ORIGINAL ARTICLE

DEVELOPMENT OF GASTRORETENTIVE FLOATING TABLETS OF DILTIAZEM HYDROCHLORIDE AND ITS STATISTICAL OPTIMIZATION

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Abstract

This study aimed to develop gastroretentive floating tablets of diltiazem hydrochloride, using a release retarding polymer and to apply statistical approach of response surface methodology for further formulation optimization. Response surface methodology using the central composite design was used to study the effect of formulation variables on the floating lag time (FLT), time taken for 90% of drug to be released ($t_{90\%}$) and total floating time (TFT), and to optimize the formulations. The floating tablets were prepared using direct compression method using Polyethylene Oxide (PEO WSR) coagulant as the release retarding polymer and sodium bicarbonate as the gas generating agent. A 3^2 factorial design was applied to optimize the drug release profile. The quantity of PEO WSR coagulant and concentration of sodium bicarbonate were selected as the independent variables. The floating lag time (FLT) and total floating time (TFT) of conventional formulations (BC1 - BC4) were varied from 10 - 40 sec and 6-8 hrs respectively. The FLT of statistical formulations (BS1 - BS9) were in the range of 5 - 53 sec and the TFT for the same formulations were in the range of 0.12 - 10 hrs. The statistically optimized formula suggested by the central composite design was 34.45 mg of PEO WSR coagulant and 30 mg of sodium bicarbonate. The statistically optimized formulation passed all the physicochemical tests. From the *in vitro* buoyancy studies, the FLT of the statistical optimized formulation (Bso) was found to be at 19 sec. The experimental $t_{90\%}$ and TFT were 6.4 hours and 8.5 hours respectively. The calculated relative errors of all variables were within 5%, concluding that the statistically optimized formulation is valid. The applied FTIR and DSC studies on the statistically optimized formulation led to the conclusion that there were no interactions between drug and polymer.

Rezumat

Studiul a avut drept scop dezvoltarea şi evaluarea unor tablete gastroretentive de clorhidrat de diltiazem, folosind un polimer care întârzie eliberarea substanţei active precum şi abordarea statistică a metodologiei de răspuns pentru optimizarea formularii. Tabletele au fost preparate prin comprimare directă, folosind polietilenoxid (PEO WSR) agent de întârziere a eliberăării şi bicarbonat de sodiu ca generator de gaze. Pentru optimizarea profilului de dizolvare s-a utilizat un model factorial 3^2. Variabilele independente alese au fost cantităţile de PEO WSR şi concentraţia de bicarbonat de sodiu. Erorile relative calculate, pentru pentru parametrii luaţi în considerare, au fost de până la 5%. Studiile FTIR şi DSC au demonstrat faptul ca în formula dezvoltată nu există interacţiuni între substanţa activă şi excipienţi.

Keywords: diltiazem hydrochloride, gastroretentive, floating drug delivery, central composite design, polyethylene oxide WSR coagulant

Introduction

Oral route drug delivery is the most utilized route of various pharmaceutical dosage forms, due to its ease of administration and patient compliance [1, 2]. The oral controlled drug delivery system was developed to allow a controlled rate of drug release over an extended period of time. This system, however, has a disadvantage of short gastric retention time, resulting in the incomplete release of drugs with narrow absorption window in the upper part of the gastrointestinal tract [2, 3]. To overcome this drawback, gastroretentive drug delivery systems (GRDDS) were introduced [3].

GRDDS prolongs the gastric residence time and hence improves the oral bioavailability of drugs with the absorption window in the upper part of the gastrointestinal tract [1-5]. The approaches to GRDDS include the floating drug delivery system, high density system, swelling system and mucoadhesive system [3-5]. The floating system is the most used system as it is a simple and practical approach to increase the gastric retention time and to control the drug release [1, 2].

Diltiazem hydrochloride was chosen as the model drug for this study. It is a non-dihydropyridine calcium channel blocker and it is widely used to treat hypertension and stable *angor pectoris* [6, 7]. It undergoes extensive first pass metabolism, resulting a low absolute bioavailability of 30% - 40%. Diltiazem hydrochloride has an elimination

half-life of 2 - 4 hours, an absorption window in the upper part of the gastrointestinal tract and it is insoluble in the high pH environment of the intestine [7]. Due to these properties, diltiazem is a suitable drug candidate for the development of floating gastroretentive drug delivery system.

