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Formulation Design and Optimization of Sustained Released Matrix Tablets of Propranolol HCl Using Natural and Synthetic Polymers

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ABSTRACT

The proposed research work aimed to design, formulate and finally to evaluate sustained released matrix tablets of propranolol hydrochloride using the combination of hydrophilic and hydrophobic polymers. Formulation and optimization of Propranolol HCl was done by direct compression technique using 3^2 factorial design. The amount of polymer Mastic gum (X_1) and HPMC (X_2) were chosen as independent variables and their effect on amount of drug release at 2 hours (Y_1) , 4 hours (Y_2) and 8 hours (Y_3) at three levels low (-1), medium(0) and high(+1) was taken as dependent variable. Drug-excipient compatibility studies were performed by FTIR and DSC analysis. A total of 9 combinations of sustained released tablets were formulated and evaluated for both pre and post compression parameters. Design expert software version 10 was used to evaluate the effect of independent variable over dependent variable and to generate polynomial equation to represent experimental results. The B7 formulation containing 5 % of mastic gum and 25% of HPMC K-15 combination showed 60.13% drug release in 8 hours and was chosen as optimized formulation. Release kinetic mechanism indicated that the optimized formulation fitted well into Kosmeyer Peppas model (R^2= 0.9974). Stability studies indicated that selected formulation was stable for 90 days. Formulation containing 5% of mastic gum and 25% HPMC was found to be effective and can be explored further to develop sustained released formulations.

Keywords: Sustained release, mastic gum, factorial design, propranolol HCl.

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INTRODUCTION

Sustained drug delivery is specialized form of modified drug delivery that offer the advantage of reducing the dose frequency as compared to conventional dosage forms for those drug candidate that have rapid clearance rate due to short elimination half life. Oral sustained release formulations are capable of achieving a steady therapeutic drug blood level by continuously releasing the drug for long duration after a single dose administration thus offering better patient compliance and control over therapy.[1, 2] Depending upon release kinetics these systems are designated as continuous release, delayed transit and continuous release and delayed released systems. The mechanism involved in drug release may be dissolution, diffusion, and dissolution along with diffusion. Among all these systems, dissolution controlled system are the most acceptable one. The dissolution controlled release system is further classified as matrix dissolution control/ encapsulating/ or reservoir device type. Matrix systems are mostly preferred for sustained release dosage forms because they are simple to design, economical. Formulation of matrix systems involves the dispersion or dissolving the drug into polymeric matrix that retard the drug release and then blending with other additives to formulate a tablet dosage form.[3, 4] Releases retardant mainly used are hydrophilic and hydrophobic polymers. Different natural and synthetic polymers are matix forming agents in order to control the drug release. Mastic gum is a natural oleoresin exudate isolated from the stems and leaves of *Pistacia lentiscus*. It is known to posse's anti-oxidant, antimicrobial, anti-inflammatory and hepatoprotective activity. Recent studies demonstrated its use as tablet binder, microencapsulating agent and matrix former in the formulation of sustained released dosage forms. Propranolol hydrochloride is a non selective beta adrenergic blocking agent prescribed in high blood pressure, angina pectoris and many other cardiovascular disorders.[5] The oral bioavailability of Propranolol hydrochloride is low. It is a highly water soluble drug with relatively short biological half life of 3-6 hours and a dose of 40 mg thrice daily. This high dosing frequency results in fluctuation of plasma drug level; therefore it is needed to have in sustained release dosage form to reduce dose frequency and improve patient compliance. The purpose of the present study is to formulate and optimize sustained released matrix tablets of Propranolol HCl using hydrophilic polymer HPMC K-15 and hydrophobic polymer mastic gum as a material for matrix formation with improved patient compliance.[6]

METHODOLOGY

Propranolol HCl and mastic gum were procured from Yarrow chem, Mumbai, India. HPMC K-15 was taken from Loba chemie Pvt. Ltd, Mumbai, India. All other chemical used were of laboratory and analytical grade

Standard calibration of Propranolol hydrochloride

A standard calibration curve of Propranolol HCl was plotted in Phosphate buffer pH 6.8 and 0.1N HCl having pH 1.2. A stock solution of drug was prepared by dissolving 100 mg of drug in phosphate buffer pH 6.8 and 0.1N HCl. The volume was made up to 100ml to prepare stock solution (A) to get a concentration of 1000 µg/ml.10 ml of stock solution (A) was further diluted to 100 ml to obtain stock solution (B) with concentration 10 µg /ml. Aliquots of stock solution (B) was diluted to obtain working solutions of concentration 2 to 20 µg/ml.[7] The absorbance of the final solutions were taken at 290nm using double beam UV spectrophotometer, Systronics (AU – 2701).

Compatibility studies of drug and excipients

Compatibility studies were carried by FTIR and DSC analysis. FTIR spectrum of pure drug Propranolol HCl, Polymer (mastic gum) and mixture of drug with polymer (1:1) was taken using Bruker Alpha T instrument by KBr pellet method. The spectra were scanned over a frequency range 4000-400 cm^{-1}. The possibility of drug-excipient interaction was also investigated by DSC. The samples set in a DSC instrument Mettler Toledo (model number: Star 1). The DSC thermograms of pure drug, a mixture of drug with mastic gum, HPMC, Magnesium stearate, aerosil, microcrystalline cellulose were taken. The thermal analysis was performed at a heating rate of 10.00° C/min over a temperature range 98-80°C.

