International Journal of Drug Delivery 4 (2012) 375-385

http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Formulation Design and Optimization of Sustained Release Tablet of Ambroxol hydrochloride

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Abstract

A sustained release matrix formulation for Ambroxol hydrochloride was designed and developed to achieve a 12 h release profile. Using HPMC K15M and Eudragit RSPO as an inert matrix forming agent to control the release of Ambroxol hydrochloride. The matrix tablets for these formulations were prepared by direct compression and their *in-vitro* release tests were carried out for a period of 12 hours using USP dissolution test apparatus (type I- Basket) at 37±0.5°C and 100 rpm speed. A 32 full factorial design was used for optimization by taking the concentration of HPMC K15M (X1) and Eudragit RSPO (X2) were selected as independent variables, where as initial release at the 2 hrs (Y1, % drug release), release rate at the 8 hrs (Y2, % drug release) and the concentration of Ambroxol hydrochloride released in 12 hrs (Y_3, % drug release) were chosen as dependent variables. The optimized formulation F4 follows Hixon Croswell order release kinetics with non-Fickian diffusion mechanism. From the study, it was concluded that the release of Ambroxol hydrochloride can be effectively sustained using combination of HPMC K15M and Eudragit RSPO.

Keywords: Ambroxol hydrochloride; HPMC K15M; Eudragit RSPO; Direct compression; Factorial design

Introduction

Sustained release is most preferred drug delivery system because of safety better patience compliance and increased complication during the development of new drug entity. Sustained release drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after the administration of a single dose[1]. Various systems such as dissolution controlled release systems, diffusion controlled release systems, dissolution and diffusion controlled release systems, ion exchange resin- drug complexes, pH dependent formulation and osmotic pressure controlled systems. Among all this system dissolution controlled system is most preferred one. The Dissolution controlled release a system is further classified into matrix and reservoir system. Matrix systems are important among the sustained release dosage forms because of their simplicity, low cost, small influence of physiological variables on their release behavior and their suitability for manufacture on modern high speed equipment [2,.3] It involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. The retardant mainly includes both hydrophilic and hydrophobic polymers.

In the present investigation, Ambroxol hydrochloride was selected as a model drug. Ambroxol is metabolite of bromohexine with similar actions and uses. It is chemically described as Trans-4-[(2-Amino-3, 5-dibromobenzyl) amino] cyclohexanol and structure is shown in Fig. 1 It is an expectoration improver and a mucolytic agent in the treatment of acute and chronic disorders characterized by the production of excess of thick mucus. It has been successfully used for decades in the form of its hydrochloride as a secretion releasing expectorant in a variety of respiratory disorders.[4-5] Its short biological half life (3-4 hrs) that calls for frequent daily dosing (2 to 3 times) and therapeutics use in chronic respiratory disease necessitates its formulation into sustained release dosage form.[6-8] Therefore, to reduce frequency of dosing as well as to increase bioavailability and enable better patient compliance, formulating sustained release dosage form was necessary.[9-11]

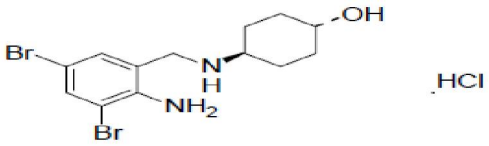


Figure 1 Structure of Ambroxol hydrochloride.

Among different technologies used in controlled drug delivery, hydrophilic matrix systems are the most popular because of the simplicity of formulation, ease of manufacturing, low cost, FDA (Food and Drug Administration) acceptance, and applicability to drugs with wide range of solubility.[12-15] HPMC K15M (Hydroxy Propyl Methyl Cellulose) is an odorless and tasteless, white or creamy-white fibrous or granular powder.[16] HPMC, a semisynthetic derivative of cellulose, is a swellable and hydrophilic polymer It is very suitable to use as a retardant material in controlled release matrix tablets, as it is nontoxic and easy to handle.[17]

Eudragit RSPO is fine, white powders with a slight amine-like odor. Eudragit RSPO having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Eudragit RSPO is water-insoluble and contain ≥97% of dry polymer.[18] The acrylate methacrylate polymers have been used in the preparation of matrix tablets for oral sustained release, in tablet coating and in the microencapsulation of drugs.[19-21]

The objective of the study is formulation and evaluation of sustained release drug delivery of ambroxol hydrochloride using computer aided optimization technique i.e. 3^2 - Full Factorial Design. [22-24] The concentration of HPMC K15M (X_1) and Eudragit RSPO (X_2) were selected as independent variables, where as drug release at the 2 hrs (Y_1), 8 hrs (Y_2) and 12 hrs (Y_3) % drug release of Ambroxol hydrochloride were chosen as dependent variables.

Materials and Methods

Materials

Ambroxol Hydrochloride drug obtained as gift sample from Shilpa Medicare Ltd., India, Hydroxy Ppropyl Methyl Cellulose K15M were gifted by Colorcon, India. Eudragit RSPO was gifted by Evonic Industries, India, and all other excipients used were of analytical grade, and procured from commercial sources.