The PEO WSR coagulant was the polymer chosen for this study. It is a hydrophilic polymer with a high molecular weight [8]. PEO WSR coagulant hydrates and forms gel with an extremely fast rate [8]. Due to these properties, upon the contact with the gastric fluids in the stomach, PEO WSR coagulant forms a gel layer, enabling a controlled release of the drug [9]. The effervescent agent used in this research was sodium bicarbonate.

Floating tablets of diltiazem hydrochloride had been developed by Gambhire *et al*. and Iqbal *et.al* [10, 11]. In those studies, however, different polymers had been used- hydroxypropyl methylcellulose (HPMC), Compritol 888 ATO and xantham gum [10, 11]. Therefore, although studies have been carried out using diltiazem hydrochloride as the model drug, there is yet a study on the development of floating tablets of diltiazem hydrochloride using PEO WSR coagulant, justifying the objective of this research.

This study was conducted with the aim of formulating gastroretentive floating tablets of diltiazem hydrochloride that floats and releases the drug content in a controlled manner over the period of 8 hours.

Materials and Methods

Diltazem hydrochloride, pharmatose, magnesium stearate and talc were purchased from Labchem Sdn Bhd Malaysia. PEO WSR coagulant was a gift sample from Colorcon Asia Pacific Ltd (Singapore). Sodium bicarbonate was purchased from Ajax Finechem (Malaysia). All other reagents and chemicals were of analytical grade.

UV analytical method development of diltiazem hydrochloride

The stock solution of 100 µg/mL diltiazem hydrochloride stock was prepared by dissolving 10 mg of diltiazem hydrochloride in 100 mL 0.1 N HCl. The stock solution was scanned in the UV range of 200 - 400 nm using a UV spectrophotometer (Perkin Elmer UV-Vis Spectrophotometer) to determine the absorption maximum (λmax). The working standard solutions of diltiazem (3 - 15 µg/mL) were then prepared from the stock solution and the absorbance at each concentration were measured. The standard curve of absorbance against concentration was plotted.

Experimental design

In the present study, initially, the formulations for the floating tablets were prepared using a conventional method and the conventional batches were conventionally optimized. Then, using the central composite design, new formulations of the floating tablets were prepared and statistically optimized. The central composite design of 2 factors evaluated at 3 levels was utilized. Experimental trials were then carried out on the resulting 9 possible combinations. The quantity of PEO WSR coagulant and concentration of sodium bicarbonate were selected as the independent variables. The floating lag time (FLT), the time taken for 90% of the drug to be released ($t_{90\%}$) and the total floating time (TFT) were selected as the dependent variables. The range and levels of the independent variables are shown in Table I.

Table I

Experimental range and levels of the independent variables in PEO WSR Co based formulations

Variables	Range and levels		
	-1	0	+1
PEO WSR Co (mg)	15	30	45
% w/w Sodium bicarbonate	5	10	15

Preparation of effervescent GRDDS of diltiazem hydrochloride

All the adequate ingredients for a batch of 50 tablets were carefully weighed and sieved with sieve no. 35 (500 microns mesh) using the formulae listed in Table II and III. Diltiazem hydrochloride (30 mg) was geometrically mixed with PEO WSR coagulant until a homogeneous blend was obtained. Pharmatose and sodium bicarbonate were then added to the mixture and carefully mixed for 5 minutes in a polybag. The blend was lubricated with 1% of magnesium stearate and talc (w/w) and further mixed until homogeneous. The final blend was then directly compressed into tablets using a 10-station rotary tablet punching machine (Rimek Mini Press 1) with 8 mm round plain punches. BC1-BC4 were the floating tablets prepared using the conventional formulations and BS1-BS9 were prepared using the formulae suggested by the central composite software. Table II and III show the working formulae of all 13 batches of floating tablets.