Design of Experiment

A 3^2 full factorial design given in **Table 1** was used to assess the combined effect of independent variables on the dependent variable. Two factors were assessed at three levels, high, medium and low. The experimental trials were taken on all 9 possible combinations. Statistical model including mathematical polynomial equation was generated to study the response.[8]

Table 1. Design format of 3^2 factorial designs

Formulation batches	Variable X_1	Variable X_2
B1	-1	-1
B2	0	-1
B3	+1	-1
B4	-1	0
B5	0	0
B6	+1	0
B7	-1	+1
B8	0	+1
B9	+1	+1

Where +1 is higher level,-1is lower level and 0 is mid level for the independent variables.

Polynomial equation generated by this design is as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2 \qquad \text{Equation: 1}$$

Where Y is the response variable b_0 is the arithmetic mean response of the 9 trials, and b_1 and b_2 are the regression coefficients. The main effects (X_1 and X_2) are represents the average results of changing 1 factor at time from its low to high value. The interaction terms (X_1 X_2) show how the response varies when two factors are simultaneously varied. The polynomial terms (X_1 X_1 and X_2X_2) are included to investigate nonlinearity. The level of independent variables and their coding is given in **Table 2**.

Table 2. Levels for independent variables and coding of variable

Levels	Coded value	Concentration of HPMC (%)X_1	Concentration of Mastic gum (%)X_2
Low	-1	5	5
Medium	0	15	15
High	+1	25	25

Preparation of sustained release tablets

The propanolol HCl matrix tablets having a net weight of 200 mg were compressed by direct compression method. All the excipients as per the composition were previously passed through sieve no.60 to get uniform particle size were weighed accurately and mixed thoroughly for 15 min. After mixing powder blend was transferred to double punch tablet punching machine (A.K industries) for compression. The detailed composition of the prepared tablets using 3^2factorial design is given in **Table 3**.

Table 3. Composition of factorial design batches

Ingredients (mg)	B1	B2	B3	B4	B5	B6	B7	B8	B9
Propanolol HCl	40	40	40	40	40	40	40	40	40
HPMC K 15	10	10	10	30	30	30	50	50	50
Magnesium stearate	2	2	2	2	2	2	2	2	2
Mastic gum	10	30	50	10	30	50	10	30	50
Microcrystalline cellulose	136	116	96	76	96	76	96	76	56
Aerosil	2	2	2	2	2	2	2	2	2

Net weight of each tablet = 200 mg

Evaluation of sustained released matrix tablets

Pre compression parameters

The micromeritics of all the compositions (B1to B9) were evaluated by calculating their bulk density, tapped density, angle of repose, carr's index and hausner's ratio.[9]

Post compression parameters:

Weight variation

To ensure uniformity in tablets weight, twenty tablets were selected at random from each batch and average weight was determined. Then the individual tablet weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation as per the official specifications.[10]

% deviation= Average weight - Individual weight /Average weight X 100

Thickness

The thickness of tablets was measured by Vernier calipers to ensure uniformity in thickness. This is done by taking three tablets at random from each batch. It is expressed in mm.

Hardness

To find tablet hardness Monsanto hardness tester was used. Three tablets from each batch were taken and the average value with standard deviation was taken as tablet hardness. It is expressed in kg/cm^2.

Percent Friability

Tablets friability was assessed using Roche friabilator. Ten tablets from each formulation batch were initially weighed and placed in Roche friabilator rotated at 25 rpm for 4 minutes with 100 revolutions.[11] Then final weight was taken. The percentage friable loss was calculated using the formula:

% Friability = initial weight –final weight / initial weight X 100

Content uniformity

Uniformity in drug distribution was carried out by triturating ten tablets to fine powder. Powder equivalent to the 40 mg of drug was weighed and dissolved in 100 ml of phosphate buffer pH 6.8 and after suitable dilution absorbance was measured using UV-visible spectrophotometer at λ_{max} 290nm.[12]

Swelling index

Swelling index of formulated batches was estimated by placing the initially weighed tablet into a petriplate containing 5ml of phosphate buffer pH 6.8. After a regular interval of time the tablets were removed and swollen tablets were weighed. This was done for the period of 6hours.[13]

In vitro dissolution studies

The *in vitro* drug release studies were done using basket type dissolution test apparatus in 900 ml of 0.1 N HCl pH 1.2 as dissolution medium for 2 hours followed by phosphate buffer pH 6.8. The basket was adjusted at 50rpm and the temperature of 37±1°C was maintained throughout the experiment. A sample of 5ml was withdrawn at different time intervals for 8 hours. Each sample was filtered using membrane filter with a pore size of 0.45 mm and was analyzed after appropriate dilution by UV spectrophotometer at λ_{max} 290nm.[14]

Drug release kinetic study

To assess release kinetics, various mathematical equations have been used, namely zero order, first order, Higuchi model and Kosmeyer Peppas equation.[15] The most suitable model was selected on the basis of the value of regression coefficient near to unity.

Selection of optimized formulations

For the selection of optimized formulation, a simple exhaustive grid search was done. The regression equations were calculated for different combinations of independent variables and the response values were compared for the selection of optimized formulation. The areas that give the optimum value for each studied response was found using overlay plot.

Comparison of optimized formulation with commercial brand

The optimized formulation selected by design expert software was then compared with one of commercial brand of propranolol HCl tablet, Inderal 40 (Abott India Ltd) for its *in vitro* drug release.

Stability studies

The optimized formulation was subjected to stability studies after packing in aluminum pack as per ICH guidelines for 90 days at 40°C ± 2°/ 75% RH ± using stability test chamber (Remi elektrotechnik Ltd; Vasai, India). Test sampling was done at different time points for analysis.[16]

RESULTS and DISCUSSION

Preformulation studies

Standard calibration curve of propranolol Hydrochloride

Standard calibration curve of drug plotted in 0.1N HCl and pH 6.8 phosphate buffers is shown in **Figure 1 and 2,** the R^2 value was found to be 0.9995 and 0.9857 respectively which indicated the linearity of the graph.

