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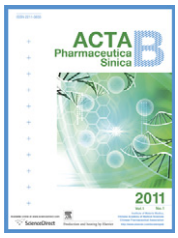

ORIGINAL ARTICLE

Statistical design and evaluation of a propranolol HCl gastric floating tablet

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KEY WORDS

Gastric floating tablet;
Propranolol HCl;
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Buoyancy;
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Abstract The purpose of this research was to apply statistical design for the preparation of a gastric floating tablet (GFT) of propranolol HCl and to investigate the effect of formulation variables on drug release and the buoyancy properties of the delivery system. The contents of polyethylene oxide (PEO) WSR coagulant and sodium bicarbonate were used as independent variables in central composite design of the best formulation. Main effects and interaction terms of the formulation variables were evaluated quantitatively using a mathematical model approach showing that both independent variables have significant effects on floating lag time, % drug release at 1 h ($D_{1\,h}$) and time required to release 90% of the drug (t_{90}). The desired function was used to optimize the response variables, each with a different target, and the observed responses were in good agreement with the experimental values. FTIR and DSC studies of the statistically optimized formulation revealed there was no chemical interaction between drug and polymer. The statistically optimized formulation released drug according to first order kinetics with a non-Fickian diffusion mechanism. Evaluation of the optimized formulation *in vivo* in human volunteers showed that the GFT was buoyant in gastric fluid and that its gastric residence time was enhanced in the fed but not the fasted state.

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1. Introduction

Drug absorption from the gastrointestinal tract (GIT) is a complex process influenced by many variables. It has been reported that the extent of drug absorption from the GIT is related to contact time with the small intestinal mucosa. Gastroretentive drug delivery systems are designed to retain drug in the gastric region for several hours and assist in improving sustained delivery of orally administered drugs that have an absorption window in a particular region of the GIT[1]. These systems provide continuous release of drug before it reaches the absorption window and thereby enhance bioavailability.

A variety of approaches have been adopted to retain dosage forms in the gastric region, including mucoadhesive, floating, expanding and magnetic systems, systems with modified shape and those based on superporous hydrogels[2]. Among these, the gastric floating drug delivery system (GFDDS) offers a number of applications for drugs with poor bioavailability because of a narrow absorption window in the upper part of the GIT. It retains the dosage form at the site of absorption and thus enhances the bioavailability[3,4]. This paper reports the development and evaluation of an effervescent gastric floating tablet (GFT) to prolong gastric retention.

In the present investigation, propranolol HCl was selected as a model drug in the development of the GFT. Propranolol HCl is a synthetic β-adrenoceptor blocker with the chemical name 1-(1-methylethylamino)-3-(1-naphthyloxy)-propan-2-ol hydrochloride and structure is shown in Fig. 1. It is used as an antihypertensive, antianginal and antiarrhythmic agent and for the treatment of migraine[5,6]. It is highly lipophilic and almost completely absorbed after oral administration but undergoes high first-pass metabolism by the liver such that only about 25% of drug reaches the systemic circulation[7]. Propranolol HCl has a short half life (3–4 h) and is insoluble in intestinal fluids (acid soluble basic drug). Because of these characteristics, it was selected as a model for drugs requiring extended gastric retention.

Khattar et al.[8] formulated a gastroretentive hydrodynamically balanced capsule containing propranolol HCl that was shown to be buoyant *in vivo* by endoscopy. In a more recent study, Strübing et al.[9] investigated the floating mechanism and *in vitro* dissolution behavior of a poly(vinyl acetate)-based gastric floating tablet (GFT) with membrane controlled drug delivery. A GFT containing propranolol HCl developed by Jagdale et al.[10] using various polymers (hydroxypropyl methylcellulose, hydroxypropyl cellulose and xanthan gum) was evaluated *in vitro* and *in vivo* buoyancy studies. Bodea and Leucuta[11] applied factorial design to optimize sustained release pellets of propranolol HCl prepared using Eudragit® RS as release retarding agent by the conventional pan method. The plasticizer concentration was taken as an independent variable and the coating dispersion was applied to the pellets in the coating pan.

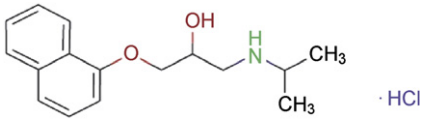

Figure 1 Structure of propranolol HCl.

Despite this evident interest in GFDDS, the development and evaluation of such a system containing propranolol HCl and with polyethylene oxide (PEO) as retarding polymer has not been reported. PEO is a hydrophilic polymer, which, in the presence of water, controls the release of active moiety either by swelling or swelling/erosion to form a hydrogel. Its widespread use in formulations is a consequence of its physical and chemical stability, compressibility, high swelling ability and good solubility in water. In fact, PEO has been proposed as an alternative to cellulose or other ethylene glycol derivatives in the production of controlled release drug delivery systems[12,13]. In the present investigation, response surface methodology (RSM) was used to formulate a GFT of propranolol HCl using PEO WSR coagulant as retarding polymer and sodium bicarbonate as effervescing agent.

RSM is widely employed to optimize formulations with suitable experimental design because it permits a deeper understanding of a process or product and has important applications in establishing the robustness of that product. Central composite design is a progression from factorial designs, which have been widely used in response surface modeling and optimization[14].