Table II

Floating tablet formulae of the conventional formulations

Ingredients (mg)	BC1	BC2	BC3	BC4
Diltiazem	30	30	30	30
PEO WSR coagulant	30	45	15	30
Sodium bicarbonate	12	12	20	20
Pharmatose	46	31	131	116
Magnesium stearate	1	1	2	2
Talc	1	1	2	2
Total weight	**120**	**120**	**200**	**200**

Table III

Floating tablet formulae of the central composite design formulations

Ingredients (mg)	BS1	BS2	BS3	BS4	BS5	BS6	BS7	BS8	BS9
Diltiazem	30	30	30	30	30	30	30	30	30
PEO WSR coagulant	15	45	15	45	8.79	51.21	30	30	30
Sodium bicarbonate	10	10	30	30	20	20	5.86	34.14	20
Pharmatose	141	111	121	91	137.2	94.79	130.14	101.86	116
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total weight	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Evaluation of effervescent GRDDS

The prepared floating tablets were evaluated for hardness, weight variation, friability [12], FLT, TFT and percentage (%) of drug release over the period of 8 hours.

In vitro buoyancy studies

All the formulated floating tablets of each batch were subjected to *in vitro* buoyancy studies. The floating lag time (FLT) and the total floating time (TFT) were determined by placing the tablet in a beaker containing 900 mL of 0.1 N hydrochloric acid (HCl). The FLT is the time taken for the tablet to rise to the surface and float and the TFT is the time taken for the tablet to remain floated.

In vitro dissolution studies

The dissolution test was performed using USP type II (paddle) apparatus using 900 mL of 0.1 N HCl at 37°C ± 0.5°C and 75 rpm [12]. Samples of 5 mL of the solution were withdrawn from the dissolution apparatus at the designated time intervals using a syringe equipped with 0.45 µm of prefilter. The samples were replaced with 5 mL of fresh 0.1 N HCl. The samples were diluted to a suitable concentration using 0.1N HCl and the absorbance values were measured at 235 nm using the UV-Spectrophotometer.

Release Kinetics

The dissolution profiles of all the batches were fitted into zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer and Peppas models [13-16]. The model with the highest correlation coefficients was selected. The mathematical equations for the mentioned models are shown in Table IV.

An independent model approach (Akaike information criterion) was used to test the applicability of the release kinetics models. The models were compared using the statistical parameters, coefficient of determination (r^2) and Akaike information criterion (AIC). Whereas, r^2 is calculated simply from correlation coefficient (r), AIC measures the goodness of fit when comparing several models and is based on maximum likelihood. It is a standard statistical parameter for dissolution comparison. The minimum value of AIC indicates the best fit model.

Table IV

The mathematical equations [13-16] of the models

Model	Equation
Zero-order	$Q_t = Q_o + k_0 t$
First-order	$\ln Q_t = \ln Q_o - k_1 t$
Higuchi	$Q_t = k_H \sqrt{t}$
Hixson-Crowell	$Q_o^{1/3} - Q_t^{1/3} = k_x t$
Korsmeyer-Peppas	$Q_t/Q_\infty = k_p t^n$
Akaike information criterion (AIC)	AIC = n*ln(wssr) + 2.p

Q_t: amount of drug released at time t; Q_0: the initial amount of drug in the tablet; Q_t/Q_∞: fraction of drug released at time t; k_0, k_1, k_H, k_x, k_p: release rate constants; n: the release exponent indicating the mechanism of drug release; o: number of dissolution data points; p: number of parameters in each model; wssr: weighed sum squares of residues

Statistical analysis of the data and optimization

The results obtained from the *in vitro* buoyancy and *in vitro* dissolution studies for all 9 central composite design based formulations were inserted into the Design Expert Software and were analysed. Using the software, polynomial analysis was performed for each response (FLT, $t_{90\%}$ and TFT) and the best fitting model (linear, quadratic or cubic) was selected. Furthermore, analysis of variance (ANOVA) was used to associate the significant effects of factors (quantity of PEO WSR Co and concentration of sodium bicarbonate) on the response regression coefficients (FLT, $t_{90\%}$ and TFT). In addition, the F-test and p values were determined using the software.

Using the contour and response surface plots, the relationship between the dependent and independent variables were established. The plots studied the effects of formulation factors on the responses at a given time and at intermediate levels of the formulation factors. Following that, numerical and graphical optimizations were used to generate new formulations with desired responses.