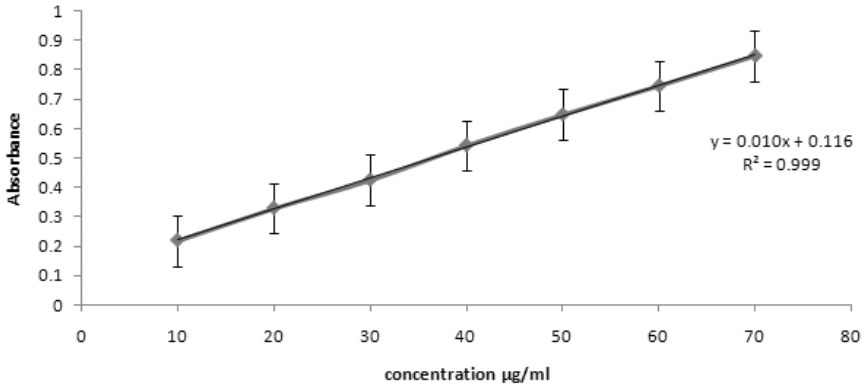

Figure 1. Standard plot of drug in 0.1N HCL

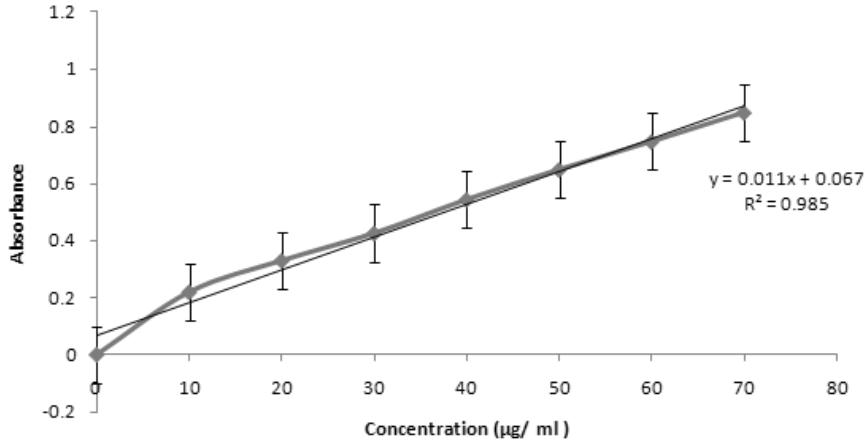

Figure 2. Standard plot of drug in Phosphate buffer pH 6.8

Compatibility studies of drug and excipients

FTIR Analysis

FTIR spectra of propanolol hydrochloride showed a characteristics peak of OH stretch at 3435.84 cm^{-1}. -NH stretch at 3330.11 cm^{-1}, -CH stretch at 2928.33. A Peak of acryl C=C symmetric aromatic ring stretching at 1632.65 cm- ¹and aryl coupling C-O-Stretching at 1268.17 cm^{-1} which peak was obtained from 1500 cm^{-1}. An aryl O-CH_2 asymmetric stretching at 1240.96 and symmetric stretching at 1074.95 cm^{-1}. A peak at 796.90 $cm^{-1}$is due to naphthalene ring. Spectra of mastic gum showed a characteristics peak of OH group at 3440.25 cm^{-1}. FTIR spectra of mastic gum and drug showed a characteristics peak of -NH stretching at 3330.34, -CH aromatic at 2925.40, C=C aryl group attached at 1691.09 and 1637.70, –CH_3 bending at 1456.71and 1401.01, C-O-C Stretching at 1267.46. All characteristic peaks of drug are shown in FTIR spectra of drug and mastic gum which indicates the compatibility of drug and mastic gum. FTIR spectra of Propranolol hydrochloride, Mastic gum and physical mixture of mastic gum HPMC K-15 and drug are given in **Figure 3, 4 and 5** respectively.

