THERMAL SINTERING: A NOVEL TECHNIQUE USED IN THE DESIGN OF GASTRORETENTIVE FLOATING TABLETS OF PROPRANOLOL HCl AND ITS STATISTICAL OPTIMIZATION USING BOX-BEHNKEN DESIGN

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Abstract

The objective of the present investigation was to formulate thermally sintered floating tablets of propranolol HCl using experimental design (Box Behnken) to study the effect of sintering conditions on drug release as well as buoyancy properties. Formulations were prepared using four independent variables namely polymer quantity, sodium bicarbonate concentration, sintering temperature and sintering time, where as floating lag time, and t_{95} are taken as dependent variables. The formulations were prepared by the direct compression method using polyethylene oxide (PEO) as release retarding polymer and were evaluated for *in vitro* dissolution studies. It was confirmed that the Quadratic model is suggested for floating lag time and the linear model is suggested for t_{95}. *In vitro* dissolution studies were carried out on the optimized formulation for verification of the theoretical prediction and found that experimental findings are in close agreement with the model predictions. The % relative error between the predicted values and experimental values of each response was found to be < 5%. The optimized formulation (PTSso) followed first order kinetics with erosion mechanism. The statistically optimized formulation was characterized with FTIR (Fourier transformation - infrared spectroscopy) and DSC (differential scanning calorimetry) studies and found no chemical interactions between drug and polymer.

Rezumat

Obiectivul lucrării a fost formularea tabletelor cu propranolol HCl sinterizate termic prin metoda *design*-ului experimental (Box Behnken). Formulările au prevăzut folosirea a patru variabile: cantitatea de polimer, concentrația de carbonat acid de sodiu, temperatura și timpul de sinterizare. Formularea optimă din punct de vedere statistic a fost caracterizată prin studii de spectroscopie în infraroșu cu transformată Fourier și calorimetrie diferențială, ne fiind evidențiate interacțiuni chimice între substanța activă și polimer.

Keywords: Sintering, Propranolol HCl, Gastro retentive, Polyethylene oxide, Floating.

Introduction

Sintering is a method of heating the material in a sintering furnace below its melting point (solid state sintering) until its particles adhere to each other. In this process polymer particles undergo fusion or formation of welded bonds between the particles. Sintering occurs at elevated temperature and involves mainly 3 major steps: joining of the adjacent particles together termed as neck growth, formation of interconnecting pore channels termed as densification followed by formation of spherical shape of particles which tends to flow into the pores within it due to the difference between vapour pressure and cross-sectional area of the pore's neck. These stages of sintering result in bonding of the particles together and ultimately in removal of internal porosity, causing external shrinkage and achievement of desirable physical properties [1].

Sintering occurs by diffusion of atoms through the microstructure. This diffusion is caused by a gradient of chemical potential by which atoms move from an area of higher chemical potential to an area of lower chemical potential.

Controlled release oral dosage forms were developed by sintering the polymer matrix to its glass transition temperature.

The sintering method involves the exposure of the dosage form to temperature which softens the polymer matrix and leads to formation of welded bonds. The drug particle gets entrapped in the matrix formed and this results in the controlled release of the active ingredient. However this method may be applied only to those drugs that are temperature resistant on exposure which is the limiting factor for many drugs that degrade at elevated temperatures.

There are only few reports on the applicability of thermal sintering technique for controlled release of drugs. The waxy material, carnauba wax was incorporated into the pellets by Singh R et al. using the thermal sintering technique. Inclusion of ground or emulsified carnauba wax did not control the release of theophylline for more than 3 hrs, whereas optimized temperature and duration of exposure for sintering of the matrix pellets controlled the release of the drug for a period of 12 hrs [2].

Siegel R et al. have shown that it was possible to form hemispheres by the sintering methods above the glass transition temperature of the polymer. Initial results with such sintered hemispheres have shown near constant release of polypeptides such as insulin at more than 70 $^{\circ}$C [3].

Ethylene vinyl acetate copolymers, carnauba wax were evaluated by Ramana Murthy K.V et al. in the preparation of controlled release systems of rifampacin and diclofenac sodium respectively. The release rate of the

drug was inversely related to the time of sintering which may be due to the fusion of polymer particles and formation of compact matrix [4-6].

There were no reports found till now on gastroretentive floating drug delivery systems with sintering technology. Hence in the present investigation the authors targeted to develop floating drug delivery systems of propranolol using the thermal sintering technology.

Propranolol is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity used for the treatment of hypertension [7]. It is highly lipophilic and almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver and on average, only about 25% of the amount of propranolol reaches the systemic circulation [8]. Polyethylene oxide (PEO), a hydrophilic polymer having the melting point in the range 70-80 °C, is selected for sintering in the present investigation.

The objective of the present study was to develop the thermally sintered floating tablets of propranolol HCl using Box Behnken design. In this study PEO quantity, sodium bicarbonate concentration, the sintering temperature and sintering time were selected as independent variables, while the floating lag time and t_{95} were selected as dependent variables. For this study Design Expert software was used, a programme that gives information regarding critical values for achieving the desired response and also the possible interaction effects of selected independent variables on dependent variable.

Materials and Methods

Materials

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

Experimental design

Thermally sintered gastroretentive floating tablets (TSGRFT) of propranolol HCl were developed by using Box Behnken experimental design. The independent variables selected were the polymer quantity, sodium bicarbonate concentration, sintering temperature and sintering time and the dependent variables selected were the floating lag time and t_{95} (time required to release 95% of the drug). The Box Behnken experimental design

suggested 29 experiments for four independent factors as shown in the Table 1.

Table I

Box Behnken design of thermally sintered formulations

Standard Order	PEO (mg) X_1	%w/w Sodium bicarbonate X_2	Sintering temperature (°C) X_3	Sintering time (hr) X_4
1	40	5	55	2.5
2	40	10	55	1
3	40	10	55	4
4	40	10	50	2.5
5	40	10	60	2.5
6	40	15	55	2.5
7	60	5	50	2.5
8	60	5	60	2.5
9	60	5	55	1
10	60	5	55	4
11	60	10	50	1
12	60	10	60	1
13	60	10	50	4
14	60	10	60	4
15	60	10	55	2.5
16	60	10	55	2.5
17	60	10	55	2.5
18	60	10	55	2.5
19	60	10	55	2.5
20	60	15	50	2.5
21	60	15	60	2.5
22	60	15	55	1
23	60	15	55	4
24	80	5	55	2.5
25	80	10	55	1
26	80	10	55	4
27	80	10	50	2.5
28	80	10	60	2.5
29	80	15	55	2.5

Preparation of floating tablets of propranolol HCl

Unsintered floating tablets

All the ingredients needed for a batch of 100 tablets according to the formulae suggested by the Design Expert software shown in Table II were accurately weighed and passed through the sieve 40. The drug was geometrically mixed with PEO until a homogeneous blend was achieved. Sodium bicarbonate was 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 in the polybag. The flow property of the final blend was found to be good, so 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 7 mm round plain punches.

Table II

Formulae of the GRFT of propranolol HCl using Box Behnken design.