Validation of the experimental design

The statistically optimized formulation was validated by comparing the experimental values of the responses with those values predicted by the software. The % relative error was then calculated using the formula:

$$\% \text{ Relative error} = \frac{[Predicted\ value - Experimental\ value]}{Predicted\ value} \times 100$$

Drug interaction studies

Fourier transformation-infrared spectroscopy (FTIR). FTIR studies were performed on the drug, the polymer and the statistically optimized formulation, in order to identify any possible interaction between the drug and the polymer. Samples were analysed using the potassium bromide pellet method in an IR spectrophotometer (SHIMADZU FTIR-8400S) in the region between 4000 - 500 cm^{-1}.

Differential scanning calorimetry (DSC). An analysis was carried out on the drug, the polymer and the statistically optimized formulation using the Differential Scanning Calorimetry (METTLER TOLEDO DSC 823^e). Samples weighing 3 - 10 mg were placed in an aluminium pan and were heated under nitrogen atmosphere from 0°C to 240°C.

From the UV analytical method development, the λ_{max} of diltiazem hydrochloride was found to be at 235 nm. The standard curve was plotted between absorbance against the concentration of diltiazem hydrochloride, which given the regression equation y = 0.0542x + 0.0175.

The conventional batches of floating tablets passed the physicochemical tests of weight variation, hardness and thickness tests; except for BC1 and BC2, which failed the hardness test. The amount of Pharmatose (binder) and hence the total weight of the tablet was then increased for the following BC3 and BC4 to achieve the desired tablet hardness of 4 - 5 kg/cm^2. Table V shown the physicochemical characterization of the conventional and software based formulations.

Results and Discussion

Table V

The physicochemical characterization of the central composite design based batches

Formulations	Weight (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
BC1	115 ± 1.28	2 - 3	2.3 - 2.4	0.28
BC2	115 ± 0.80	2 - 3	2.3 - 2.4	0.45
BC3	201 ± 0.55	4 - 5	2.8 - 2.9	0.15
BC4	201 ± 0.45	4 - 5	2.8 - 2.9	0.37
BS1	202 ± 1.05	4 - 5	2.8 - 2.9	0.35
BS2	202 ± 0.40	4 - 5	2.8 - 2.9	0.17
BS3	202 ± 1.25	4 - 5	2.8 - 2.9	0.48
BS4	203 ± 0.40	4 - 5	2.8 - 2.9	0.31
BS5	202 ± 0.55	4 - 5	2.8 - 2.9	0.36
BS6	202 ± 0.60	4 - 5	2.8 - 2.9	0.29
BS7	202 ± 0.55	4 - 5	2.8 - 2.9	0.34
BS8	202 ± 0.30	4 - 5	2.8 - 2.9	0.46
BS9	202 ± 0.45	4 - 5	2.8 - 2.9	0.41

Where n = 20 for weight variation, thickness and friability test and n = 10 for hardness test

The initial batches of BC1 and BC2 were prepared using 10% sodium bicarbonate and the FLT observed were minimal (10 seconds and 21 seconds, respectively). Similar observation was noted by Gambhire *et al*. [10], who concluded that 10% sodium bicarbonate is sufficient to achieve optimum *in vitro* buoyancy. Sodium bicarbonate forms carbon dioxide when in contact with the 0.1 N HCl. The carbon dioxide produced will get entrapped in the gel layer formed by the hydrated polymer, providing the buoyant force for the tablets to float [10, 17, 18].

BC1 and BC2, however, failed to achieve the desired tablet hardness of 4 - 5 kg/cm^2. Hence, by increasing the amount of Pharmatose used, BC3 and BC4 were prepared. When compared, BC4, which had higher concentration of sodium bicarbonate, had shorter FLT than BC1.

BS1-BS9 passed all the physicochemical tests of weight variation, hardness, thickness and friability tests. The FLT of all the formulations were found to be within the range of 3 - 53 seconds. As reported by several literature reviews [23-28], it was observed in BS6 to BS9, that the concentration of sodium bicarbonate is inversely proportional to the FLT. As the concentration of sodium bicarbonate increases, the FLT decreases. At high concentration of sodium bicarbonate, more carbon dioxide is formed. The increased amount of carbon dioxide entrapped in the gel layer causes the tablets to float faster, decreasing the FLT [18-23].