The objective of this study was to systematically investigate the impact of several formulation variables on drug release and buoyancy properties of a GFT containing propranolol HCl as model drug. To achieve this objective, the quantity of PEO and concentration of sodium bicarbonate were selected as independent variables, while the floating lag time, drug release at 1 h ($D_{1\,h}$) and time required to release 90% of drug (t_{90}) were taken as dependent variables. The ranges of these formulation variables were chosen based on the results obtained in preliminary studies conducted in our laboratory. In this study, Design Expert software was used to give information not only on the critical values required to achieve the desired response but also the possible interactions of the selected independent variables on the dependent variables.

2. Materials and methods

2.1. Materials

Propranolol HCl was provided by Dr Reddy's Laboratories Ltd. (Hyderabad, India). PEO WSR coagulant, sodium bicarbonate and magnesium stearate were kindly provided by Unichem Laboratories Ltd. (Goa, India). All other reagents and chemicals were analytical grade and used as received.

2.2. Experimental design

RSM aims to establish the relative importance of two or more factors and also to indicate whether or not interaction occurs between the factors and thereby affects the magnitude of the response. Central composite design can be used to derive two or more factors. A two-factor (X_1, X_2), three-level (-1, 0, $+1$) design can be developed by inclusion of a central point. Horizontal and vertical lines are drawn through the central point to form the axes of a central composite design. Further experiments are positioned along the axes at a distance α from the central point and the points $X_2=0$, $X_1=\pm\alpha$, and $X_1=0$, $X_2=\pm\alpha$ are called axial points. For a two-factor design, the domain becomes a circle centered on (0, 0) and passing through the factorial points (-1, -1), ($+1$, -1), and so on.

Table 1 Experimental range and levels of the independent variables.

Variable	Range and level		
	−1	0	+1
PEO WSR coagulant amount X_1 (mg)	80	100	120
Sodium bicarbonate concentration X_2 (%, w/w)	5	10	15

Table 2 Presentation of real values of 3 levels for the central composite design.

Formulation	PEO WSR coagulant quantity X_1 (mg)	Sodium bicarbonate X_2 (%, w/w)
PPEOR 01	71.72	10
PPEOR 02	80.00	5
PPEOR 03	80.00	15
PPEOR 04	100.00	2.93
PPEOR 05	100.00	17.07
PPEOR 06	100.00	10
PPEOR 07	100.00	10
PPEOR 08	100.00	10
PPEOR 09	100.00	10
PPEOR 10	100.00	10
PPEOR 11	120.00	5
PPEOR 12	120.00	15
PPEOR 13	128.28	10

This means that α has a value of $2^{1/2}$ and all the axial points are situated at ± 1.414 from the central point[14].

In the present study, central composite design was employed containing 2 factors evaluated at 3 levels with experimental trials being performed at all 13 possible combinations. The levels and the real values of the two independent variables are shown in Tables 1 and 2, respectively. The formulation variables evaluated were X_1: quantity of PEO WSR coagulant (mg); X_2: concentration of sodium bicarbonate (%, w/w) and the response variables were Y_1: floating lag time (s); Y_2: $D_{1\,h}$ (%); Y_3: t_{90} (h).

2.3. Preparation of the GFT of propranolol HCl

All the ingredients listed in Table 3 were accurately weighed and passed through a # 40 (420 μm) sieve. Propranolol HCl (80 mg) was geometrically mixed with PEO WSR coagulant until a homogeneous blend was achieved. Sodium bicarbonate was then added to the above blend followed by the lubricant, magnesium stearate (1%, w/w). The flow property of the final blend was found to be satisfactory to allow the mixture to be 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 a hardness of 4–6 kg/cm^2.

Table 3 Formula of floating tablets containing 80 mg propranolol HCl using central composite design (data are mg per tablet).

Ingredient (mg/tablet)	PEO WSR coagulant	Sodium bicarbonate	Magnesium stearate	Tablet weight
PPEOR 01	71.72	17.28	2	171
PPEOR 02	80	8.5	1.5	170
PPEOR 03	80	28.5	1.5	190
PPEOR 04	100	5.5	2	187.5
PPEOR 05	100	38	2	220
PPEOR 06	100	20	2	202
PPEOR 07	100	20	2	202
PPEOR 08	100	20	2	202
PPEOR 09	100	20	2	202
PPEOR 10	100	20	2	202
PPEOR 11	120	11	2	213
PPEOR 12	120	35.5	2.5	238
PPEOR 13	128.28	23.22	2.5	234

2.4. Evaluation of the GFT

2.4.1. In vitro buoyancy studies

The *in vitro* buoyancy of the GFT was determined in triplicate as the floating lag time and total floating time using the method of Srikanth et al[15]. The tablets were placed in 900 mL 0.1 mol/L HCl in a beaker and the time required to rise to the surface and float (floating lag time) and the duration of time floating on the dissolution medium (total floating time) were determined.

2.4.2. In vitro dissolution studies

Dissolution profiles of the GFT were determined in triplicate at 37 ± 0.5 °C using the USP XXIII dissolution test apparatus (LABINDIA, Disso 2000)[16]. The paddle stirrer rotating speed was 50 rpm and the dissolution medium was 900 mL 0.1 M HCl. Samples (5 mL) were withdrawn with replacement at fixed time intervals and filtered through a 0.45 μm prefilter. The filtered samples were then diluted with dissolution medium (when necessary) and the absorbance measured at 289 nm.