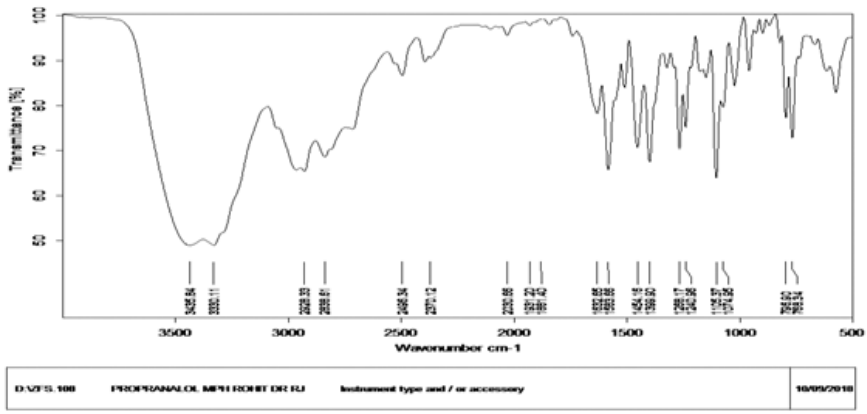

Figure 3. FTIR of drug Propanolol HCl

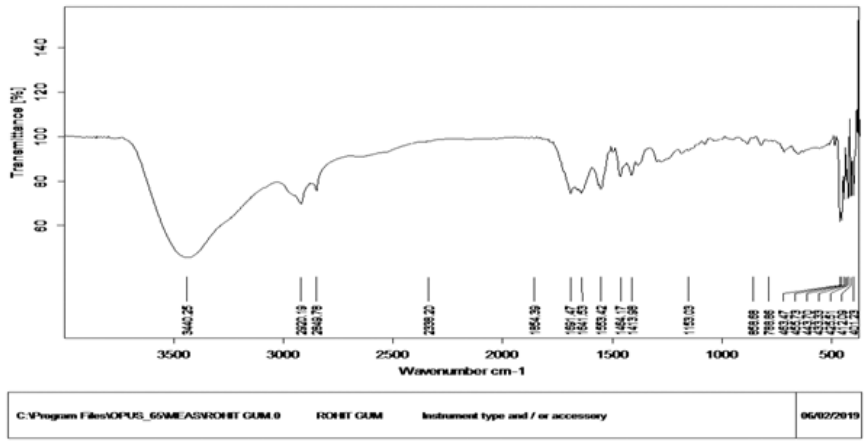

Figure 4. FTIR of Mastic gum

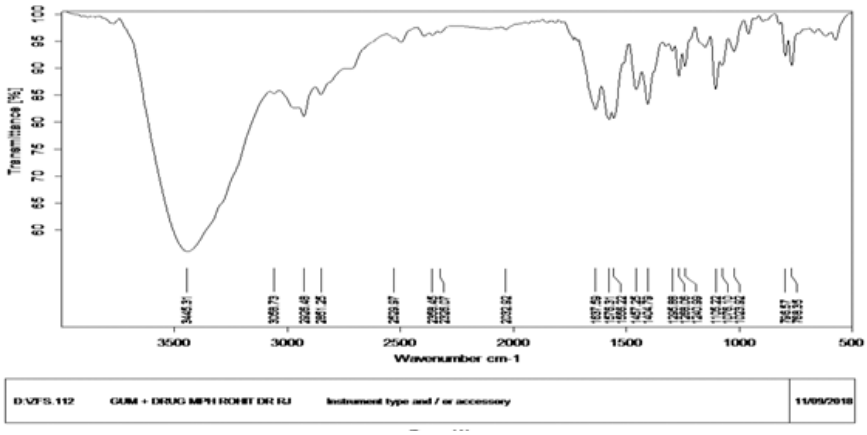

Figure 5. FTIR of HPMC-K 15

DSC Analysis

The possibility of drug excipient interaction was further investigated by DSC. DSC curve of pure drug as shown in **Figure 6** give endothermic peak at 168.74°C. DSC curve of mastic gum as shown **Figure 7** give endothermic peak at 98.80°C. DSC curve of drug and mastic gum as depicted in **Figure 8** give endothermic peak at 155.43°C. From the DSC results it was concluded that there is no incompatibility between the drug and excipient selected.

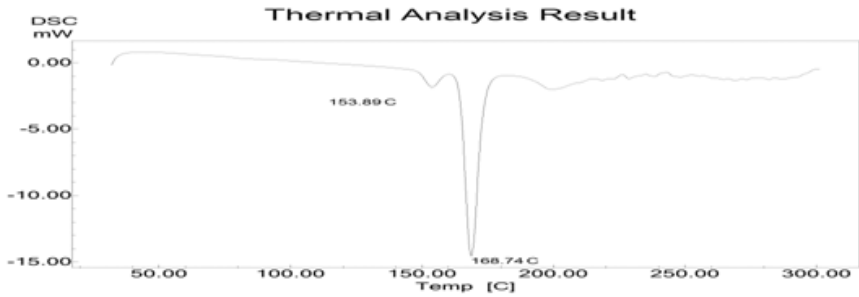

Figure 6. DSC analysis of Propanolol Hydrochloride

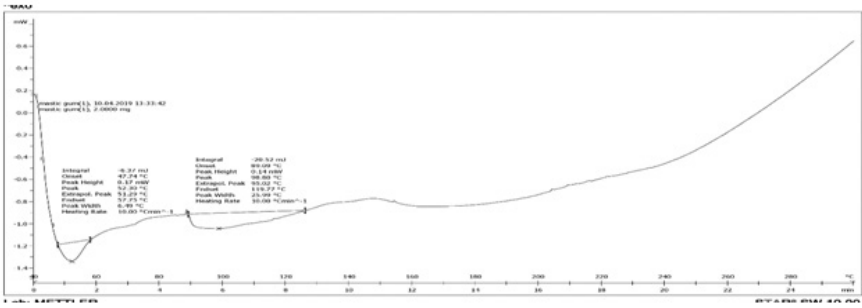

Figure 7. DSC analysis of Mastic Gum

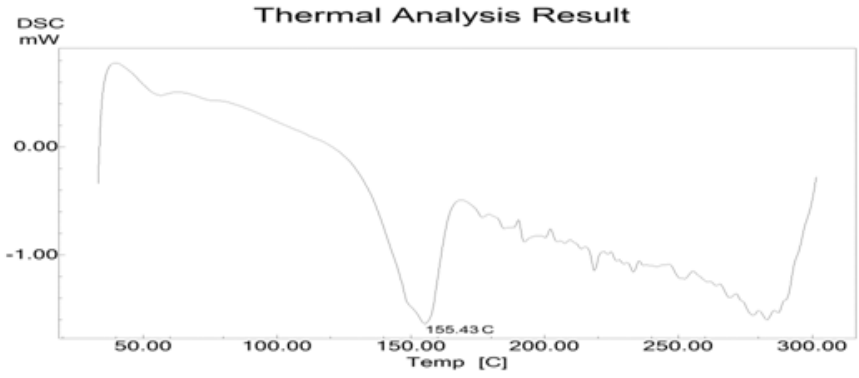

Figure 8. DSC analysis of HPMC-K15

Evaluation of 3^2 full factorial design batches B1 to B9:

Pre compression Evaluations

Bulk density was found in range of 0.24 to 0.645 gm/cm^3, tapped density ranged from 0.535 to 0.6, Angle of repose 14.0 to 26.26, Carr's index range from 22.3 to 4.2, Hausner's ratio ranged from 1.04to 1.181. Results of evaluation of precompression parameters as shown in **Table 4** indicated good micromeritic properties of all formulation batches.