Ingredients	**PTS 01**	**PTS 02**	**PTS 03**	**PTS 04**	**PTS 05**	**PTS 06**	**PTS 07**	**PTS 08**	**PTS 09**
Propranolol HCl	80	80	80	80	80	80	80	80	80
PEO	40	40	40	60	60	60	80	80	80
Sodium bicarbonate	6.5	13.5	21.5	7.5	15.5	25	8.5	18	28.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	2	2
Total weight (mg)	**128**	**135**	**143**	**149**	**157**	**166.5**	**170**	**180**	**190.5**

The general formulation code is designated as PTS X YZ, where PTS, X, Y and Z indicate propranolol thermal sintered tablet, batch no, temperature condition and time of exposure respectively.

Sintered floating tablets

The tablets were prepared as previously described. These tablets were exposed to three different temperatures, 50 °C, 55 °C and 60 °C and for three different time periods of 1, 2.5 and 4 hrs in a hot air oven maintained at the respective temperatures as suggested by the Design Expert software as shown in Table 1. The tablets were removed after the respective exposure times, cooled to room temperature and stored in a desiccator until further used.

Evaluation of the prepared floating tablets

The unsintered and sintered floating tablets were evaluated for *in vitro* buoyancy and dissolution studies. The observed responses were given in figures 1-7 and in table III.

Table III
Responses of unsintered and thermally sintered propranolol HCl formulations by Box Behnken design.

Formulation	Floating lag time (sec)	t_{95} (hr)
PTS01	231	3.5
PTS 02	184	4
PTS 03	135	6
PTS04	180	6
PTS05	142	5.8
PTS06	99	6
PTS07	110	6
PTS08	80	8
PTS09	45	9.8
PTS01 55-2.5	200	4.8
PTS02 55-1	170	7.6
PTS 02 55-4	155	8.8
PTS 02 50-2.5	175	6.8
PTS 02 60-2.5	153	8.7
PTS 03 55-2.5	125	8.2
PTS 04 50-2.5	171	8.8
PTS 04 60-2.5	146	11.2
PTS 04 55-1	165	8.9
PTS 04 55-4	152	10.4
PTS 05 50-1	136	6.8
PTS 05 60-1	115	9.7
PTS 05 50-4	121	11.2
PTS 05 60-4	103	13.2
PTS 05 55-2.5	126	11.3
PTS 05 55-2.5	124	11.2
PTS 05 55-2.5	127	11.3
PTS 05 55-2.5	125	11.2
PTS 05 55-2.5	128	11.2
PTS 06 50-2.5	91	7.3
PTS 06 60-2.5	72	13.1
PTS 06 55-1	86	8.9
PTS 06 55-4	72	12.8
PTS 07 55-2.5	104	12
PTS 08 55-1	66	10.8
PTS 08 55-4	52	13.9
PTS 08 50-2.5	75	11.1
PTS 08 60-2.5	56	15.3
PTS 09 55-2.5	35	12.9

In vitro buoyancy studies

All the formulated floating tablets (n=5) were subjected to *in vitro* buoyancy studies. The floating lag time was determined in one liter glass beaker containing 900 mL of 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as the floating lag time. The

period of time the dosage form constantly remained on the surface of medium was determined as the total floating time [9].

In vitro dissolution studies

In vitro release of propranolol hydrochloride from the prepared floating tablets was studied using USP XXIII dissolution test apparatus (LABINDIA, Disso 2000) employing the paddle stirrer (Apparatus-II). 900 mL of 0.1N HCl was used as dissolution medium maintained at a temperature of 37±0.5ºC and the paddle was rotated at 50 rpm [10]. Aliquots (5 mL each) were withdrawn at predetermined time intervals by means of a syringe fitted with 0.45 µm prefilter and immediately replaced with 5 mL of fresh medium maintained at 37±0.5ºC. The filtered samples were suitably diluted with the dissolution medium wherever necessary and the absorbance of the samples was measured at 289.

Statistical analysis of the data and optimization

Polynomial models including linear, interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA). The best fitting model was selected based on the comparisons of several stastical parameters including the coefficient of variation (CV), the coefficient of determination (R^2), adjusted coefficient of determination (adjusted R^2) and the predicted residual sum of square (PRESS) provided by the Design Expert software. In addition, statistical analysis namely the analysis of variance (ANOVA) to identify the significant effect of factors on response, regression coefficients, F test and P value were also calculated with the software.

The relationship between the dependent and independent variables was further elucidated by using contour and response surface plots (Figure 8-17). These plots are useful in the study of the effects of factors on the response at one time and predict the responses of dependent variables at the intermediate levels of independent variables. Subsequently, a numerical optimization technique by the desirability approach (Figure 18) and graphical optimization technique by the overlay plot (Figure 19) were used to generate the new formulations with the desired responses.

To validate the chosen experimental design, the resultant experimental values of the responses were quantitatively compared with those of predicted values and the percentual relative error was calculated by the following equation:

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

Characterization of the optimized formulation

Fourier transformation-infrared spectroscopy (FTIR)

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

Differential scanning calorimetry (DSC)

DSC analysis of the drug, polymer and statistically optimized formulation was performed using a Differential Scanning Calorimeter (Mettler Toledo Star SW 8.10, Model no: DSC 822). In this experiment, about 8-10 mg of the samples were weighed in an aluminum pan and were heated under nitrogen atmosphere from 5 °C to 250 °C.

Results and discussion

Evaluation of the tablets

All the unsintered and sintered tablets passed the physicochemical tests concerning the weight variation, assay and friability. Floating lag times of all the formulations were within the range of 35 to 210 sec (Table 3). As the sintered temperature increased, the floating lag time decreased.

The cumulative percent of the drug released from the sintered and unsintered formulations prepared by Box Behnken design with PEO are shown in the Figures 1-7. From the obtained results it was observed that the drug retarding property mainly depends upon the sintered temperature and the sintered time. The drug retarding property was directly proportional to the sintered temperature and the sintered time. The drug retarding property might be due to the formation of the welded bonds by softening of the polymer due to which the drug particles might have been entrapped in the matrix formed which results in the controlled release of the drug. From the results it was observed that as the concentration of polymer increased along with concentration of sodium bicarbonate, the drug release was retarded. This may be due to the increased intensity of air pockets surrounding the gellified surface of the tablet. The increase in the concentration of sodium bicarbonate at constant polymer concentration, also retarded the drug release due to the high intensity of the carbon dioxide gas pockets.

The responses of the sintered formulations were fitted to the linear, interaction and quadratic model using the Design Expert software. The Quadratic model and the linear model were suggested for floating lag time and t_{95} respectively.