Experimental Design

In the present study, a 3^2 full factorial design was employed for formulation containing two different polymers HPMC K15M (X_1) and Eudragit RSPO (X_2). Optimization is carried out by studying effect of independent variables, i.e. Concentration of HPMC K-15M (X_1) and Eudragit RSPO (X_2) on dependent variables. Three factorial levels coded for low, medium, and high settings (-1, 0 and +1 respectively) were considered for three independent variables. The selected dependent variables as initial release at the 2 hrs (Y_1, % drug release), concentration release rate at the 8 hr (Y_2, % drug release) and the concentration of Ambroxol hydrochloride released in 12 hr (Y_3, % drug release) Table 1 and 2 shows translation of coded values to actual values and responses and the preparation of formulations and respectively. 2.3 Preparation of Matrix tablets

The requisite quantity of the polymers was weighed and placed in a mortar, which is homogeneously triturated with the help of pestle for two minutes. The required quantity of the Ambroxol hydrochloride was weighed and uniformly triturated with the homogeneous polymer mixture for further 2 minutes. All the powders were passed through 18 mesh sieve. The flow property of the final blend was found to be satisfactory. The final blend was then directly compressed with the 8 mm concave punch using a rotatory punch tablet compression machine. (M/s.CadmachMachinery,Co.Pvt.Ltd.,India) Compression force was kept constant for all formulations. Each tablet contained 75 mg Ambroxol hydrochloride. The composition of tablets is given in Table 3. *In-vitro* drug release studies from the prepared matrix tablets were conducted for a period of 12 hours using USP dissolution test apparatus (type I- Basket) at 37±0.5°C and 100 rpm speed. The simulated gastric fluid (pH 1.2) for first 2 hours and intestinal fluid (pH 6.8) for next 10 hours without enzymes were used as a dissolution medium. Samples (10 ml) were withdrawn with replacement at fixed time intervals, the samples were then diluted with dissolution medium (when necessary). The concentrations of Ambroxol hydrochloride released from the tablet formulations were determined at 245 nm using a UV spectrophotometer.

Release Kinetics

Different mathematical models can be tested to determine which best describes the kinetics and mechanism of drug release from tablets.[25-30] In the present study, data obtained from *in-vitro* drug release studies were plotted in various kinetic models.

Zero order $Q_t = Q_0 + K_0 t$

(1)First order $\log C = \log C_0 - K_1 t/2.303$

(2)Higuchi $Q_t = k_2 t^{1/2}$

(3)Hixson_Crowell cuberoot $(W_0^{1/3} = W_t^{1/3}) = k_h t$

(4)Korsemeyer_Peppas $Q_t/Q_\infty = k_p t^n$

(5)where Q_t, Q_0 and Q_∞ are the amounts of drug dissolved initially, at time t and at time ∞, (in most cases, $Q_0=0$), C_0 and C are the concentrations of drug initially and at time t, W_0 and W_t are the amounts of drug in the pharmaceutical dosage form initially and at time t, and k_0, k_1, k_2, k_h, and k_p refer to the rate constants obtained from the linear curves of the respective models.

Statistical analysis and optimization

Cumulative percents drug release data of 2 hr, 8 hr and 12 hr of all model formulations were analysed by Design-Expert software. Suitable models for mixture designs consisting of two different components include linear, Quadratic models. The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the coefficient of variation (CV), the multiple correlation coefficient (R^2); adjusted multiple

correlation coefficient (adjusted R^2) proved by Design-Expert software. From this, indicates how well the model fits the data, and for the chosen model it should be small relative to the other models under consideration.

Linear model: $Y = b_1 X_1 + b_2 X_2$

Quadratic model: $Y = b_1 X_1 + b_2 X_2 + b_1 X_1 X_2$

To know about relationship between dependent and independent variables three dimensional response surface plots were drawn. Simultaneously point prediction technique were used to generate new formulations with the desired responses.

2.5 Validation of the experimental design

To validate the chosen experimental design, the predicted values are estimated from Design-Expert software and experimental values of the responses were compared with it, and the predicted error (%) calculated by using the following equation (Eq.6),

% Predicted error = (Predicted value-Experiment value)/ Experiment value*100 (6)

Characterization of the optimized formulation

Fourier transform infrared spectroscopy (FTIR)

FTIR study of drug and excipients were carried out to determine the interaction between them. The IR spectrum of pure drug, HPMC K15M, Eudragit RSPO and Optimized formulation were recorded in the stretching frequency range 400-4000 cm^{-1}. The samples were prepared by KBr (Potassium Bromide) press pellet technique.