2.4.3. Release kinetic

Several mathematical models can be tested to determine which best describes the kinetics and mechanism of drug release from floating tablets[17–21]. In the present study, the *in vitro* drug release data was fitted to the following mathematical models:

$$\text{Zero order} \quad Q_t = Q_0 + K_0 t \tag{1}$$

$$\text{First order} \quad \log C = \log C_0 - K_1 t/2.303 \tag{2}$$

$$\text{Higuchi} \quad Q_t = k_2 t^{1/2} \tag{3}$$

$$\text{Hixson–Crowell cube root} \quad (W_0^{1/3} - W_t^{1/3}) = k_h t \tag{4}$$

$$\text{Korsemeyer–Peppas} \quad Q_t/Q_\sigma = k_p t^n \tag{5}$$

where Q_0, Q_t and Q_∞ are the amounts of drug dissolved initially, at time t and at time ∞, (in most cases, $Q_0 = 0$), C_0 and C are the concentrations of drug initially and at time t, W_0 and W_t are the amounts of drug in the pharmaceutical dosage form initially and

at time t, and k_0, k_1, k_2, k_h and k_p refer to the rate constants obtained from the linear curves of the respective models.

2.5. Statistical analysis and optimization

Data obtained from all GFT formulations were analyzed using Design Expert software and used to generate the study design and the response surface plots. Polynomial models, including linear, interaction and quadratic terms were generated for all the response variables using the software. The best fitting model was selected based on comparisons of several statistical parameters, including the coefficient of variation (CV), coefficient of determination (R^2) and adjusted coefficient of determination (adjusted R^2) provided by Design Expert software. In addition, analysis of variance (ANOVA) was used to identify significant effects of factors on response regression coefficients. The F test and P values were also calculated using the software.

The relationship between the dependent and independent variables was further elucidated using response surface plots. These plots are useful to study the effects of various factors on the response at a given time and to predict the responses of dependent variables at intermediate levels of independent variables. Subsequently, a numerical optimization technique using the desirability approach and a graphical optimization technique using overlay plots were used to generate new formulations with the desired responses.

2.6. Validation of the experimental design

To validate the chosen experimental design, the experimental values of the responses were quantitatively compared with predicted values and the relative error (%) calculated using the following equation (Eq. 6):

$$\text{Relative error}(\%) = (\text{Predicted value} - \text{Experiment value}) / \text{Predicted value} \times 100\% \quad (6)$$

2.7. Characterization of the optimized formulation

2.7.1. Fourier transform infrared spectroscopy (FTIR)

FTIR is used to detect a drug-excipient interaction. FTIR studies of potassium bromide pellets in the region 3500–500 cm^{-1} were performed in triplicate on drug, polymer and statistically optimized formulation using a Shimadzu FTIR 8700 IR spectrophotometer.

2.7.2. Differential scanning calorimetry (DSC)

DSC is a useful tool to monitor the effect of additives on the structure of a material and to obtain information about the physicochemical interaction between drug and polymer[22]. DSC of drug, polymer and statistically optimized formulation were carried out using a Mettler Toledo Star SW 8.10, Model no: DSC 822 instrument. In this process, samples (8–10 mg) were weighed into aluminum pans and heated under nitrogen from 5 to 250 °C.

2.8. In vivo buoyancy studies

2.8.1. Study protocol

A GFT containing propranolol HCl was designed to be retained in the stomach and allow a slow delivery of drug in its absorption window to provide increased and more reproducible bioavailability. Although this is the desired outcome, the actual efficacy in a biological system must be evaluated. In the present investigation, X-ray spectroscopy was used to evaluate the intragastric floating behavior of the statistically optimized GFT in both the fasted and fed states.

The *in vivo* X-ray study of the floating ability and gastric retention of the GFT was carried out in two human volunteers administered the GFT with barium sulfate ($BaSO_4$). Two healthy male subjects with, respectively, ages 27 and 27 years, weights 58 and 78 kg and heights 165 and 175 cm participated in the study. The volunteers were judged healthy on the basis of previous medical history, physical examination and routine laboratory tests. The subjects were presented with full details of the investigation, both verbally and in writing, prior to providing written informed consent. The study was conducted under the guidance of a radiologist after approval by the Institutional Ethics Committee of Andhra University, Visakhapatnam (India).

The statistically optimized GFT was administered to the volunteers, one in the fasted state and the other in the fed state. The fasted subject fasted overnight and then swallowed the GFT with 200 mL water. No food was allowed for up to 3 h after dosing and the subject was not allowed to lie down or sleep. A glass of water (200 mL) was given at hourly intervals. The fed subject fasted overnight and in the morning consumed a high calorie high fat breakfast with a total calorific value of approximately 900 cal (slice of bread with 25 g butter—250 cal, 75 g chicken tikka—350 kcal, 40 g egg omelette—150 kcal, fruit juice—150 cal). The GFT was administered with 200 mL water 30 min after the meal. Again the subject was not allowed to eat for up to 6 h but given a glass of water (200 mL) at hourly intervals.

2.8.2. Preparation of GFT for in vivo studies

The optimized GFT containing barium sulfate (PPEORsoB) was prepared by the direct compression method. The content of propranolol HCl was reduced to 40 mg to allow incorporation of the barium sulfate (40 mg) in a tablet of the same weight. The propranolol HCl was geometrically mixed with the PEO WSR coagulant until a homogeneous blend was achieved after which the barium sulfate and sodium bicarbonate were added and the blend mixed and lubricated with magnesium stearate (1%, w/w). The final blend was directly compressed into tablets as previously described.