Table 4. Characterization of pre compression parameters of design batches B1 to B9

Parameters	B1	B2	B3	B4	B5	B6	B7	B8	B9
Bulk density (g/cm^3)	0.475± 0.01	0.5128±0.03	0.4736±0.2	0.24±0.01	0.52±0.1	0.66±0.05	0.62±0.1	0.645±0.3	0.495±0.1
Tapped density (g/ml)	0.61±0.02	0.60±0.03	0.52±0.2	0.27±0.01	0.58±0.4	0.68±.01	0.6±0.01	0.71±0.03	0.535±0.01
Angle of repose	14.0±0.03	16.69±0.12	16.17±0.04	22.7±0.05	17.7±0.12	18.2±0.11	26.26±0.1	23.26±0.2	25.17±0.21
Carr's index (%)	22.3±0.1	15.37±0.5	10.47±0.11	11.1±0.12	11.5±0.1	4.2±0.3	5.30±0.1	5.90±0.01	7.47±0.13
Hausenr's ratio	1.28±0.03	1.181±0.11	1.116±0.01	1.121±0.02	1.13±0.02	1.04±0.03	1.05±0.01	1.10±0.02	1.080±0.21

Values are expressed in mean ±SD, n=3

Post compression Evaluations

The Weight of the formulated batches passed the weight variation test as the % weight variation was within the Pharmacopoeial limits of ±7.5 % of the weight. The thickness of all tablets was in the range between 3.23 to 3.98 mm which indicates uniformity in size and shape of the tablets. The hardness of tablets was in the range between 4.66 to 7.5 kg/ cm^2 which indicated the good mechanical strength of the prepared formulations that could maintain physical integrity

during the normal course of handling, also increase in content of mastic gum increases hardness due to the strong binding character of gum mastic.[17] Friability was in the range between 0.5% to 0.94%. Friability values were in agreement with official limit of less than 1% in all cases which indicated good mechanical strength required for handling and transportation. Content of drug distributed in all tablets was found in the range between 95.3 to 99.68% this ensured the uniformity and homogeneity of the drug distribution in the tablets. Results of post compression parameters are given in **Table 5.**

Table 5. Characterization of Post compression parameters of batches B1 to B9

Parameters	B1	B2	B3	B4	B5	B6	B7	B8	B9
Weight variation	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Thickness (mm)	3.79±0.095	3.98±0.27	3.8±0.15	3.4±0.047	3.93±0.31	3.23±0.02	3.7±0.021	3.92±0.03	3.82±0.02
Hardness (kg/cm^2)	5.0±0.22	6.16±0.015	7.5±0.23	5.6±0.25	6.33±0.058	7±0.026	4.66±0.036	5.27±0.07	7±0.06
(%) Friability	0.5%±0.03	0.94%±0.08	0.5%±0.45	0.09%±0.05	0.6%±0.045	0.53%±0.015	0.21%±0.33	0.28%±0.06	0.82%±0.02
(%)Drug content	95.3±0.25	98.2±0.05	98±2.23	99.4±0.36	99.68±0.21	97.6±0.11	99.1±0.71	99.51±1.18	99.1±0.01
Swelling index (%)	135.29±0.027	22.2±0.03	31.25±0.05	66.6±0.023	35.29±0.06	26.31±0.12	56.25±0.23	16.66±0.25	25±0.045

All values are expressed as mean ±SD, n=3

In vitro drug release studies

From *in vitro* drug release it was observed that as the concentration of the mastic gum increases, the amount of drug release decreases. This may be explained due hydrophobic nature of gum which delay the hydration and swelling of polymer matrix to release drug. Decreasing content of mastic gum and increasing amount of HPMC stimulates the drug release, due to the hydrophilic nature of HPMC which dissolve the coating of mastic gum around the drug particles and increase release in early stage. From the results of *in vitro* drug study it was found that B7 tablet batch containing 5% (10mg) of mastic gum and 25% (50mg) of HPMC-K15 could sustain the drug release for 8 hours and was selected as optimized formulation, showing 19.43 at 2hours, 31.55 at 4 hours and 60.13 % drug release at 8 hours which was found to uniform and consistent, this may be attributed due to more free drug: polymer ratio and constant release of the drug embedded in the mastic gum and HPMC-K15 matrix which has a hydrophilic gel forming nature. On coming in contact with liquid medium

this polymer hydrate and swell, forming a hydro gel layer which regulate the further penetration of the liquid into the tablet matrix and control the dissolution and diffusion of drug out of the polymer matrix and there by sustain the drug release. [18]As the concentration of mastic gum increases the hydrophobic nature of the gum retarded the drug release which was due to the gummy nature and therefore poor solvent penetration into the tablet matrix that reduces the wetting and drug dissolution. Results of in vitro drug release study are shown in **Figure 9 (a), (b) and (c)**