Results and discussion

In-vitro dissolution studies

The dissolution profiles of all nine formulations given by experimental design are shown in Figure 2, and data of mean values of various responses i.e Y_1, Y_2 and Y_3 for all the nine formulations of experimental design shown in Table 4. From the Figure 1, it was observed that the formulations F1-F3 showed drug release rate 93.02%, 92.57% and 90.81% in 12 hrs, F4-F6 showed drug release rate of 93.11%, 91.01% and 90.36% in 12 hrs and F7-F9 showed the drug release rate, 89.27%, 87.26% and 85.58% in 12 hrs respectively. From the result, it was observed that when concentration of Eudragit RSPO increased the drug release rate decreases while other is kept constant for three formulations each in all F1-F9 formulation. 3.2. Release kinetics

Data obtained after dissolution profile are fitted to different mathematical models (Zero-order, First order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell) in order to describe the kinetics of drug release rate as shown in Table 5. Higher the value of regression coefficient (R^2) was chosen as criteria for selecting the most appropriate model. Korsmeyer-Peppas release exponent (n) value of optimized formulation F4 is 0.737 which is greater than 0.5 indicating non- Fickian transport. 3.3. Data analysis

Mathematical relationship was generated between the factors (independent variables) and responses (dependent variables) using the statistical Design-Expert for determining the levels of factors, which yield optimum dissolution responses.

A second order polynomial regression equation that fitted to the data is as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3 X_1^2 + b_4 X_2^2 + b_5 X_1 X_2 \quad (7)$$

Where, b_0 is the intercept representing the arithmetic mean of all the quantitative outcomes of nine experimental runs; b_1 to b_5 are the estimated coefficients from the observed experimental values of Y; X_1 and X_2 are the coded levels of factors. The term X_1X_2 is interaction terms show the change in response occurs when two factors are simultaneously changed. The X_i^2 (where i= 1, 2) is quadratic term. The equations of the responses are given below:

$$Y_1 = 19.60 - 1.46 X_1 - 4.28 X_2 \quad (8)$$

$$Y_2 = 78.50 - 7.23X_1 - 3.94X_2 + 0.37X_1X_2 - 2.27X_1^2 - 0.87X_2^2 \quad (9)$$

$$Y_3 = 91.14 - 2.38X_1 - 1.44X_2 - 0.37X_1X_2 - 1.56X_1^2 + 0.26X_2^2 \quad (10)$$

Where,

X_1= Conc. HPMC K15M,
X_2 = Conc. Eudragit RSPO
Y_1 = % drug release at 2 hr
Y_2 = % drug release at 8 hr
Y_3 = % drug release at 12 hr

The equation represents the quantitative effect of factors (X_1 and X_2) upon the responses (Y_1, Y_2 and Y_3). Coefficients with one factor represent the effect of that particular factor while the coefficients with more than one factor and those with second order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively.

Analysis of variance (ANOVA) was applied for estimating the significance of the model, at 5% significance level. A model is considered significant if the p-value (significance probability value) is less than 0.05. Data from Table 6 contains factor effects of 3^2 Full Factorial Design model and associated p-values for the responses Y_1, Y_2 and Y_3 are presented. A factor is considered to influence the response if the effects significantly differ from zero and the p-value is less than 0.05. Positive sign in front of the terms indicates synergistic effect while negative sign indicates antagonistic effect of the factors, here the response Y_1 was significantly affected by the antagonistic effect of linear term of HPMC K15M (X_1) (*p*-value 0.0105) and Eudragit RSPO (X_2) (*p*-value 0.0001), the response Y_2 was significantly affected by the antagonistic effect of quadratic term of HPMC K15M (X_1) (*p*-value 0. 0001) and Eudragit RSPO (X_2) (*p*-value 0.0001), the response Y_3 was significantly affected by the antagonistic effect of quadratic term of HPMC K15M (X_1) (*p*-value 0. 0001) and Eudragit RSPO (X_2) (*p*-value 0.0001).

Bold type figures indicates that significant effects of factors on individual responses

Response surface analysis

The 3-dimensional response surface plots were drawn to estimate the effect of independent variables on response Y_1, Y_2 and Y_3 as shown in Figure 3,4 and 5 respectively. A mathematical model also generated for response Y_1 (Eq.8). Simillarly mathematical model

Table 1 Translation of Coded Values to Actual Values and Responses

Variable levels	Low (-1)	Medium (0)	High (+1)
X_1 = Concentration of HPMC K 15 (mg)	25	30	35
X_2 = Concentration of Eudragit RSPO (mg)	15	20	25
Responses			
% drug release at the 2 hr (Y_1)	% drug release at the 8 hr (Y_2)	% drug release at the 12 hr (Y_3)	

Table 2 Factorial Design for Preparation of Formulations

Batch Code	Variable levels in Coded form	
	X_1	X_2
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Table 3 Composition of Tablets

Formulation (mg/tablet)	Drug	HPMC K15M	Eudragit RSPO	MCC	Total Weight
F1	75	25	15	115	250
F2	75	25	20	110	250
F3	75	25	25	105	250
F4	75	30	15	110	250
F5	75	30	20	105	250
F6	75	30	25	100	250
F7	75	35	15	105	250
F8	75	35	20	100	250
F9	75	35	25	95	250