In this study, it was found that the quantity of PEO WSR coagulant used also affects the FLT [11, 21].

In BS1 and BS2, at constant concentration of sodium bicarbonate, as the amount of PEO WSR coagulant increases, the FLT decreases. This was also observed in BS3 and BS4.

Furthermore, as the concentration of sodium bicarbonate increases, the TFT increases [19, 20]. This was observed in BS1 and BS3, BS2 and BS4, BS8 and BS9. The increased amount of carbon dioxide produced provided sufficient buoyancy for the tablets to float for a longer period of time [20]. Table VI shows the results of the *in vitro* buoyancy studies for all the 13 batches of floating tablets.

The *in vitro* dissolution studies showed that the drug release was further retarded as the amount of PEO WSR coagulant used increases [14]. The higher quantity of PEO WSR coagulant in the tablet enables the formation of a thicker gel layer. The rate and extend of drug release are inversely proportional to the thickness of the gel layer [18, 24]. The thicker is the gel layer, the longer it takes for the drug molecules to travel across the gel layer to reach the dissolution medium, hence, delaying the drug release [18, 24]. Figure 1 shows the *in vitro* dissolution studies.

Table VI

The levels of independent variables and the observed *in vitro* buoyancy studies responses for all the 13 batches of formulations

Formulation	Quantity of PEO WSR Co (mg) X_1	% w/w of Sodium bicarbonate X_2	Observed responses	
			Floating Lag Time (sec)	Total floating time (hr)
BC1	30	10	10	6
BC2	45	10	21	7.5
BC3	15	10	40	1.1
BC4	30	10	30	8
BS1	15	5	15	0.12
BS2	45	5	7	4
BS3	15	15	10	5
BS4	45	15	3	8
BS5	8.79	10	13	3
BS6	51.21	10	5	10
BS7	30	2.93	53	1
BS8	30	17.07	18	8.5
BS9	30	10	30	8

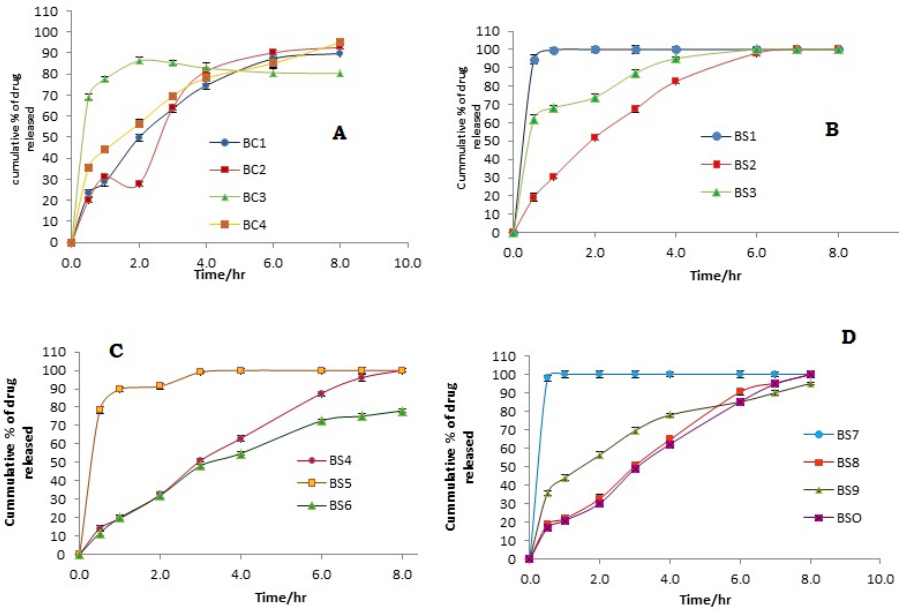

Figure 1.
Dissolution Profile of the conventional (A) and Central Composite Design batches (B-D)

All the 9 batches followed the first order kinetics with erosion mechanism for BS1-BS6 and non-Fickian diffusion mechanism for BS7 - BSO. At constant and optimum amount of PEO WSR coagulant (BS7 - BSO), the drug release mechanism changes from erosion mechanism to diffusion mechanism. AIC's values also provided the same release mechanism as that of regression values (r). The release kinetics profiles are shown in Table VII.