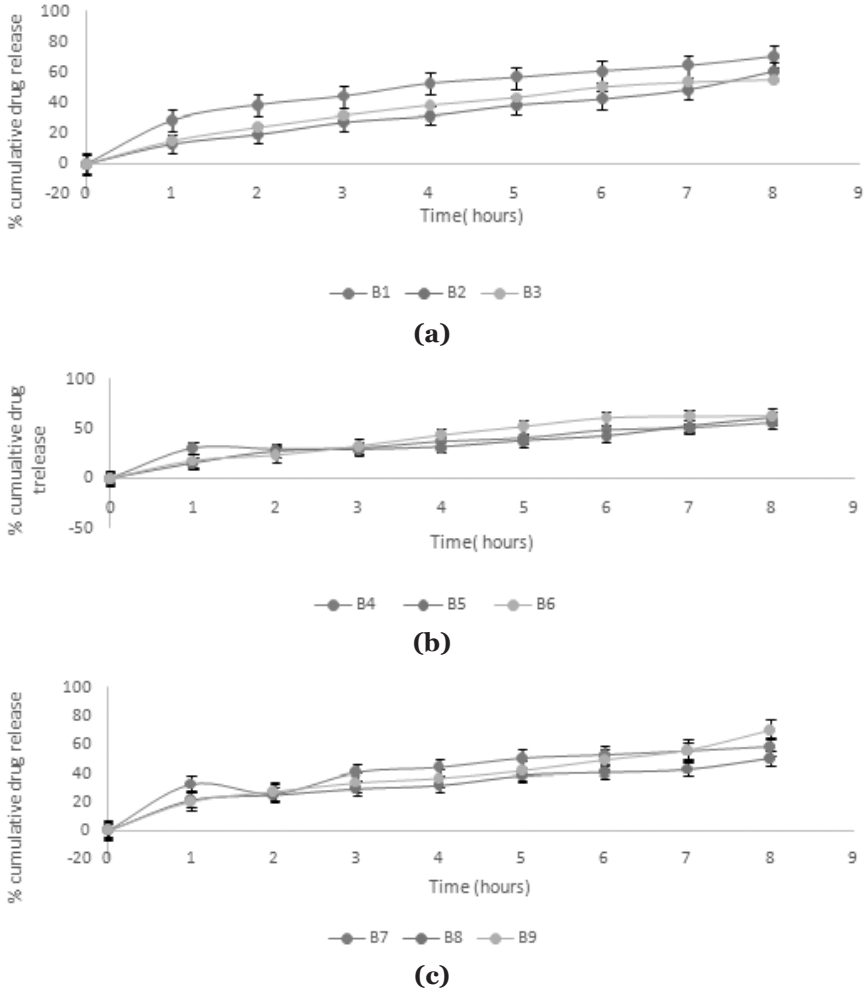

Figure 9. *In vitro* drug release of formulations. (a), B1, B2 and B3; (b), B4, B5 and B6; and (c), B7, B8 and B9.

Regression Analysis

Mathematical relationship generated in the form of polynomial equations for the studied responses are expressed as follows:

$Y1 = +26.75444 - 0.58667X_1 - 3.22500X_2 + 3.89250X_1X_2$

$Y2 = +30.75889 - 1.62833X_1 - 2.88500X_2 + 1.66500X_1X_2 + 1.42167X^2_1 \cdot 58167X_2^2$

$Y3 = +60.28444 - 0.9600X_1 + 0.61833X_2 + 6.85500X_1X_2$

The above equation demonstrates the effect of various process variables over the studied responses. The analysis of variance (ANOVA) was performed to estimate the level of significance of model at 5%. A model is said to be significant if the p value is less than 0.05. Summary of regression analysis for studied response is given in **Table 6**; all measured responses were found to be statistically significant as indicated by P value. F value measures the equality of two variances. The results are shown in **Table 7**.

Table 6. Summary of regression analysis of measured Responses

Coefficient	X_0	X_1	X_2	X_{12}	X_{11}	X_{22}	R^2
% CDR at 2 hours	+26.75444	0.58667	3.22500	+3.89250	-	-	0.998
% CDR at 4 hours	+30.75889	-1.62833	-2.885000	+1.66500	-	-	0.9782
% CDR at 8 hours	+60.28444	-0.96000	+0.61833	+6.85500	-	-	0.9360

Table 7. Results of analysis of variance of all three responses

Source	%CDR at 2 hours		%CDR at 4 hours		%CDR at 8 hours	
Model	F	P Value	F	P Value	F	P value
X_1	1.21	0.03627	0.60	0.057	5.76	0.061
X_2	3.04	0.07903	0.17	0.06936	0.70	0.05635
X_1X_2	0,82	0.0173	0.17	-0.1507	0.84	0.06103
X_1^2	0.71	-	3.80	0.01092	-	-
X_2^2	-	-	-	-	-	-

The relationship between dependent and independent variables was further elucidated using surface response, contour plots and diagnostic graph as given in **Figure. 10, 11and 12**. Correlation between predicted and actual values as indicated by diagnostic graph was found linear with R^2 value 0.998, 0.9782 and 0.9360 indicating the excellent fit.