3. Results and discussion

3.1. In vitro buoyancy studies

All GFT passed physicochemical tests for weight variation, drug content and friability. Floating lag time of all formulations was within the range 6–210 s and results are given in Table 4. All formulations floated in the 0.1 mol/L HCl for more than 7 h showing good matrix integrity during this extended period of time. The results showed that (1) as the concentration of PEO WSR coagulant (X_1) increased, the floating lag time decreased due to the increasing hydrophilic nature of the polymer allowing penetration of liquid through pores formed on the surface of the tablet, and (2) the total floating time increased due to swelling of the tablet which keeps it intact for a longer

period of time[23,24]. It was also found that the total floating time increased and the floating lag time decreased with increase in the sodium bicarbonate concentration. Sodium bicarbonate is necessary in formulations to make them float. It does this through reaction with acid to liberate CO_2, which gets trapped within the gel formed by hydration of polymer thus decreasing the tablet density to below 1 g/cm^3.

3.2. *In vitro dissolution studies*

The percentage of propranolol HCl released from the prepared GFT formulations is shown in Fig. 2. The *in vitro* release of propranolol HCl from the formulations PPEOR 01, 02, 03 and 04 reached 100% in less than 10 h; release from PPEOR 06–10 exhibited 100% at the end of the 12th hour; release from PPEOR 05, 11, 12 and 13 required more than 12 h. The results show that drug release is retarded as the amount of polymer and concentration of sodium bicarbonate increase. This may be due to increased trapping of air in the gellified surface of the tablet and increased trapping of carbon dioxide.

Table 4 Observed responses of PEO WSR coagulant based formulations by central composite design (data are mean values, $n=3$).

Formulation	X_1	X_2	Floating lag time (s)	$D_{1\,h}$ (%)	t_{90} (h)	Total floating time (h)
PPEOR 01	71.72	10	104	23.67	7.9	11
PPEOR 02	80.00	5	210	25.77	5.2	8
PPEOR 03	80.00	15	64	20.87	8.4	11
PPEOR 04	100.00	2.93	142	22.66	8.1	12
PPEOR 05	100.00	17.07	23	17.02	10.9	14
PPEOR 06	100.00	10	56	18.42	10	13
PPEOR 07	100.00	10	45	17.99	10.2	13
PPEOR 08	100.00	10	44	18.12	10.1	12
PPEOR 09	100.00	10	52	18.96	9.8	13
PPEOR 10	100.00	10	51	17.85	9.9	13
PPEOR 11	120.00	5	75	17.89	11.2	15
PPEOR 12	120.00	15	6	13.97	13.2	15
PPEOR 13	128.28	10	35	16.97	11.2	15

3.3. *Release kinetics*

Results of fitting the dissolution profiles to the various kinetic models are given in Table 5. Release from formulations PPEOR 02, 04, 05, 11–13 followed zero order kinetics whereas that from PPEOR 01, 03, 06–10 followed first order kinetics. Release from formulations PPEOR 01, 02, 04, 06–11 and 13 involved non-Fickian diffusion while that from others involved an erosion mechanism. The results show that, as the concentration of sodium bicarbonate exceeds 10% (w/w), the release mechanism changes from diffusion to erosion. This may be due to rapid disintegration of the tablets by increased formation of carbon dioxide gas pockets in the gellified tablet matrix.

3.4. *Data analysis*

All responses were fitted to linear, interaction or quadratic models using Design Expert software. A quadratic model is suggested for floating lag time and $D_{1\,h}$, and a linear model for t_{90}. All dependent variable responses are shown in Table 6.

Using the synthetic polymer PEO WSR coagulant, 13 batches of formulation were prepared within the experimental design to obtain GFTs, which were evaluated for buoyancy properties. The F value for floating lag time, $D_{1\,h}$ and t_{90} were found to be 25.81, 34.15 and 33.17, respectively (Table 6) indicating that the models are significant. The values of Prob$>F$ were found to be <0.05 for all responses again indicating that the models are significant. The response observations for floating lag time (coded units A, B, AB and B^2), $D_{1\,h}$ (A, B and A^2) and t_{90} (A and B) were found to be significant model terms (A: PEO WSR coagulant; B: sodium bicarbonate). The lack of fit F values for floating lag time, $D_{1\,h}$ and t_{90} were found to be 22.87, 6.91 and 39.93, respectively (Table 6) suggesting that the lack of fit is significant. The calculated R^2 value in the present model is close to zero indicating a good model. In all cases, the adjusted R^2 values are in reasonable agreement with the predicted R^2 values (0.9118 and 0.6499 for floating lag time, 0.9325 and 0.7553 for $D_{1\,h}$ and 0.8690 and 0.8428 for t_{90}). In all the cases precision values were in the range 15–19 indicating an adequate signal and that the model can be used to navigate within the design space (Table 7).