Table VII

Correlation coefficient values and drug release of BS1 to BS9 and BSO

Formulation	Zero order		First order		Higuchi	Hixson Crowell	Peppas	
	k_0	r	k_1	r	r	r	N	r
BS1	5.3159	0.9888	0.1142	0.9998	0.9210	0.9537		
BS2	12.181	0.9884	0.2790	0.9985	0.9488	0.9642		
BS3	8.5062	0.9860	0.2584	0.9957	0.9321	0.9591		
BS4	12.626	0.9882	0.2251	0.9997	0.9542	0.9871		
BS5	6.5795	0.9762	0.2164	0.9975	0.9215	0.9635		
BS6	9.6565	0.9751	0.0849	0.9951	0.9315	0.9562		
BS7	6.3556	0.9892	0.1014	0.9989	0.9741	0.9612	0.8552	0.9962
BS8	12.414	0.9766	0.2697	0.9975	0.9657	0.9547	0.8471	0.9871
BS9	9.546	0.9874	0.1417	0.9959	0.9740	0.9236	0.8885	0.9962
BSO	12.376	0.9817	0.2157	0.9993	0.9620	0.9450	0.8887	0.9572

Statistical analysis and optimization

The responses were fitted into linear, quadratic or cubic models using the Design Expert Software. Quadratic model was suggested for the FLT and a linear model for $t_{90\%}$ and TFT. The summary of ANOVA results for the formulation responses are shown in Table VIII.

Table VIII

Summary of ANOVA results

Parameters	Sum of squares	df	Mean square	F value	p-value Prob > F	Remark
Response 1 (Floating Lag Time (min)) [Quadratic]						
Model	1403.68	5	280.74	1.47	0.3981	Not Significant
A-PEO	86.55	1	86.55	0.45	0.5485	
B-Sodium Bicarbonate	427.74	1	427.74	2.25	0.2309	
AB	0.25	1	0.25	1.313 E-003	0.9734	
Residual	571.20	3	190.40	5.968 E-003		
Cor Total	1974.89	8				
Response 2 ($t_{90\%}$ (hrs)) [Linear]						
Model	61.16	2	30.58	10.93	0.0100	Significant
A-PEO	41.19	1	41.19	14.72	0.0086	
B-Sodium Bicarbonate	19.97	1	19.97	7.14	0.0369	
Residual	16.79	6	2.80			
Cor Total	77.95	8				
Response 3 (Total Floating Time (hrs)) [Linear]						
Model	82.69	2	41.34	14.90	0.0047	Significant
A-PEO	35.21	1	35.21	12.69	0.0119	
B-Sodium bicarbonate	47.48	1	47.48	17.11	0.0061	
Residual	16.65	6	2.77			
Cor Total	99.34	8				

From the ANOVA, the F value for FLT, $t_{90\%}$ and TFT were 1.47, 10.93 and 14.90 respectively. For the FLT, the value of Prob > F value was found to be at 0.3981, indicating that the model terms (quantity of PEO WSR Co and concentration of sodium bicarbonate) were not significant. Elsewhere, the Prob > F values for $t_{90\%}$ and TFT were 0.0100 and 0.0047 respectively, which indicates that the model terms were significant.

The R-squared values for FLT, $t_{90\%}$ and TFT were close to zero, which is ideal for a good model. The Adjusted R-squared and Predicted R-squared values for $t_{90\%}$ (0.7129 and 0.5876 respectively) and TFT (0.7766 and 0.6770 respectively) were in reasonable agreement, since the values of both adjusted and predicted r-squared for each of the responses were within 0.20 of each other. The statistical parameters are shown in Table IX.

Table IX

Statistical Parameters

Parameters	Floating lag time	$t_{90\%}$	Total floating time
Std Dev	13.80	1.67	1.67
Mean	17.11	4.25	5.29
C.V. %	80.64	39.39	31.48
PRESS	N/A	32.15	32.09
R-Squared	0.7108	0.7847	0.8324
Adj R-Squared	0.2287	0.7129	0.7766
Pred R-Squared	N/A	0.5876	0.6770
Adeq Precision	3.683	7.972	9.430

Based on the ANOVA data, it can be concluded that the independent variables (quantity of PEO WSR coagulant and concentration of sodium bicarbonate) had significant effect on the responses and using these responses, optimization was carried out.