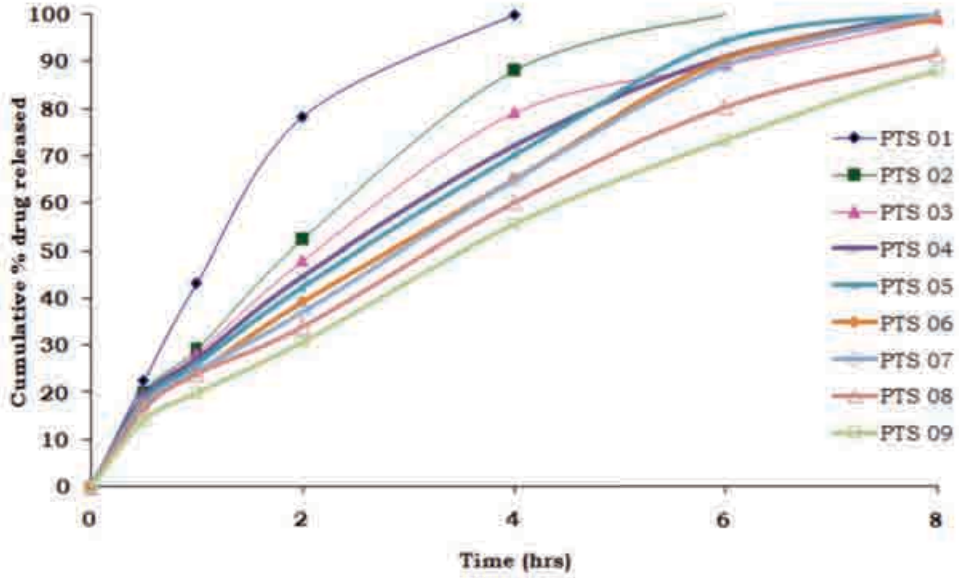

Figure 1
Dissolution profile of unsintered propranolol HCl formulations PTS 01 to PTS 09.

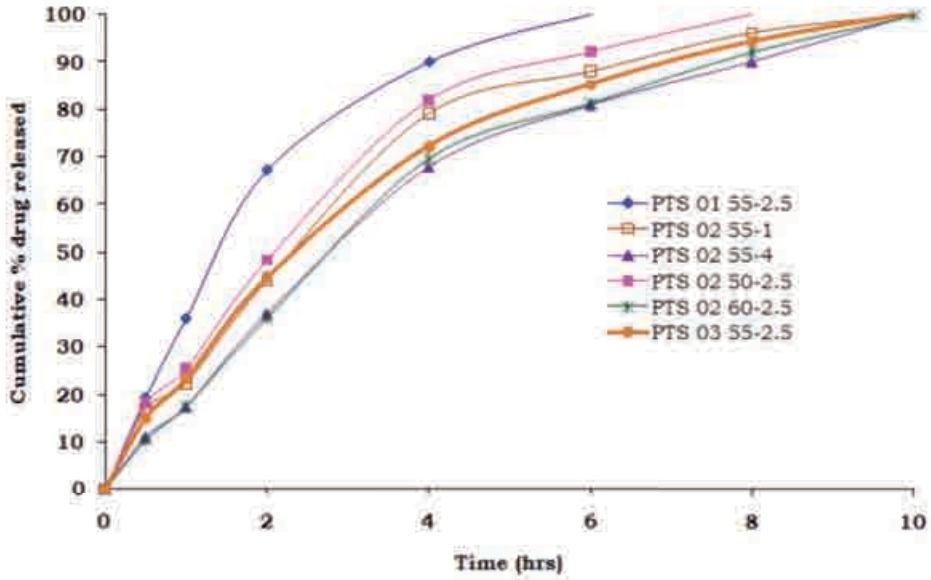

Figure 2
Dissolution profile of TSFT of PTS 01 to PTS 03.

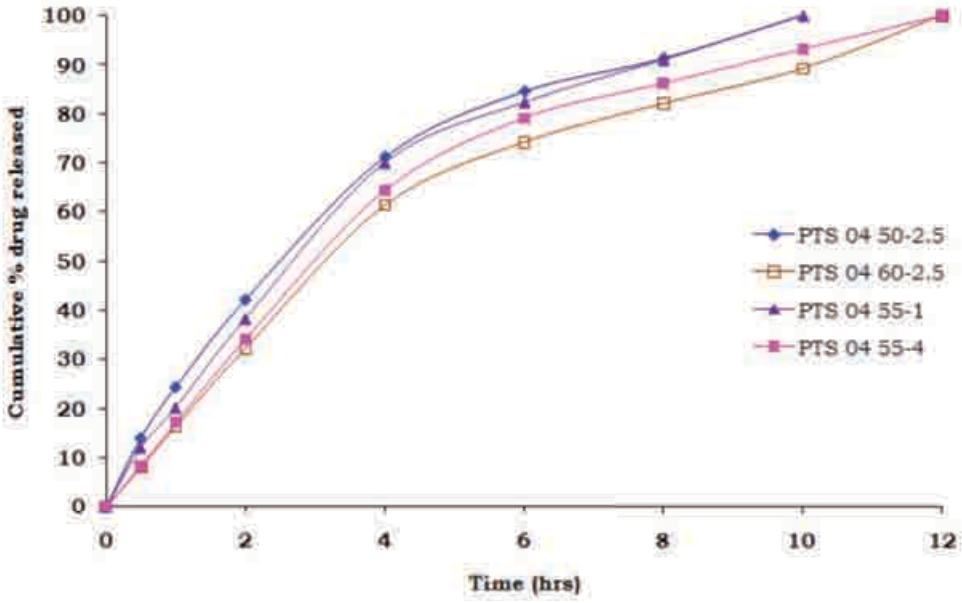

Figure 3
Dissolution profile of TSFT of PTS 04.

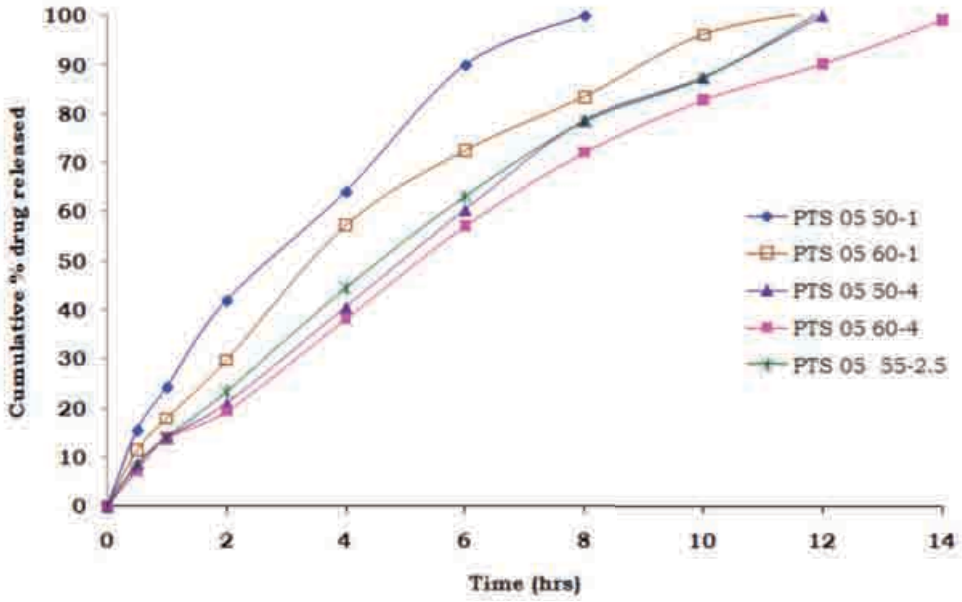

Figure 4
Dissolution profile of TSFT of PTS 05.