(Each Formulation contains 5% PVP K-30, 2% Magnesium sterate and 1% Talc)

Table 4 Data of Mean Values of Various Responses i.e Y_1, Y_2 and Y_3 for all the nine Formulations of Experimental Design

Formulation run	Responses		
	Y_1 (% release at 2 hr)	Y_2 (% released in 8 hr)	Y_3 (% released in 12 hr)
F1	25.16±2.86	87.58±3.34	93.02±1.54
F2	19.23±2.43	82.84±1.34	92.57±3.60
F3	16.66±4.34	78.26±1.42	90.81±1.36
F4	27.12±2.43	80.61±4.11	93.11±0.87
F5	19.99±2.50	78.61±1.44	91.01±4.39
F6	15.38±3.85	74.11±2.65	90.36±3.45
F7	20.26±2.83	72.02±2.21	89.27±1.56
F8	17.70±3.43	69.08±1.11	87.26±2.44
F9	14.15±1.56	64.17±1.24	85.58±0.45

Mean, ± S.D., n=3

Table 5 Kinetics of drug release based on dissolution profile of ambroxol hydrochloride tablets

Formulation	Zero order		First order		Higuchi	Hix.-Crow.	K-Peppas	
	k_0	r	k_1	r	r	r	N	R
F1	18,69	0.897	0.120	0.989	0.953	0.975	0.766	0.968
F2	12.79	0.915	0.108	0.987	0.963	0.977	0.860	0.966
F3	8.68	0.929	0.097	0.987	0.968	0.983	0.935	0.967
F4	15.81	0.954	0.103	0.988	0.988	0.995	0.737	0.989
F5	7.55	0.968	0.101	0.966	0.979	0.981	0.844	0.982
F6	2.78	0.977	0.097	0.961	0.966	0.981	0.947	0.982
F7	8.45	0.973	0.092	0.953	0.961	0.970	0.781	0.967
F8	2.53	0.970	0.086	0.948	0.948	0.963	0.852	0.955
F9	1.12	0.973	0.078	0.948	0.942	0.968	0.932	0.967

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

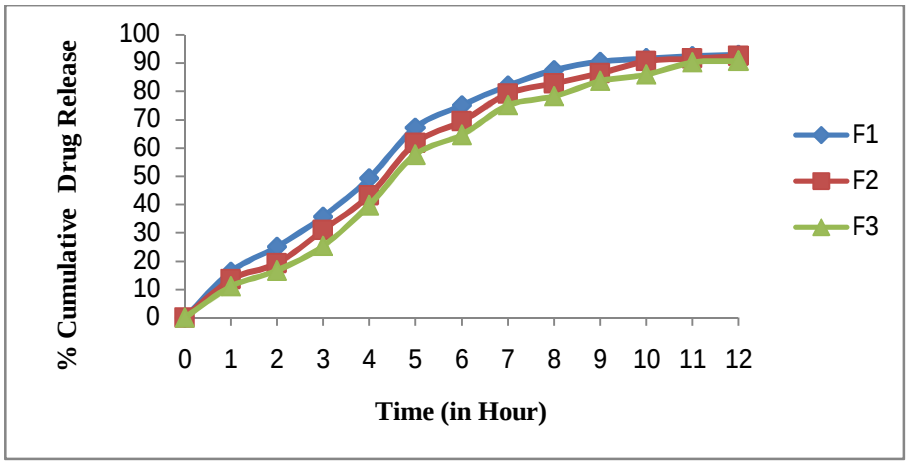
Table 6 Summary of analysis of variance (ANOVA) for the measured response i.e Y_1, Y_2 and Y_3 for amount of drug released at at the 2 hrs, at the 8 hrs and at the 12 hrs respectively.

Factor	Y_1		Y_2		Y_3	
	Factor effect	p-value	Factor effect	p-value	Factor effect	p-value
X_1	-1.46	**0.0105**	-7.23	**<0.0001**	-2.38	**<0.0001**
X_2	-4.28	**<0.0001**	-3.94	**<0.0001**	-1.44	**<0.0001**
X_1X_2			+0.37	0.2374	-0.37	0.0761
X_1^2			-2.27	**0.0003**	-1.56	**0.0002**
X_2^2			-0.87	**0.0394**	+0.26	0.2695