Numerical optimization technique by the desirability function and graphical optimization technique by the overlay plot was utilized to optimize all the responses. Constraints were applied on the dependent and independent variables to obtain an optimized formulation. The constraints applied were: minimal floating lag time, 90% of drug releases within 6 - 7 hours and TFT of 8 hours or beyond. Through the desired response and overlay plot, the software calculated and recommended the statistically optimized formulation (figure 2). The optimum values of the independent and dependent variables obtained using the software was 34.45 mg of PEO WSR coagulant and 15% (% w/w) sodium bicarbonate. The formulation of the statistically optimized formula, BSO is shown in Table X. BSO followed first order kinetics with non-Fickian diffusion mechanism.

Table X

The statistically optimized formula suggested by the software

Ingredients	BSO
Diltiazem	30
PEO WSR Co	34.45
Sodium bicarbonate	30
Pharmatose	101.55
Magnesium stearate	2
Talc	2
Total weight	**200**

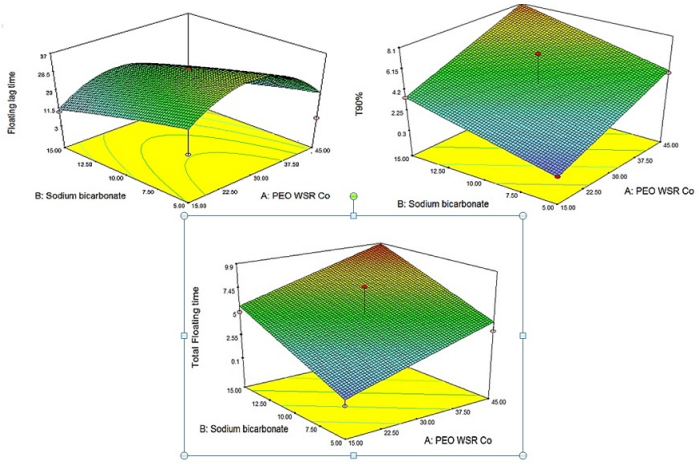

Figure 2.

Response surface plots for (from left) the effect of PEO WSR Co and sodium bicarbonate concentration on FLT, effect of PEO WSR Co and sodium bicarbonate concentration on $t_{90\%}$ and the effect of PEO WSR Co and sodium bicarbonate concentration on TFT

The evaluation and the validation of statistically optimized formulation

The statistically optimized formulation passed all the physicochemical tests. The results of the physicochemical, *in vitro* buoyancy and $t_{90\%}$ are shown in Table XI. From the *in vitro* buoyancy studies, the FLT was found to be at 19 seconds. The predicted value was 19.9 seconds. The percentage of relative error between the experimental and predicted value was 4.52% which is within 5%. The experimental $t_{90\%}$ and TFT were 6.4 hours and 8.5 hours respectively, compared to the 6.5 hours and 8.35 hours predicted by the software. The calculated relative errors were 1.80% for $t_{90\%}$ and 1.54% for TFT, all within 5%, concluding that the statistically optimized formulation is valid.

Table XI

Physicochemical, buoyancy characterization and $t_{90\%}$ of the B_{SO}

Formulation	Physicochemical characteristics				Buoyancy characteristics		$t_{90\%}$ (hr)
	Weight (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	FLT (sec)	TFT (hr)	
B_{S0}	202 ± 0.5	4 - 5	2.8 - 2.9	0.05	19	8.5	6.4

Drug interaction studies

Fourier transformation-infrared spectroscopy (FTIR)

Diltiazem HCl showed characteristic peaks at 2837 cm^{-1}, 2397 cm^{-1}, 1744 cm^{-1} and 1676 cm^{-1} which represented the aromatic CH stretch, the amine HCl N-H stretch, the esteric C=O stretch and the lactam C=O stretch respectively.

The FTIR spectrum of PEO WSR coagulant showed the characteristic –OH stretch at 3433 cm^{-1},

asymmetrical –C-O-C stretch at 1260 cm^{-1} and symmetrical –C-O-C stretch at 1060 cm^{-1}.