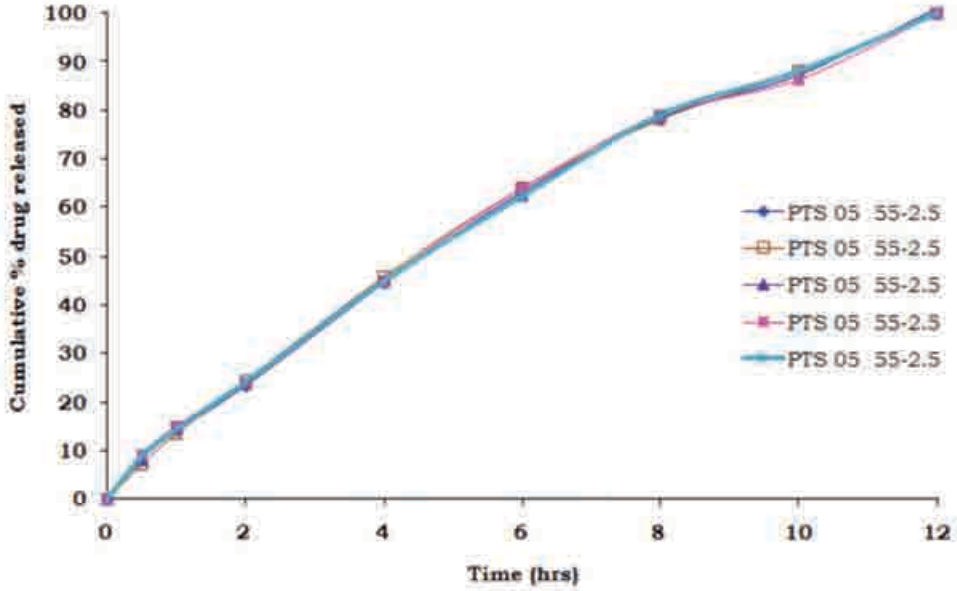

Figure 5
Dissolution profile of TSFT of PTS 05 at constant temperature.

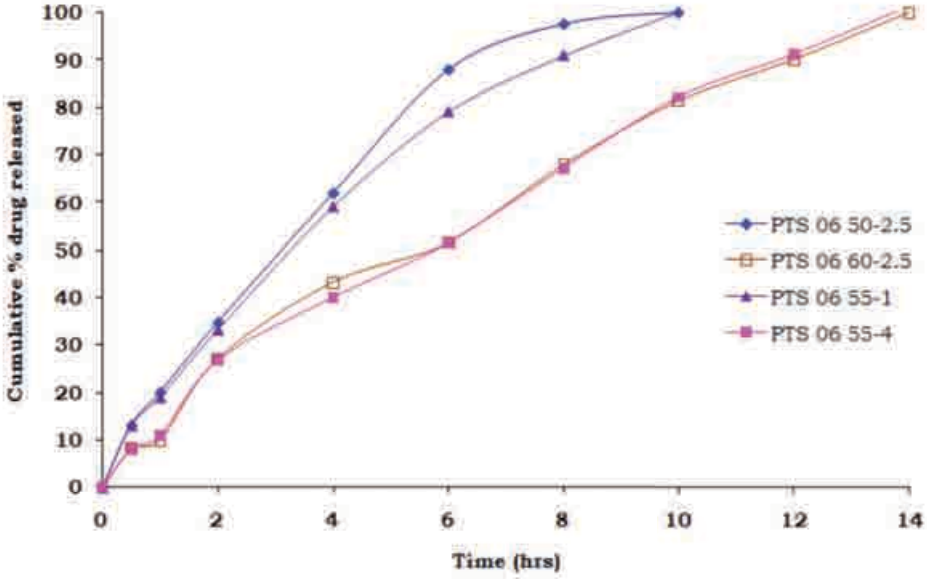

Figure 6
Dissolution profile of TSFT of PTS 06.

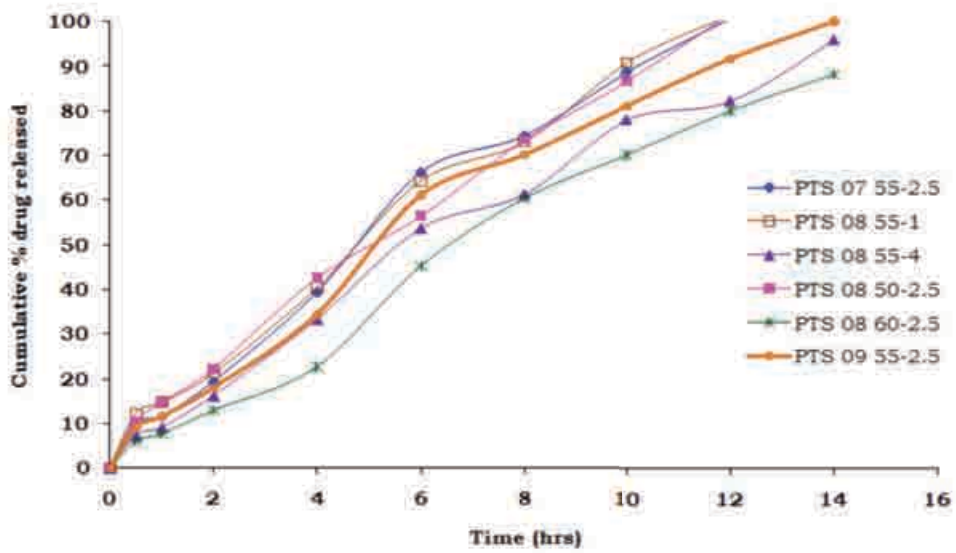

Figure 7
Dissolution profile of TSFT of PTS 07 to PTS 09.

Data analysis

The model parameters obtained from the analysis of variance (ANOVA) for the responses of all the formulations are shown in tables IV-VII. These parameters were used to construct the models that describe the effect of the independent variables on the responses.

Different batches of formulations within the experimental design were prepared to obtain floating tablets which were evaluated for their floating lag time and t_{95}. The F values for the responses floating lag time and t_{95} were found to be 425.37 and 37.69 respectively, which indicate that the models are significant. The values of Prob >F less than 0.05 for all the responses are indicating that the models are significant. The response of model terms A, B, C, D, A^2, C^2 and D^2 for floating lag time and A, B, C, D, BC, A^2 and B^2 for t_{95} were found to be significant. The F value of lack of fit for floating lag time and t_{95} was found to be 4.20 and 374.77 respectively which implies that the lack of fit is significant. Similarly 'R-squared' value was also calculated for all responses and found to be closer to the ideal value (i.e. zero). High 'R- squared' value signifies that the model terms are highly correlated to each other leading to a poor model. In contrast to this 'R- squared' value obtained in the present model is close to zero, which indicates a good model. In all the cases 'Pred R squared' values are in reasonable agreement with the 'Adj R squared' values. In all the cases 'Adeq Precision' values are in the range of 11 – 85 indicating an adequate

signal and that the model can be used to navigate the design space. The VIF (variance inflation factor) values for the all models were found to be near to one indicating a good estimation of coefficient.