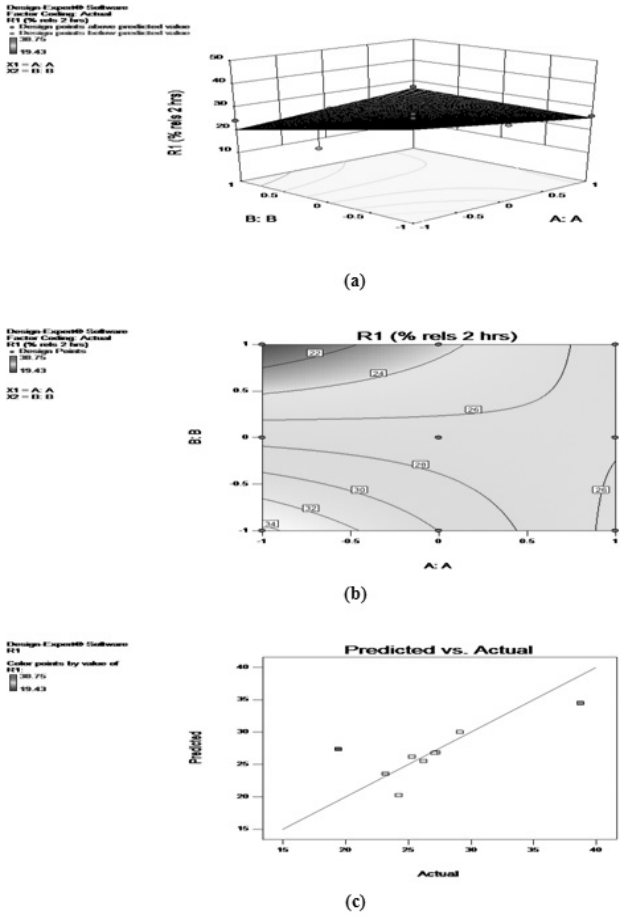

Figure 10. (a) Response surface plot for 2 hours drug release; (b) Contour plot for drug release at 2 hours and (c) Diagnostic plot for drug release at 2 hours.

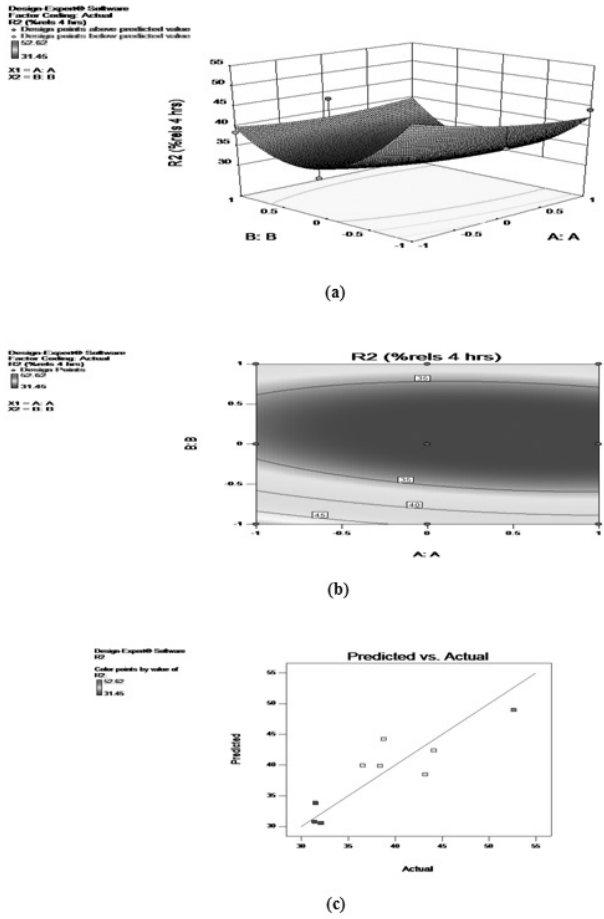

Figure 11. (a) Response surface plot for drug release at 4 hours; (b) Contour plot for drug release for 4 hours; and (c) Diagnostic plot for drug release at 4 hours.

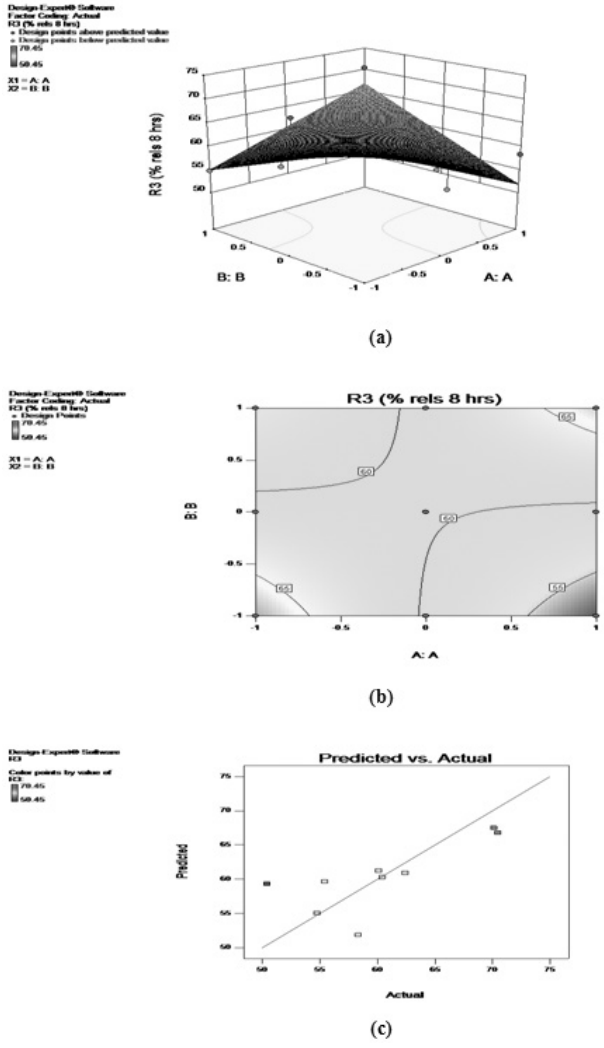

Figure 12. (a) Response surface plot for drug release at 8 hours; (b) Contour plot for drug release for 8 hours; and (c) Diagnostic plot for drug release for 8 hours

Formulation optimization

A numerical optimization using desirability approach was used to develop a new formulation with desired response. Upon evaluation a formulation having desirability closer to 1 was observed. The percentage prediction error between the predicted and experimental values for each response was calculated which was found to be within 5%. The formulation B7 was selected as optimized batch as error was minimum for studied responses.[19, 20] ,

Table 8. Predicted and Experimented values of three Responses with % error

Response	Predicted value	Experimental value	% Error
R1(2hours)	19.82	19.43	1.96
R2(4 hours)	32.05	31.45	1.87
R3(8hours)	62.12	60.43	2.27

Comparison between experimented (E) and predicted value (P) of B2 formulation are given in **Table 8**. Desirability and predicted values of the response R1, R2 and R3 are shown in **Figure 13**.