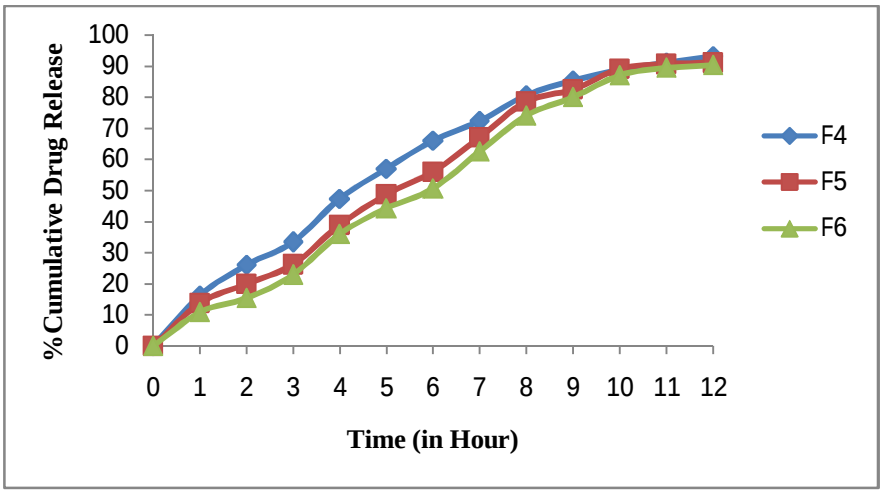
Bold type figures indicates that significant effects of factors on individual responses

Table 7 The Experimental and Predicted Values for Responses Y_1, Y_2 and Y_3 along with Percentage Prediction Error (%PE) observed for Optimum Formulation F4 and Random Formulation.

Response	(X_1 X_2)	F4 (30,15)	V1 (26,16)	V2 (29,18)	V3 (31,19)	V4 (32,21)	V5 (34,23)
Y_1	Experimental Value	26.12	24.48	22.32	20.65	18.28	15.60
	Predicted Value	25.43	24.62	22.27	20.59	18.38	15.59
	% PE	2.641	-0.571	0.224	0.290	-0.547	0.064
Y_2	Experimental Value	80.61	85.72	81.09	77.82	74.53	68.80
	Predicted Value	81.58	85.67	81.32	77.70	74.44	68.76
	% PE	-1.20	0.058	-0.140	0.154	0.120	0.058
Y_3	Experimental Value	93.11	92.99	92.20	91.01	89.75	87.33
	Predicted Value	92.84	93.12	92.14	90.91	89.63	87.28
	% PE	0.28	-0.139	0.065	0.109	0.133	0.057



A



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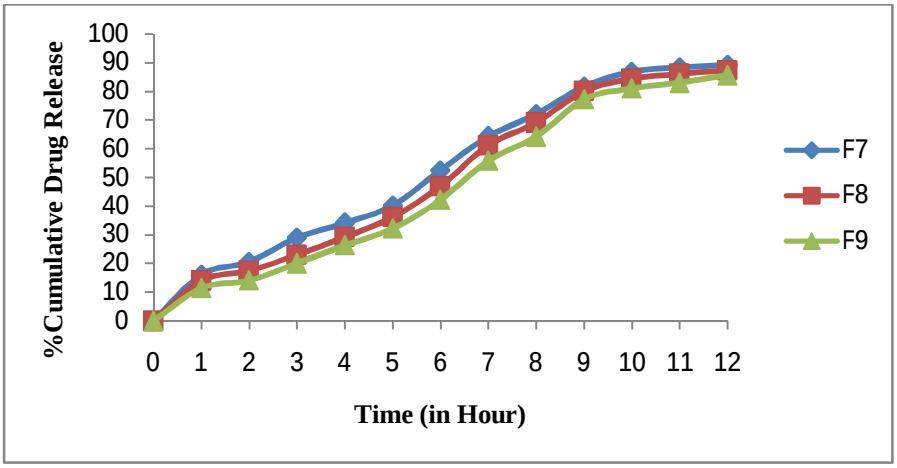


C

Figure 2 Dissolution profiles of all nine formulations (A) F1-F3 (B) F4- F6 (C) F7-F9

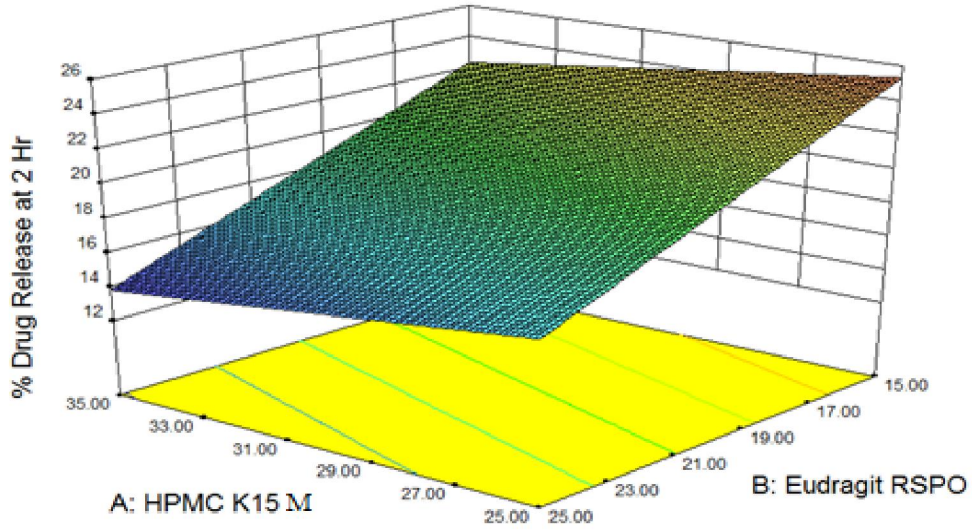


Figure 3 Response Surface Plot Showing the Influence of the HPMC K15M and Eudragit RSPO on the % release at the 2 hr.