The statistically optimized PEO WSR coagulant based formula showed all the characteristic peaks of diltiazem HCl with minor shifts in the FTIR spectrum. The spectrum showed aromatic CH stretch at 2850 cm^{-1}, amine HCl N-H stretch at 2397 cm^{-1}, esteric C=O stretch at 1750 cm^{-1} and lactam C=O stretch at 1680 cm^{-1}. The FTIR spectrum of diltiazem HCl, PEO WSR coagulant and the statistically optimized formulation are shown in Figure 3.

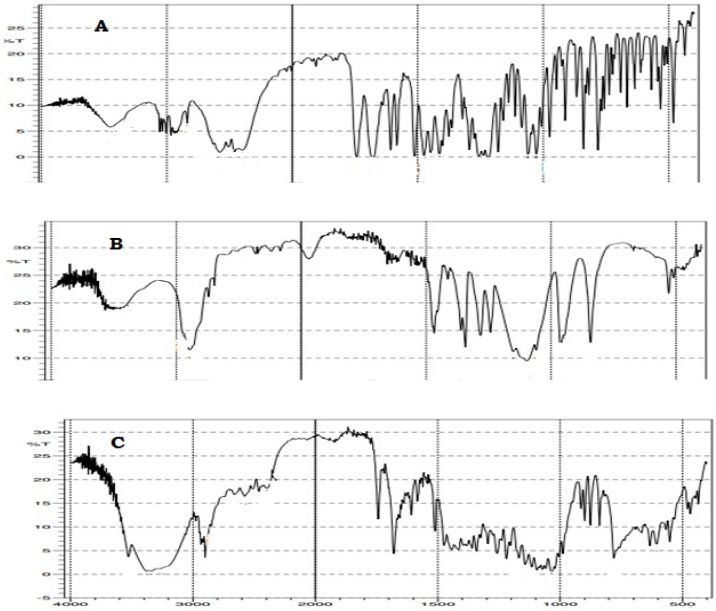

Figure 3.
FTIR spectra of A) diltiazem HCl, B) PEO WSR coagulant and C) BSO

Differential scanning calorimetry

The DSC thermogram of pure diltiazem HCl and PEO WSR coagulant showed endothermic peaks at 215°C and 72°C respectively, corresponding to their melting points. The statistically optimized formula showed endothermic peaks at 209°C and 68°C, representing the diltiazem HCl and PEO WSR coagulant respectively. A slightly decrease in energy indicates a small change in crystallinity which may be due to the physical interaction and not chemical interaction between the drug and polymer. The DSC thermograms for diltiazem HCl, PEO WSR coagulant and the statistically optimized formulation are shown in Figure 4.

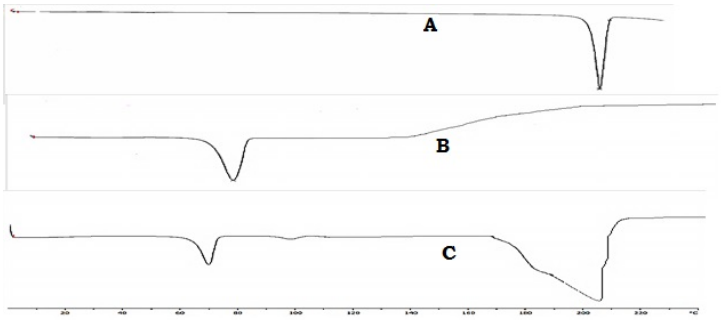

Figure 4.
DSC thermogram of A) diltiazem HCl, B) PEO WSR coagulant and C) BSO

Conclusions

This study involved the development of floating tablets of diltiazem HCl using the drug retarding agent PEO WSR coagulant and sodium bicarbonate as the gas generating agent. The statistical optimization technique such as central composite design had been employed to formulate the diltiazem HCl tablets. This technique is useful to get more accurate formulation with minimum number of experiments, so that wastage of excipients can be avoid. To further validate the experimental design, predicted values were compared with experimental values. The effect of formulation variables including

amount of polymer and gas generating agent on *in vitro* buoyancy and dissolution studies had been studied and discussed. A systemic study using the Central composite design revealed the optimized formulation that fulfilled all the requirement targets of FLT, $t_{90\%}$ and TFT.

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