The application of response surface methodology yielded the following regression equations (A: PEO, B: Sodium bicarbonate):

$$\text{Floating lag time} = 49.60 - 36.32A - 47.91B + 19.25AB + 13.14A^2 + 19.64B^2 \quad (7)$$

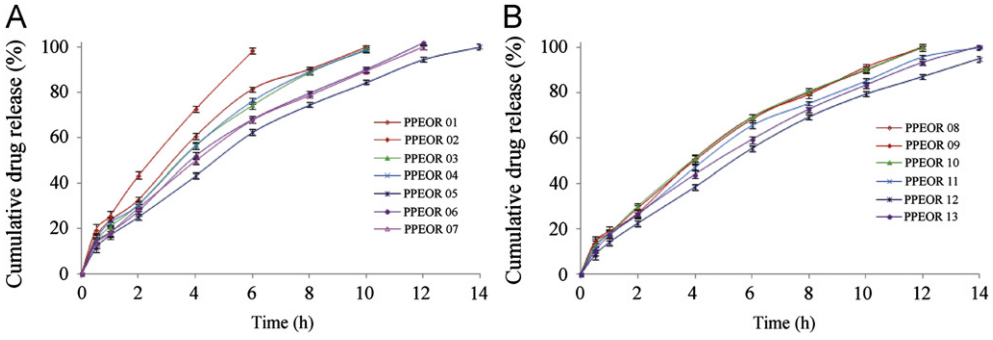

Figure 2 Dissolution profiles of floating tablet formulations (A) PPEOR 01 to PPEOR 07 and (B) PPEOR 08 to PPEOR 13.

Table 5 Correlation coefficient values and kinetics of drug release based on dissolution profiles of propranolol HCl GFT tablets.

Formulation	Zero order		First order		Higuchi	Hixson–Crowell	Peppas	
	k_0	r	k_1	r	r	r	n	r
PPEOR 01	9.8339	0.9767	0.2863	0.9936	0.9920	0.9749	0.6634	0.9933
PPEOR 02	15.548	0.9913	0.6057	0.9378	0.9851	0.9764	0.7462	1.0000
PPEOR 03	9.7564	0.9861	0.2577	0.9882	0.9911	0.9956	0.7049	0.9970
PPEOR 04	9.6698	0.9840	0.3565	0.9529	0.9942	0.9922	0.6777	0.9940
PPEOR 05	7.137	0.9844	0.2139	0.9739	0.9924	0.9952	0.7023	0.9975
PPEOR 06	8.2218	0.9850	0.2174	0.9911	0.9927	0.9917	0.7050	0.9971
PPEOR 07	8.0792	0.9851	0.2087	0.9919	0.9934	0.9734	0.6983	0.9986
PPEOR 08	8.1235	0.9843	0.2158	0.9921	0.9933	0.9990	0.6998	0.9984
PPEOR 09	8.1463	0.9835	0.2236	0.9863	0.9922	0.9787	0.6994	0.9956
PPEOR 10	8.1771	0.9822	0.2218	0.9927	0.9938	0.9914	0.7007	0.9977
PPEOR 11	7.1289	0.9795	0.2174	0.9673	0.9939	0.9938	0.6819	0.9965
PPEOR 12	6.3322	0.9839	0.1898	0.9766	0.9920	0.9967	0.7345	0.9978
PPEOR 13	7.0602	0.9866	0.1997	0.9775	0.9986	0.9958	0.6875	0.9994

k_0: Zero order rate constant; k_1: First order rate constant; r: Correlation coefficient; n: Diffusion exponent.

Table 6 Summary of ANOVA results in analyzing lack of fit (LOF) and pure error for the responses of GFT formulations.

Parameter	Sum of squares	df	Mean square	F value	P value Prob > F	Remark
Floating lag time (Quadratic model)						
Model	33875.2	5	6775	25.81	0.0002	Significant
Residual	1837.14	7	262.4			
Lack of Fit	1735.94	3	578.6	22.87	0.006	Significant
Pure Error	101.2	4	25.3			
D_{1h} (Quadratic model)						
Model	117	5	23.4	34.15	< 0.0001	Significant
Residual	4.7965	7	0.685			
Lack of Fit	4.0206	3	1.34	6.909	0.0463	Significant
Pure Error	0.7759	4	0.194			
t_{90} (Linear model)						
Model	40.391	2	20.2	33.166	<0.0001	Significant
Residual	6.0891	10	0.609			
Lack of Fit	5.9891	6	0.998	39.927	0.002	Significant
Pure Error	0.1	4	0.025			

df: degrees of freedom.

Table 7 Statistical parameters for the responses of the GFT formulations.

Parameter	Floating lag time	$D_{1\,h}$ (%)	t_{90} (h)
Mean	69.7692	19.2431	9.7000
SD	16.2003	0.8278	0.7803
CV (%)	23.2198	4.3017	8.0446
R^2	0.9486	0.9606	0.869
Adj R^2	0.9118	0.9325	0.843
Pred R^2	0.6499	0.7553	0.72306
Adeq Precision	15.3070	18.2495	16.424

SD: Standard deviation; CV: Coefficient of variation.

$$D_{1\,h} = 18.27 - 3.03A - 2.10B + 0.25AB + 0.91A^2 + 0.67B^2 \quad (8)$$

$$t_{90} = 9.70 + 1.93A + 1.14B \quad (9)$$

The contour and response surface plots for all responses of all formulation factors are shown in Figs. 3 and 4. The contour and response plots of the response surface as a function of two factors at a time, with all other factors fixed, are more helpful in understanding both the main and interaction effects of the two factors.