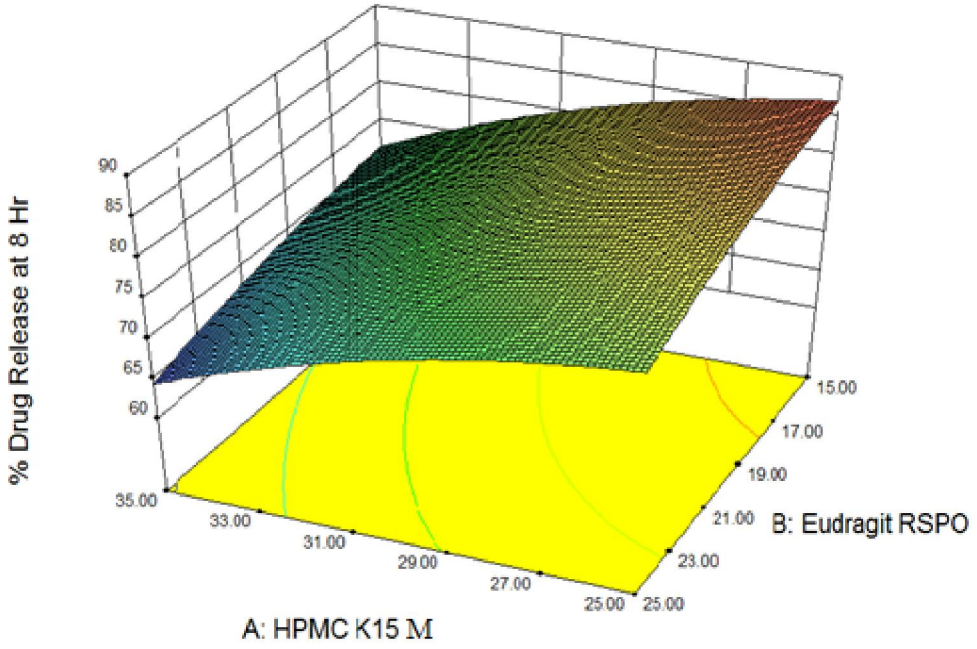


Figure 4 Response Surface Plot Showing the Influence of the HPMC K15M and Eudragit RSPO on the % Release at the 8 hr,

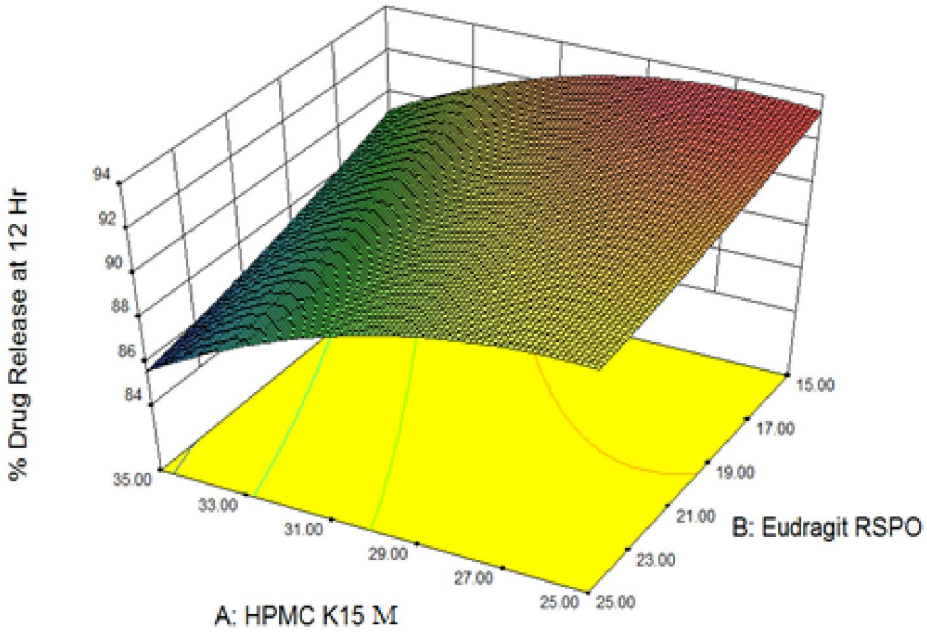
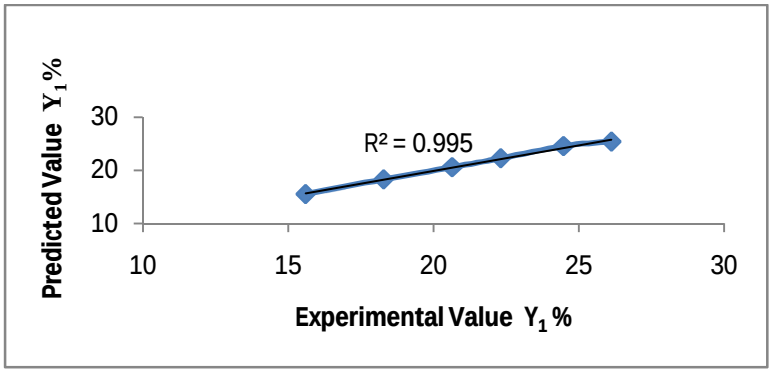
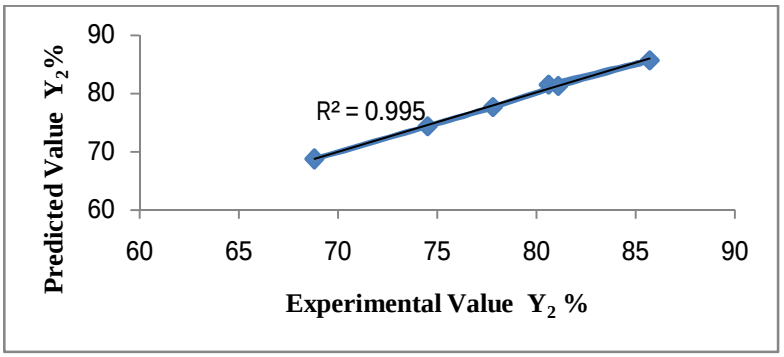