The application of response surface methodology yielded the following regression equations which give an empirical relationship between the logarithmic values of floating lag time and t_{95}. Test variables in coded units:

Floating lag time = 126.00 – 49.17*A – 38.08*B – 10.33*C – 6.92*D + 1.50*A*B + 0.75*A*C + 0.25*A*D + 1.50*B*C – 0.25*B*D + 0.75*C*D – 8.75*A^2 – 2.13*B^2 – 2.75*C^2 – 5.38*D^2

t_{95} = 10.32 + 2.59*A + 0.59*B + 1.60*C + 1.47*D

Table IV

Analysis of variance (ANOVA) of thermally sintered formulations on floating lag time. (Quadratic model)

Parameters	Sum of squares	df	Mean Square	F value	p value Prob>F	Remark
Model	48882.53	14.00	3491.61	425.37	< 0.0001	significant
A-PEO	29008.3	1.00	29008.3	3534.01	< 0.0001	
B-Sodium bicarbonate	17404.0	1.00	17404.0	2120.29	< 0.0001	
C-Sintered temperature	1281.33	1.00	1281.33	156.10	< 0.0001	
D-Sintered time	574.08	1	574.08	69.94	< 0.0001	
AB	9.00	1	9.00	1.10	0.313	
AC	2.25	1	2.25	0.27	0.609	
AD	0.25	1	0.25	0.03	0.864	
BC	9.00	1	9.00	1.10	0.313	
BD	0.25	1	0.25	0.03	0.864	
CD	2.25	1	2.25	0.27	0.609	
A^2	496.62	1	496.62	60.50	< 0.0001	
B^2	29.29	1	29.29	3.57	0.08	
C^2	49.05	1	49.05	5.98	0.028	
D^2	187.40	1	187.40	22.83	3E-04	
Residual	114.92	14	8.21			
Lack of Fit	104.92	10	10.49	4.20	0.09	NS
Pure Error	10.00	4	2.50			
Cor Total	48997.45	28				

Std. Dev.	2.87	R-Squared	0.9977
Mean	118.14	Adj R-Squared	0.9953
C.V. %	2.43	Pred R-Squared	0.9873
PRESS	619.95	Adeq Precision	84.6879

df: degree of freedom, NS: not significant

Table V

Model coefficients of thermally sintered formulations estimated by multiple regression on floating lag time (significance of regression coefficients)

Factor	Coefficient estimate	df	Standard error	95% CI low	95% CI high	VIF*
Intercept	126.00	1	1.28	123.25	128.75	
A-PEO	-49.17	1	0.83	-50.94	-47.39	1.00
B-Sodium bicarbonate	-38.08	1	0.83	-39.86	-36.31	1.00
C-Sintered temperature	-10.33	1	0.83	-12.11	-8.56	1.00
D-Sintered time	-6.92	1	0.83	-8.69	-5.14	1.00
AB	1.50	1	1.43	-1.57	4.57	1.00
AC	0.75	1	1.43	-2.32	3.82	1.00
AD	0.25	1	1.43	-2.82	3.32	1.00
BC	1.50	1	1.43	-1.57	4.57	1.00
BD	-0.25	1	1.43	-3.32	2.82	1.00
CD	0.75	1	1.43	-2.32	3.82	1.00
A^2	-8.75	1	1.12	-11.16	-6.34	1.08
B^2	-2.13	1	1.12	-4.54	0.29	1.08
C^2	-2.75	1	1.12	-5.16	-0.34	1.08
D^2	-5.38	1	1.12	-7.79	-2.96	1.08

* - Variance inflation factor CI – Confidence interval

The contour and response surface plots for the responses of all formulation factors are shown in Figure 8-17. In contour and response plots, the response surface is established as a function of two factors at a time, holding all other factors at fixed levels which is more helpful in understanding both the main and the interaction effects of these two factors. Contour and surface plots were drawn for polymer quantity (mg) and %w/w

of sodium bicarbonate, polymer quantity and sintered temperature (°C), polymer quantity and sintered time (hrs), % w/w of sodium bicarbonate and sintered temperature and % w/w of sodium bicarbonate and sintered time. The contour and surface plots depend upon the number of dependent variables considered for the design.

Table VI

Analysis of variance (ANOVA) of thermally sintered formulations on t_{95}. (Linear model)

Parameters	Sum of squares	df	Mean Square	F value	p value Prob>F	Remark
Model	141.34	4	35.33	37.69	< 0.0001	significant
A-PEO	80.60	1	80.60	85.98	< 0.0001	
B-Sodium bicarbonate	4.20	1	4.20	4.48	0.0448	
C-Sintered temperature	30.72	1	30.72	32.77	< 0.0001	
D-Sintered time	25.81	1	25.81	27.54	< 0.0001	
Residual	22.50	24	0.94			
Lack of Fit	22.49	20	1.12	374.77	< 0.0001	significant
Pure Error	0.01	4	0.00			
Cor Total	163.83	28				

Std. Dev.	0.97	R-Squared	0.8627
Mean	10.32	Adj R-Squared	0.8398
C.V. %	9.38	Pred R-Squared	0.7975
PRESS	33.18	Adeq Precision	20.8528

df: degree of freedom, NS: not significant

Table VII

Model coefficients of thermally sintered formulations estimated by multiple regression on t_{95}. (significance of regression coefficients)

Factor	Coefficient estimate	df	Standard error	95% CI low	95% CI high	VIF*
Intercept	10.32	1	0.18	9.95	10.70	
A-PEO	2.59	1	0.28	2.01	3.17	1.00
B-Sodium bicarbonate	0.59	1	0.28	0.01	1.17	1.00
C-Sintered temperature	1.60	1	0.28	1.02	2.18	1.00
D-Sintered time	1.47	1	0.28	0.89	2.04	1.00

* - Variance inflation factor CI – Confidence interval

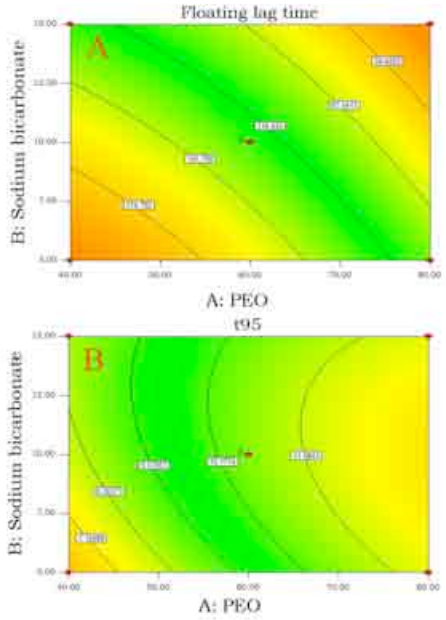

Figure 8
Contour plot for the effect of PEO and sodium bicarbonate on dependent variables. (A): Floating lag time (B):t_{95}