To optimize all the responses with different targets, a multicriteria decision approach (a numerical optimization technique by the desirability function and a graphical optimization technique by the overlay plot) was used (Figs. 5 and 6). The optimized formulation was obtained by applying constraints on dependent variable responses and independent variables. The constraints were: Minimal floating lag time; $D_{1\,h} < 20\%$ (fixed by the USP dissolution conditions[16]); t_{90} 10–11 h. These constrains are common for all the formulations. The recommended concentrations of the independent variables were calculated by the Design Expert software from the above plots which has the highest desirability near to 1.0. The extensive grid and feasibility searches provided that the optimum formulations and the respectively desired function

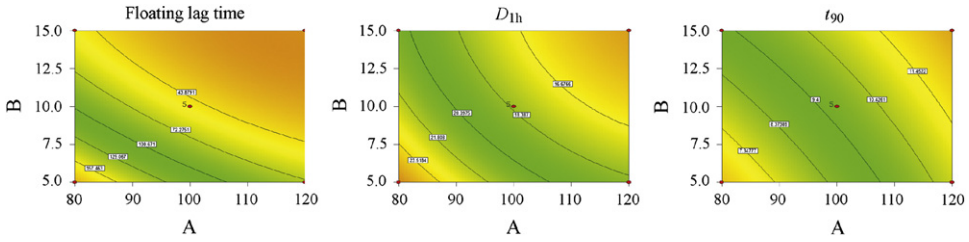

Figure 3 Contour plots for the effect of PEO WSR coagulant (A) and sodium bicarbonate (B) on responses related to buoyancy.

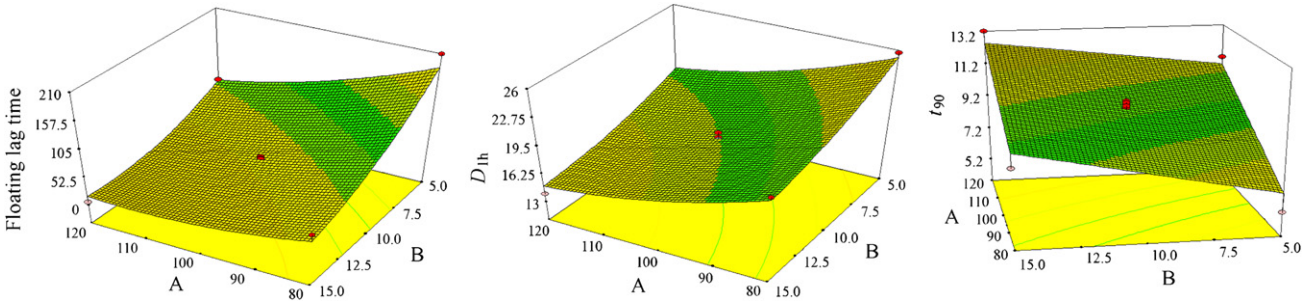

Figure 4 Response plots for the effect of (A) amount of PEO WSR coagulant (mg) and (B) concentration of sodium bicarbonate (%, *w*/*w*) on responses related to buoyancy.

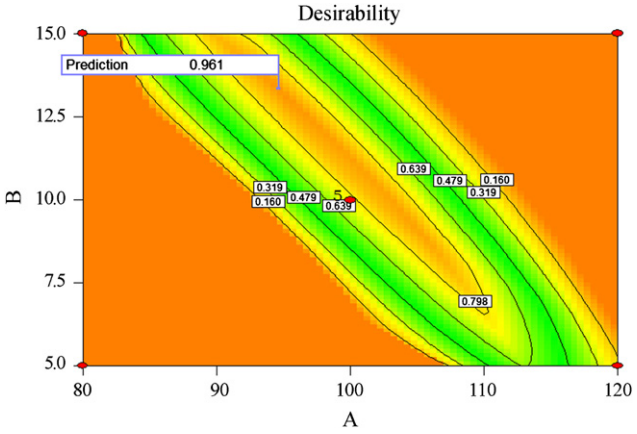

Figure 5 Desirability for optimization of gastric floating tablets of propranolol HCl. (A) amount of PEO WSR coagulant (mg) and (B) concentration of sodium bicarbonate (%, *w*/*w*).

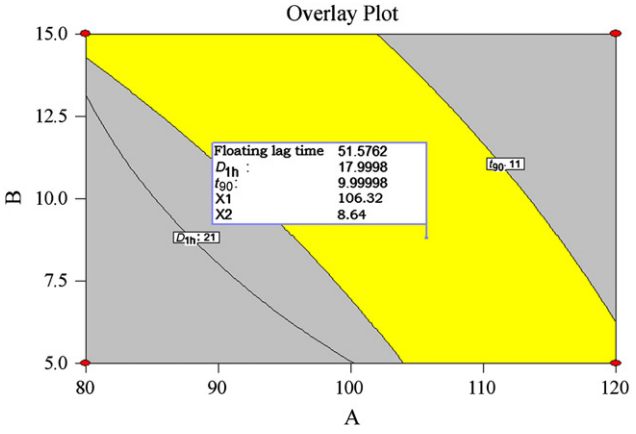

Figure 6 Overlay plot for optimization of gastric floating tablets of propranolol HCl. (A) amount of PEO WSR coagulant (mg) and (B) concentration of sodium bicarbonate (%, *w*/*w*).

response plot and overlay plot are as shown in Figs. 5 and 6, where one solution was found with a highest desirability.