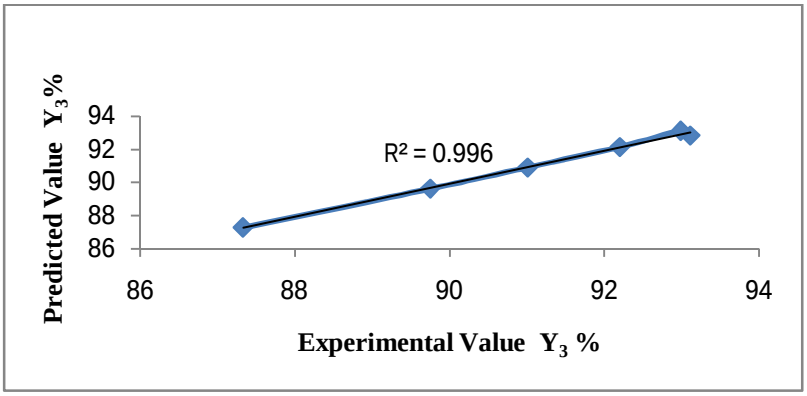
Figure 5 Response Surface Plot Showing the Influence of the HPMC K15M and Eudragit RSPO on the % Release at the 12 hr



(A)



(B)



(C)

Figure 6 Correlation between Experimental and Predicted (A) for % drug release at 2 hrs Y_1, (B) % drug release at 8 hrs, Y_2 and (C) % drug release in 12 hrs, Y_3.