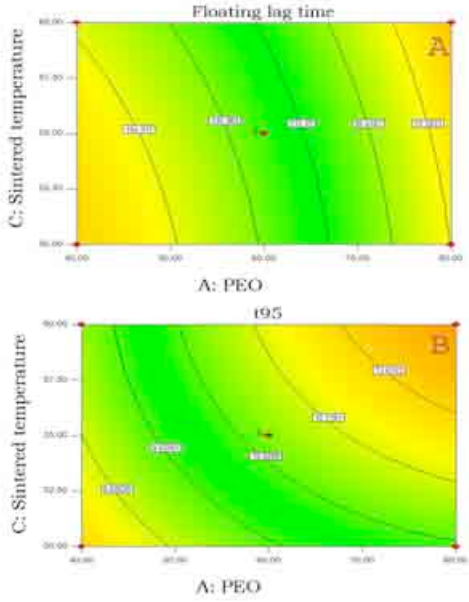

Figure 9
Contour plot for the effect of PEO and sintered temperature on dependent variables. (A): Floating lag time (B): t_{95}

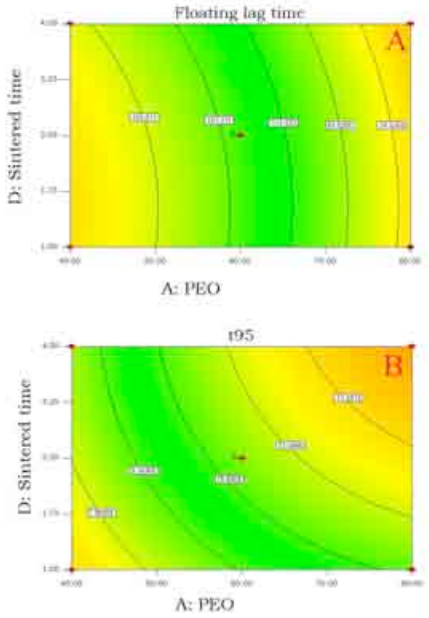

Figure 10
Contour plot for the effect of PEO and sintered time on dependent variables. (A): Floating lag time (B):t_{95}

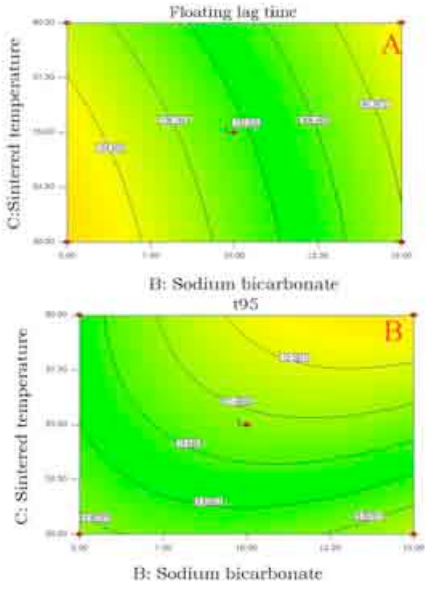

Figure 11
Contour plot for the effect of sodium bicarbonate and sintered temperature on dependent variables. (A): Floating lag time (B):t_{95}

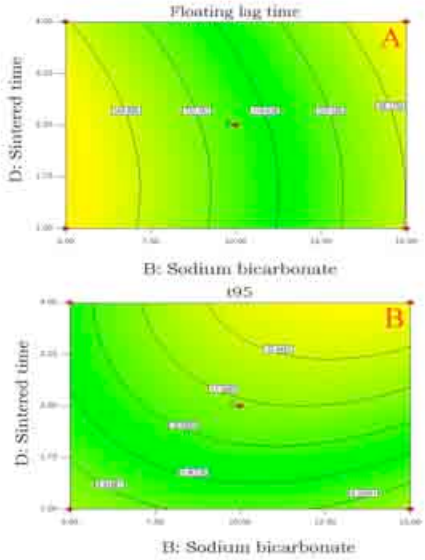

Figure 12
Contour plot for the effect of sodium bicarbonate and sintered time on dependent variables. (A): Floating lag time (B): t_{95}

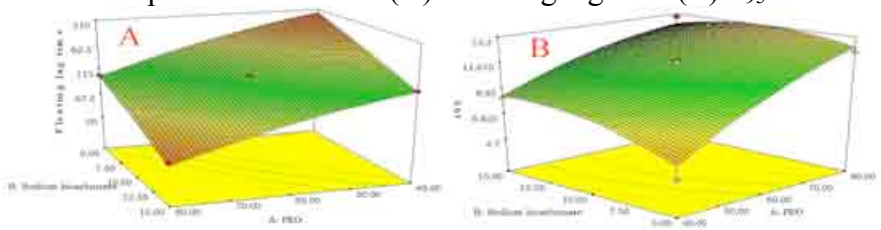

Figure 13
Response surface plot for the effect of PEO WSR Coagulant and sodium bicarbonate on dependent variables. (A): Floating lag time (B): t_{95}

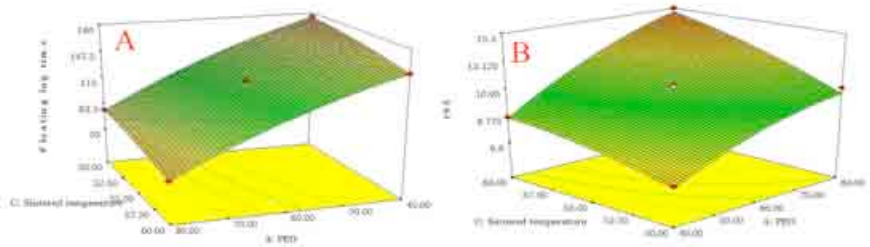

Figure 14
Response surface plot for the effect of PEO WSR Coagulant and sintered temperature on dependent variables. (A): Floating lag time (B): t_{95}

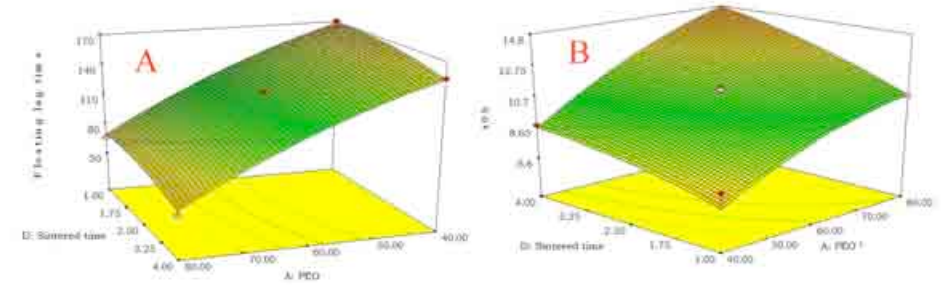

Figure 15
Response surface plot for the effect of PEO WSR Coagulant and sintered time on dependent variables. (A): Floating lag time (B): t_{95}