The optimum values of selected variables obtained using Design Expert software were 106.32 mg PEO WSR coagulant and 8.64% (*w*/*w*) sodium bicarbonate. The final composition comprised 80 mg propranolol HCl, 106.32 mg PEO WSR coagulant, 17.68 mg sodium bicarbonate and 2 mg magnesium stearate.

3.5. *Evaluation and validation of the optimized formulation*

The statistically optimized formulation (PPEORso) fulfilled all the physicochemical criteria. *In vitro* buoyancy and dissolution studies were carried out on the prepared optimized formulation to verify the theoretical prediction. The *in vitro* buoyancy study showed that the floating lag time was 51 s and is in close agreement with the model predictions (Table 8). The relative errors (%) between the predicted and experimental values for each response were calculated and the values found to be within 5%. The experimental values were in agreement with the predicted values confirming the predictability and validity of the model.

The optimized formulation gave floating lag time, $D_{1\,h}$ and t_{90} values of 51 s, 17.56% and 9.98 h, respectively. Drug release from the optimized formulation followed first order kinetics with a non-Fickian diffusion mechanism.

Table 8 Comparison of predicted and observed responses for the statistically optimized formulation PPEORso.

Formulation	Response	Observed	Predicted	Relative error (%)
PPEORso	Floating lag time (s)	51	51.58	1.12
	$D_{1\,h}$ (%)	17.56	17.99	2.39
	t_{90} (h)	9.98	9.999	0.19

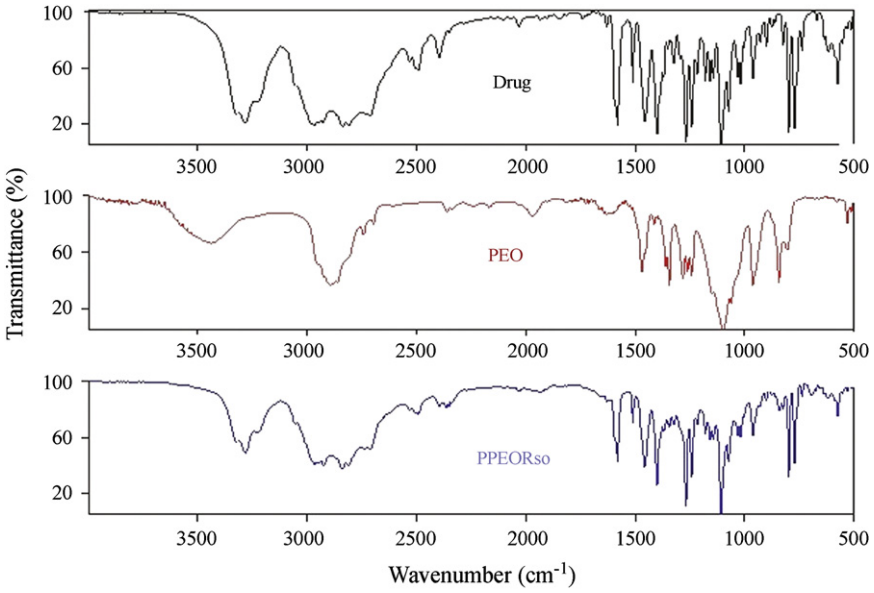

Figure 7 FTIR spectra of propranolol HCl (drug), PEO WSR coagulant and statistically optimized formulation PPEORso.

3.6. *Characterization of the optimized formulation*

3.6.1. *FTIR*

The FTIR spectrum of PEO WSR coagulant showed a characteristic alcoholic –OH stretch at 3433/cm, a –C–O–C asymmetric stretch at 1260/cm and a –C–O–C symmetric stretch at 1060/cm. The FTIR spectrum of propranolol HCl showed a characteristic secondary amine –NH stretch at 3280/cm, a C–H stretch at 2964/cm, an aryl C=C stretch at 1579/cm, an aryl O–CH_2 asymmetric stretch at 1240/cm, an aryl O–CH_2 symmetric stretch at 1030/cm and a peak at 798/cm due to alpha-substituted naphathalene[25] (Fig. 7). Corresponding peaks in PPEORso were at 3280/cm, 2963/cm, 1577/cm, 1241/cm, 1031/cm and 797/cm. The FTIR data indicate the absence of chemical interaction between propranolol HCl and PEO WSR coagulant.

3.6.2. *DSC*

The DSC thermograms of propranolol HCl, PEO and PPEORso are shown in Fig. 8. The DSC thermograms of pure propranolol HCl and PEO WSR coagulant show sharp endothermic peaks at 167.56 and 69 °C, respectively, corresponding to their melting points. PPEORso showed sharp endothermic peaks at 166.23 and 68.9 °C representing drug and polymer, respectively. A slight decrease in the energy change of melting endotherm of PPEORso indicates a small reduction in crystallinity, which may be due to a physical (but not chemical) interaction between the drug and polymer.

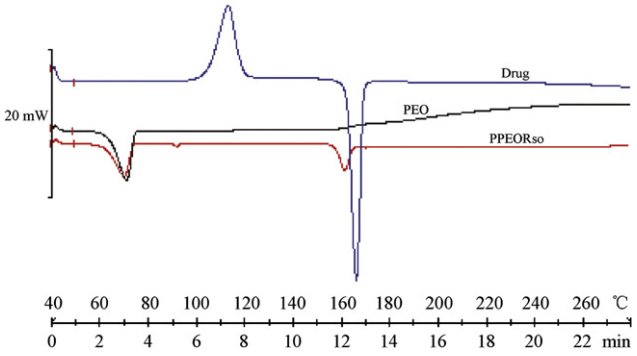

Figure 8 DSC thermograms of propranolol HCl (drug), PEO WSR coagulant and statistically optimized formulation PPEORso.