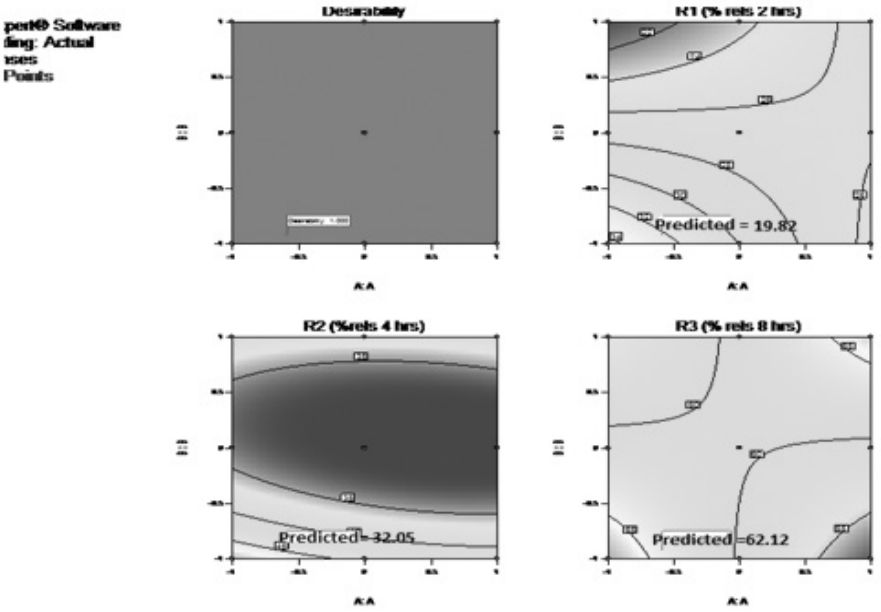

Figure 13. Desirability and Predicted values Responses R1, R2 and R3

Drug Release Kinetic Study

From the results of drug release kinetics it was found that the release mechanism follows swelling and diffusion best demonstrated by Korsmeyer Peppa model giving R^2 value of 0.9942. Results of drug release kinetic study are shown in **Table 9.**

Table 9. *In vitro* release kinetics study of sustained released matrix tablets (B1-B9)

Formulations	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer-Peppas R^2
B1	0.9747	0.9498	0.9927	0.9922
B2	0.9856	0.9928	0.9586	0.9942
B3	0.9666	0.9908	0.9891	0.9974
B4	0.9428	0.8735	0.9636	0.9358
B5	0.9616	0.9511	0.8917	0.8793
B6	0.9498	0.9867	0.9606	0.9877
B7	0.8957	0.8879	0.9384	0.9233
B8	0.9815	0.9053	0.9607	0.9768
B9	0.9683	0.9709	0.9175	0.9694

Comparison of marketed formulation of Inderal 40 with optimized B7formulation

In vitro drug release of optimized formulation was compared with marketed tablet of Propanolol HCl, Inderal 40 for 8 hours. Results of % cumulative drug release are shown in **Figure 14**. The *in vitro* drug release of B7 formulation showed more sustained release behavior as comparison to Inderal 40

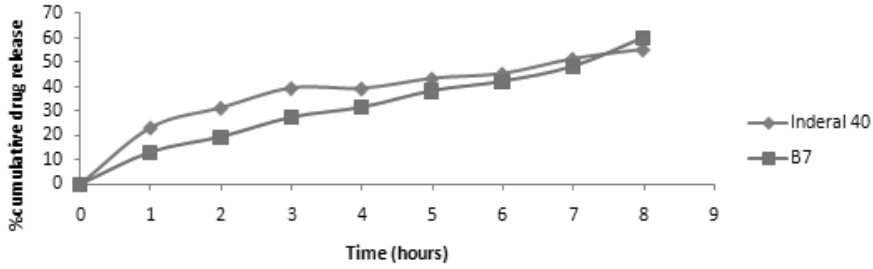

Figure 14. Comparison of marketed formulation with Optimized B7 formulation

Table 10. Stability study of optimized B7 formulation (40^{0C} with 75% RH)

Test Parameters	Time Points (days)					
	0	15	30	45	60	90
% CDR at 2 hours	19.43	18.70	19.40	19.23	19.42	19.41
% CDR at 4 hours	31.45	31.23	31.29	31.43	31.45	31.40
% CDR at 8 hours	60.43	60.45	60.43	61.0	60.89	60.42

Stability Studies

Results of stability studies of optimized batch are give in **Table10** which indicated that all the physical parameters of formulation remains with the prescribed limit during the test periods. The percentage drug release estimated at different time points does not showed any variation, which means that the selected formulation is stable.

The current research work was done with the objective of formulation of sustained released tablets of propanolol HCl using combination of gum mastic and HPMC-K15 utilizing 3^2 factorial design approaches. It was concluded that mastic gum (5%) and HPMC- K15 (25%) exhibited desired sustained drug release and followed Kosmeyer Peppas kinetic; the drug release mechanism may be diffusion or swelling of matrix. Therefore, mastic gum and HPMC- K15 can be a suitable combination for formulation of sustained released tablets.

CONFLICTS OF INTEREST

Authors has no conflicts of interest

AUTHORS' CONTRIBUTIONS

All authors contributed equally

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