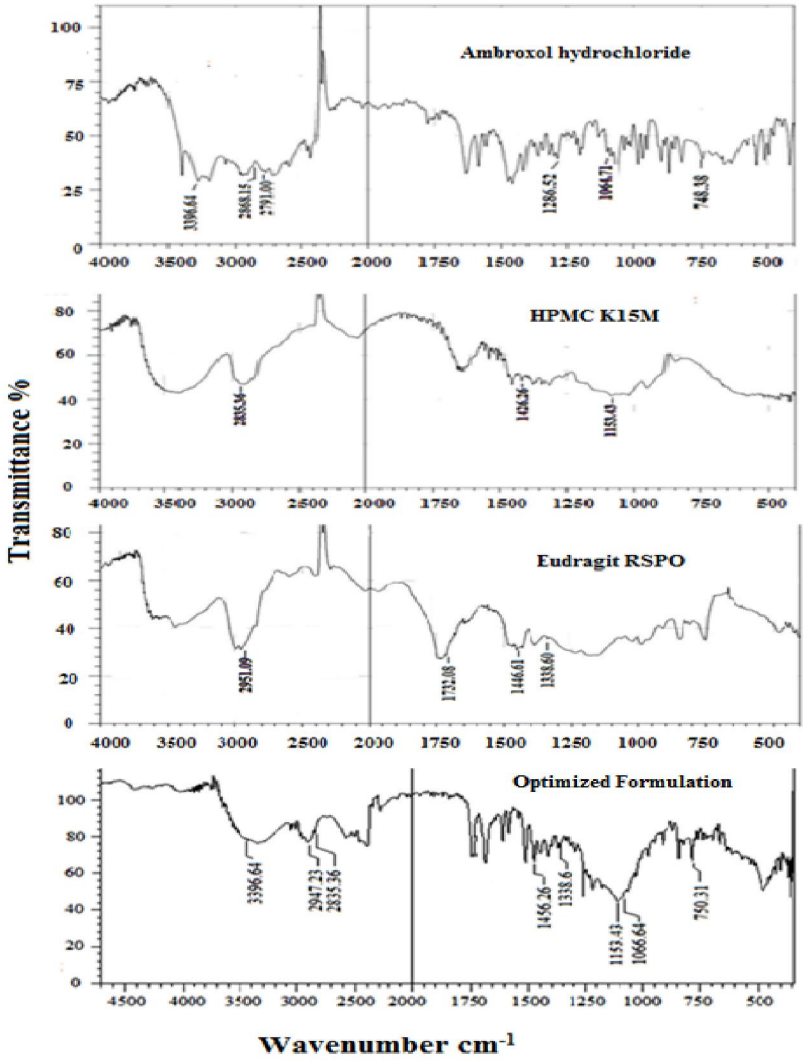


Figure 7 FTIR Spectra of Ambroxol hydrochloride, HPMC K15M, Eudragit RSPO and Optimized formulation.

also generated for response Y_2 (Eq.9) and Y_3 (Eq.10). 3.5. Evaluation and validation of the optimized formulation

The experiments were carried out according to the composition obtained after applying constraints and the optimum formulation

was evaluated for the dissolution profile. In order to evaluate the reliability of the developed mathematical model, five additional checkpoint points were taken estimated by use of generated model covering the entire experimental domain. Table 7 gives the levels of variables of optimum formulation and five random checkpoint points with their experimental values, predicted values and percentage prediction error. The percentage prediction errors between the predicted and experimental values for each response were calculated and the values found to be within 5%. The experimental values were in agreement with the predicted values confirming the predictability and validity of the model.

Table 7 shows the experimental and predicted values for responses Y_1, Y_2 and Y_3 along with percentage prediction error (%PE) observed for optimum formulation F4 and random formulation and Figure 6 shows correlation between observed and predicted Y_1, Y_2 and Y_3. Correlation coefficient in both graphs r^2 >0.9 shows goodness of fit of model. Thus, the lower magnitude of error as well as significant values of r^2 (>0.9) in the current study indicate the robustness of the mathematical model and high prognostic ability of Response Surface Models.

The optimized formulation F4 gave % drug release at 2 hrs, 8 hrs and 12 hrs values of 27.12%, 80.61% and 93.11% respectively. Drug release from the optimized formulation followed Hixson-Crowell is best fit model for F4 (R^2=0.995). Korsmeyer-Peppas release exponent (n) value of optimized formulation is 0.737 which is greater than 0.5 indicating non- Fickian transport. 3.6. Characterization of the optimized formulation

FTIR

From the Figure 7, it was observed that in IR spectra of Ambroxol hydrochloride, the peak showed 748.38 cm^{-1} for out of plane C-H deformation, 1064.71 cm^{-1} for CO equatorial absorption of cyclohexane, 1286.52 cm^{-1} for Ar-NH_2, 2791 cm^{-1} for N-CH_2 streching, 2868.15 cm^{-1} for C-H stretching and 3396.64 cm^{-1} for N-H stretching, In IR spectra of HPMC K15M, the peak showed 1153.43 cm^{-1} for saturated ethers, aliphatic ethers, 1426.26 cm^{-1} for C-H deformation methyl, propyl, 2835.36 cm^{-1} for C-H streching of alkyl group. In IR spectra of Eudragit RSPO, the peak showed 1338.60 cm^{-1} for CO stretching of carboxylic acid, 1446.61cm^{-1} for C-H deformation methyl, propyl, 1732.08 cm^{-1} for C=O stretching of carboxylic acid and 2951.09 cm^{-1} for salt of quaternary ammonium ion. The peaks showed no significant changes in material characteristic when Ambroxol hydrochloride used with HPMC K-15 and Eudragit RSPO.

Conclusions

A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at three levels and experimental trials were performed at all nine possible combinations. This study revealed that the concentration of HPMC K15M and Eudragit RSPO had significantly affect the drug release of Ambroxol hydrochloride, it is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in shortest time with minimum efforts.

Author's contributions

Mr. Abhijeet Uttamraao Bankar - Carried out experimental part of study.

Dr.V.H. Bankar, Ms. P.D. Gaikwad and Dr. S.P. Pawar - Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data, also involved in drafting or revising it critically for important intellectual content and given final approval of the version to be published.

Acknowledgments

The authors are thankful to Shilpa Medicare Pvt. Ltd. (Raichur, India), Colorcon Asia Pvt. Ltd.(Mumbai, India) and Evonic Industries Pvt. Ltd. (Mumbai, India) is gratefully acknowledged for providing the gift samples of Ambroxol hydrochloride, HPMC K15M and Eudragit RSPO respectively.

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