Table 9 *In vivo* residence time and position in the GIT of the optimized GFT of propranolol HCl containing barium sulfate (PPEORsoB) in the fasted and fed states.

Time (h)	Position of the tablet in GIT	
	Fed state	Fasted state
0.5	Stomach	Stomach
3	Stomach	Small intestine
6	Stomach	Disappeared from gastric region
9	Disappeared from gastric region	

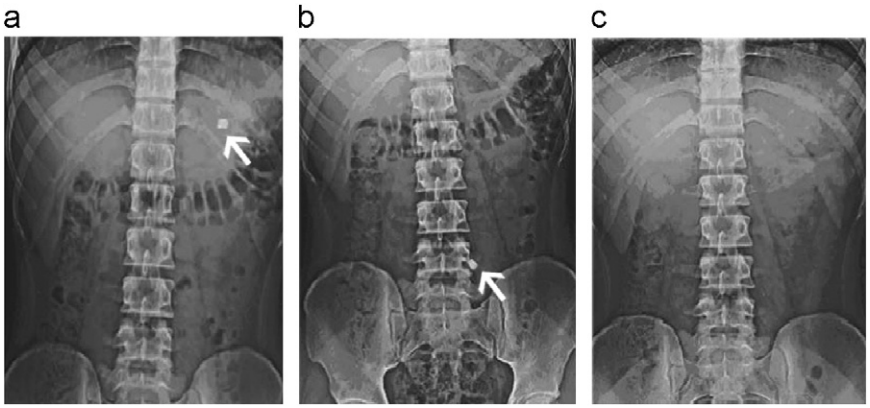

Figure 9 X-ray photographs of gastric floating tablet of statistically optimized formulation PPEORsoB in a human volunteer in the fasted state after (a) 0.5 h (b) 3 h and (c) 6 h.

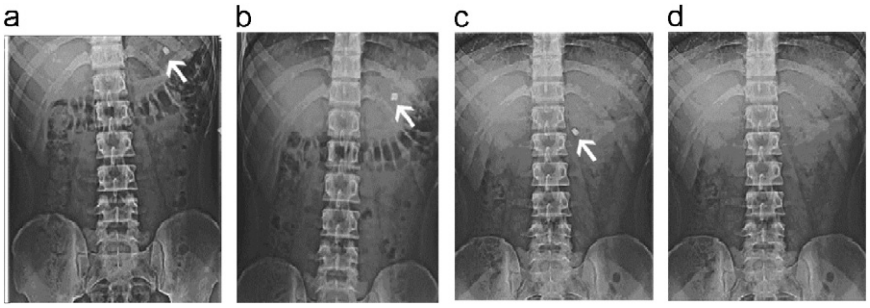

Figure 10 X-ray photographs of gastric floating tablets of statistically optimized formulation PPEORsoB in a human volunteer in the fed state after (a) 0.5 h (b) 3 h (c) 6 h and (d) 9 h.

3.7. In vivo buoyancy studies

This study aimed to confirm that the GFT would actually float and be retained in the stomach. A radiological method was used to monitor the developed GFT in the gastric region of human volunteers under fasting and fed conditions. It was found that the GFT remained buoyant in gastric contents in both fasted and fed states although floating and the gastric retention time (GRT) depended on the feeding conditions as shown in Table 9.

In the fasted state, the GFT was observed to be buoyant in gastric fluid after 0.5 h (Fig. 9a), to be present in the small intestine after 3 h (Fig. 9b) and to have disappeared after 6 h (Fig. 9c). Therefore, under these conditions, the ability to float did not enhance GRT. The rapid emptying was attributed to periods of strong contractile activity which occurs under fasting conditions every 1.5–2 h effectively sweeping undigested material from the stomach. As a result, a GFT administered to fasted subjects could be removed within as little as 1–2 h depending on the strength of the motor induced contractile activity.

In the fed state, the GFT was observed to be buoyant in gastric contents at 0.5 h (Fig. 10a), at 3 h (Fig. 10b) and at 6 h (Fig. 10c) but to have disappeared at 9 h (Fig. 10d). Therefore, in the fed state, the GRT was prolonged by 4–5 h compared to the fasted state.

This study has demonstrated that, in the fasted state under the influence of strong motor activity (the migrating myoelectric complex), there is no enhancement of the GRT of the GFT, whereas there was a prolonged GRT of approximately 6 h in the fed state.

4. Conclusions

This study examines the preparation of a GFT containing propranolol HCl using the synthetic polymer PEO WSR coagulant as retarding polymer and sodium bicarbonate as gas generating agent. A systematic study using a central composite design revealed the most suitable content of PEO and sodium bicarbonate in the GFT. The optimized formulation fulfilled all the requirements of the target set and exhibited suitable values of floating lag time, $D_{1\,h}$ and t_{90}. The intragastric behavior of the statistically optimized GFT in human volunteers showed the floatability of the tablet in gastric contents and a prolonged GRT of approximately 6 h in the fed state. The present study clearly indicates the applicability of statistical optimization techniques to predict the composition of a formulation that gives optimum product parameters.

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