristic peaks of propranolol HCl with minor shifts in its FTIR spectrum. This spectrum showed secondary amine -N-H stretch at  $3280\text{ cm}^{-1}$ , C-H stretch at  $2963\text{ cm}^{-1}$ , Aryl C=C stretch at  $1577\text{ cm}^{-1}$ , Aryl O-CH<sub>2</sub> asymmetric stretch at  $1241\text{ cm}^{-1}$ , Aryl O-CH<sub>2</sub> symmetric stretch at  $1031\text{ cm}^{-1}$  and the peak at  $797\text{ cm}^{-1}$  due to  $\alpha$ -substituted naphthalene (Fig. 4). The results showed no significant change in the spectrum, indicating no interaction between the polymer and drug.

As a conclusion, the effervescent based floating drug delivery is a promising approach to achieve *in vitro* buoyancy, by using hydrophilic polymers of polyethylene oxide grades, such as PEO WSR N 60K, PEO WSR 300 and sodium bicarbonate as a gen-

erating agent. The results concluded that PEO WSR 303 and PEO WSR N 60K-based formulations at the drug: polymer ratio of 1:3 and 1:0.75, respectively, retarded the drug release more effectively than all other formulations. High molecular weight PEO grade exhibited higher retarding and better buoyancy properties. The optimized formulation gives the best result in terms of the required lag time (4-5 minutes) and floating duration of 12 h. The optimized formulation showed no interactions between drug and polymer, when characterized with FTIR studies. Hence, PEO is a suitable polymer for the development of gastric floating drug delivery systems.

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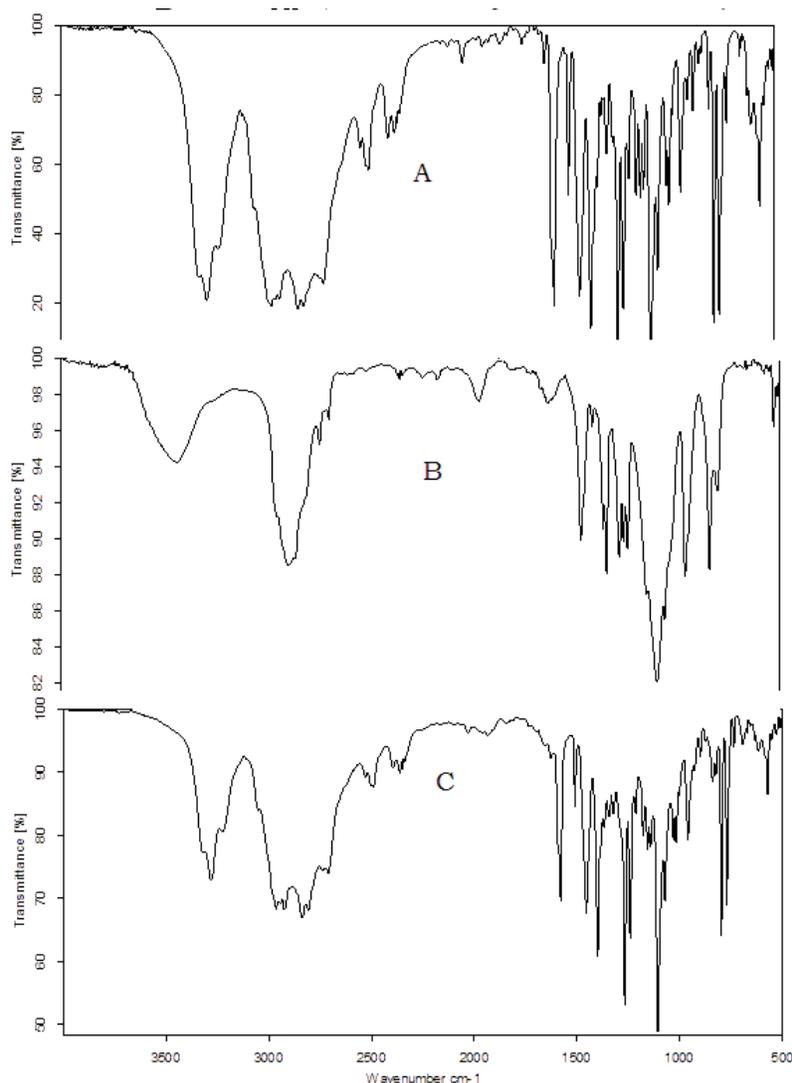


Fig. 4. FTIR spectra of (A) Propranolol HCl (B) PEO WSR 301 (C) formulation P 9.

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