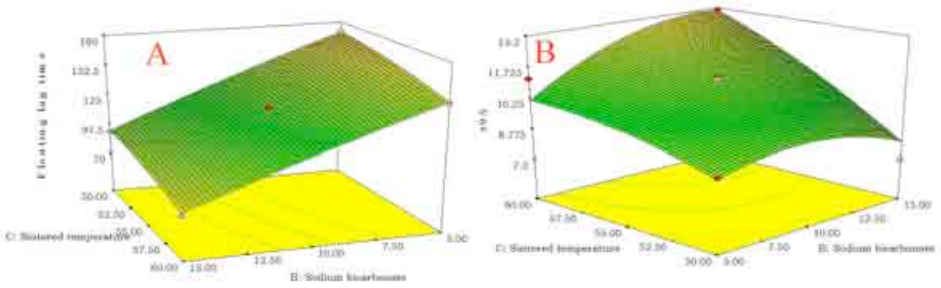

Figure 16
Response surface plot for the effect of sodium bicarbonate and sintered temperature on dependent variables. (A): Floating lag time (B): t_{95}

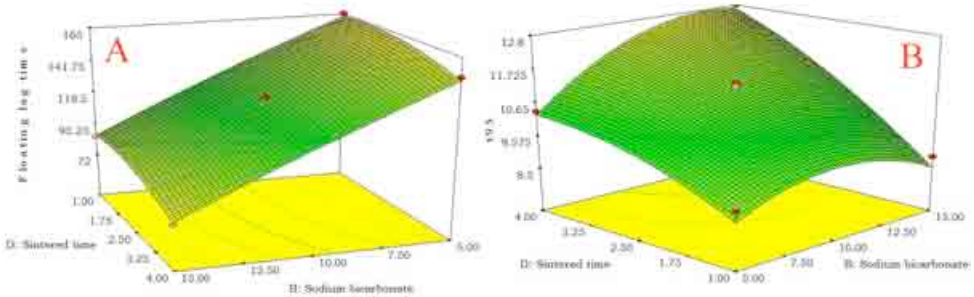

Figure 17
Response surface plot for the effect of sodium bicarbonate and sintered time on dependent variables. (A): Floating lag time (B): t_{95}

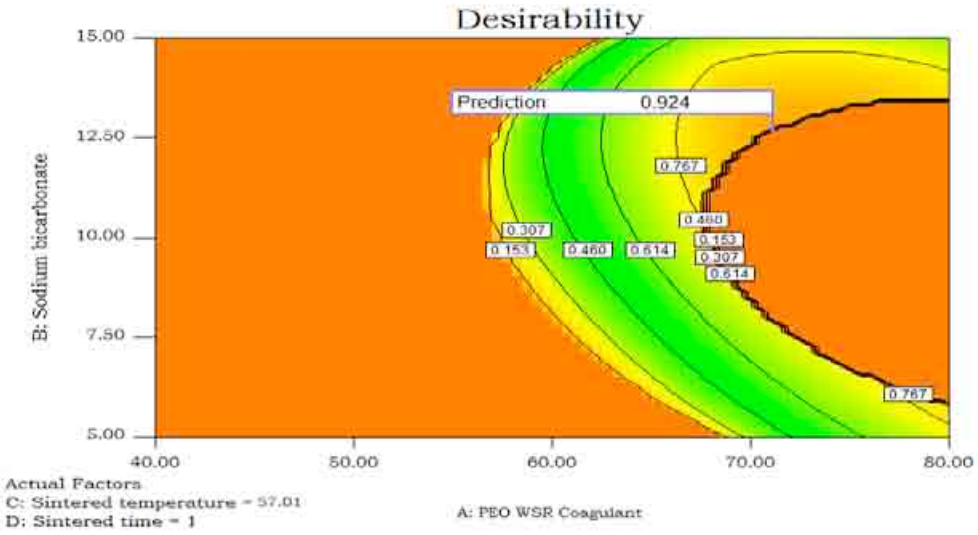

Figure 18

Desirability for optimization of thermally sintered floating tablets of propranolol HCl.

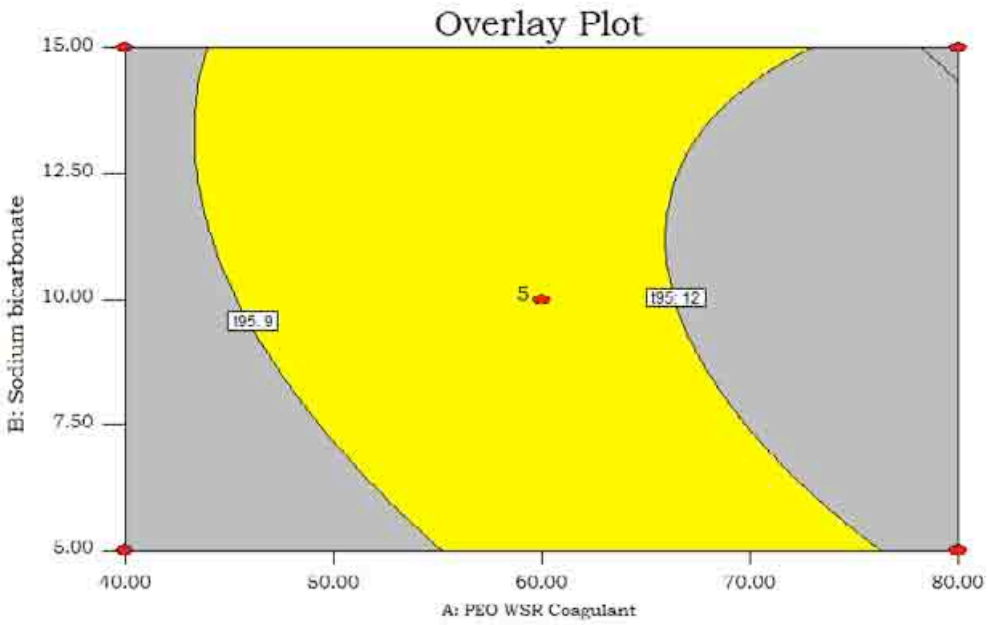

Figure 19

Overlay plot for the optimization of thermally sintered floating tablets of propranolol HCl.

Optimization

To optimize all the responses with different targets, a multi criteria decision approach like a numerical optimization technique by the desirability function and graphical optimization technique by the overlay plot were used (Figure 18 -19). The optimized formulation was obtained by applying constraints on dependent variable responses and independent variables.

The optimized formulation was selected based on the criteria to attain the minimal floating lag time and 95% of the drug to be released in between 11 to 12 hrs and these constrains are common for all the formulations. Various feasibility and grid searches were executed to establish the optimum formulation by plotting desirability function response plot and overlay plot. The recommended concentrations of the independent variables were calculated by the Design Expert software from the above plots which indicated the highest desirability close to 1.0.

The optimum values of selected variables were obtained by using Design Expert software which are given in Table VIII. 70.47 mg of PEO and 12.77 %w/w of sodium bicarbonate along with 57.01 °C of sintered temperature and 1hr sintered exposure time were found to be optimal conditions for the development of TSFT designated as PTSso and the formula is given in Table IX.

Table VIII

The obtained optimal values of independent variables.

Optimal (critical) values	PTSso
PEO: A (mg)	70.47
% w/w of sodium bicarbonate: B	12.77
Sintered temperature: C (°C)	57.01
Sintered time: D (hrs)	1

Table IX

Formula of statistically optimized formulation

Ingredients	PTSso
Propranolol HCl	80
PEO	70.47
Sodium bicarbonate	22.53
Magnesium stearate	2
Total weight (mg)	**175**

Table X

Tabletting characteristics of statistically optimized TSFT of propranolol HCl.

Formulation	Weight[x] (mg)	Assay[y] (%)	Hardness (Kg/cm^2)	Friability (%)	Floating lag time (sec)	Total floating time (hrs)
PTSso	175±0.26	99.94±0.49	4 - 6	0.21	74	12

x: mean ± s.d. (n=20) ; y: mean ± s.d. (n=10)

Table XI

Comparison of predicted and observed responses of statistically optimized TSFT of propranolol HCl

Formulation	Response	Observed	Predicted	% Relative error
PTSso	Floating lag time (sec)	74	73.67	-0.45
	t_{95} (hrs)	11.2	11.18	-0.18

Evaluation and validation of optimized formulations

The optimized formulation fulfilled all the criteria of physicochemical properties shown in Table X. *In vitro* dissolution studies were carried out on the optimized formulation for the verification of the theoretical prediction. These experimental findings are in close agreement with the model predictions and are shown in Table XI. The % relative error between the predicted values and experimental values of each response was calculated and the values were found to be <5%. The experimental values were in agreement with the predicted values, which confirmed the predictability and validity of the model.

The optimized formulation showed a 74 sec floating lag time, 12 hrs of total floating time. The obtained t_{95} was found to be 11.2 hrs which followed the first order with erosion mechanism.

Characterization of the optimized formulation

Fourier Transformation-Infrared Spectroscopy (FTIR)

The FTIR spectrum of propranolol HCl, PEO and statistically optimized formulation are shown in Figure 20. Propranolol HCl showed characteristic secondary amine –N–H stretch at 3282cm^{-1}, C-H stretch at 2961 cm^{-1} , Aryl C=C stretch at 1581 cm^{-1} , Aryl 0-CH_2 asymmetric stretch at 1240 cm^{-1} , Aryl 0-CH_2 symmetric stretch at 1031 cm^{-1} and the peak at 793 cm^{-1} due to alpha- substituted naphathalene.

The FTIR spectrum of PEO showed the characteristic alcoholic –OH stretch at 3433 cm^{-1}, -C-O-C asymmetric stretch at 1260 cm^{-1} and -C-O-C symmetric stretch at 1060 cm^{-1}.

Thermally sintered optimized PEO based formulation showed all the characteristic peaks of propranolol HCl with minor shifts in its FTIR spectrum. This spectrum showed secondary amine –N–H stretch at 3285 cm^{-1}, C-H stretch at 2973 cm^{-1} , Aryl C=C stretch at 1581 cm^{-1} , Aryl 0-CH_2 asymmetric stretch at 1237 cm^{-1} , Aryl 0-CH_2 symmetric stretch at 1022cm^{-1} and the peak at 790 cm^{-1} due to alpha- substituted naphthalene. The absence of any changes in the FTIR spectra for the selected formulations indicated no chemical interaction between the PEO and drug.

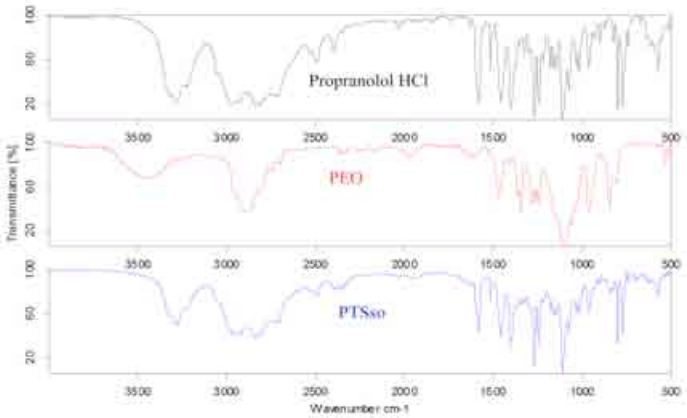

Figure 20
FTIR spectra of propranolol HCl, PEO WSR Coagulant and statistically optimized sintered formulation (PTSso)

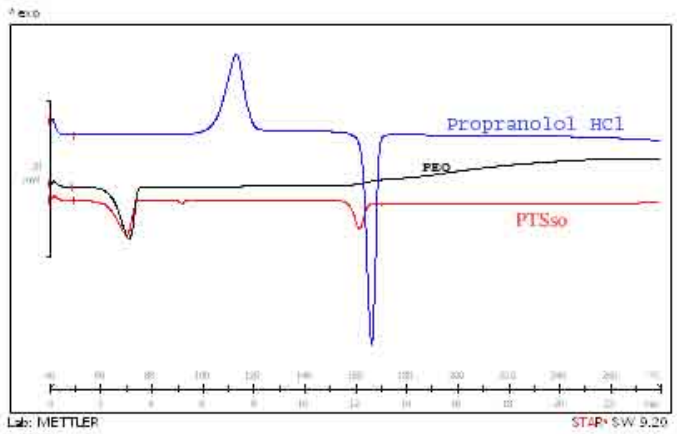

Figure 21
DSC thermogram of propranolol HCl, PEO WSR Coagulant and statistically optimized sintered formulation (PTSso)

Differential scanning calorimetry (DSC)

The DSC thermogram of propranolol HCl, PEO and PTSso are shown in Figure 21. The DSC thermogram of pure drug propranolol HCl showed a sharp endothermic melting peak at 168.12°C, similarly PEO WSR Coagulant at 71°C that corresponds to the respective melting points. The formulation PTSso showed sharp endothermic peaks at 69.1°C and 167.13°C, representing the polymer and drug peaks respectively. From the obtained results, it was observed that the PTSso thermogram showed a slight decrease in the energy change of melting endotherm, which confirmed minor extent of reduction in the crystallinity of the drug but without statistical significance. From the obtained results, it can be concluded that the shift observed in the endothermic peak of the propranolol HCl in the formulation PTSso may be due to the physical interaction between the drug and the polymer and that there were no chemical interactions.

Conclusions

The present study clearly indicates the applicability of statistical optimization for the prediction of the optimized concentrations of the excipients which influences the product parameters. The theoretical predictions suggested were obtained practically, which is an experimental success as in the present case. The concept of the thermal sintering was studied in order to reduce the polymer quantity with the desired dissolution profile.

From the experimental data it is concluded that there was a decrease in the floating lag time, an increase in the total floating time with the duration of exposure to varying temperatures. In addition, *in vitro* drug release was retarded with the increase in the duration of exposure to the sintering temperature. Hence, it can be concluded that the thermal sintering technique can be used in the design of gastroretentive floating tablets of propranolol HCl using PEO as retarding polymer.

Acknowledgements

The author M.V.Srikanth is thankful to UGC (University Grants Commission, India) for awarding Junior Research Fellowship for carrying out this project. One of the authors, M.V.Srikanth, is thankful to G.V.Murali mohan babu, C. Vasu and K Praveen kumar for providing valuable information to carry out the research work.

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Manuscript received: November 21st 2011