Design of dual release drug delivery system of roxythromycin and ambroxol HCl

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ABSTRACT

Upper respiratory tract infections are the illnesses caused by an acute infection which involves the upper respiratory tract: nose, sinuses, pharynx or larynx. Roxithromycin (macrolide antibiotic) and ambroxol HCl (mucolytic) are use for this treatment. The dual release system of roxythromycin and ambroxol HCl was successfully prepared by bi-layer tablet approach for management of URTI. Quick release of roxithromycin was achieved by using disintegrants and slow release of ambroxol HCl was achieved by using matrix formulation of drug with HPMC K4M and ethyl cellulose. The 3^2 full factorial design was adopted for optimization of polymer concentration to achieve identical drug release with theoretical dissolution profile. The amount of HPMC K4M and ethyl cellulose were selected as independent variable and the similarity factor with theoretical dissolution profile and percentage drug release at 10th hr was selected as dependent variables. The prepared dual release tablets were evaluated for physical parameters, drug content, in-vitro drug release study, etc. All the parameter found to be acceptable in range. As the concentration of HPMC K4M is increase, the drug release is decrease and the effect of ethyl cellulose was found to be less compare to HPMC K4M.

Key words: dual release system, ambroxol HCl, roxithromycin, factorial design
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INTRODUCTION

Dual drug delivery systems are designed to release drug at two different rates or in two different periods of time. This type of system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. This type of system is also used when one drug require immediate release and one drug for sustained release effect to get best therapeutic response [1]. The solid oral dual drug delivery is possible by compressed matrix core tablet, bi-layer tablet, matrix tablet/capsule containing SR granules & IR granules. The bi-layer tablet is important because of their simplicity, low cost and their suitability for manufacture on modern high speed equipment.

The purpose of the present research was to produce quick and slow release biphasic (dual release) system of ambroxol HCl and roxithromycin for Upper respiratory tract infections. Upper respiratory tract infections (URTI) are the illnesses caused by an acute infection which involves the upper respiratory tract : nose, sinuses, pharynx or larynx. This commonly includes: tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media, and the common cold [2]. Ambroxol HCl is a systemically active mucolytic agent used for decades in the treatment of respiratory disorders associated with excessive mucus, chronic inflammatory pulmonary conditions, bronchitis, and/or pneumonia [3]. It has short biological half-life (4 h) and require frequent daily dosing (2 to 3 times) and therapeutic use in chronic respiratory diseases necessitates formulating sustained release dosage form [4]. Roxithromycin is macrolide antibiotics used to treat respiratory tract, urinary and soft tissue infections.

Immediate release part of dual release tablet can be design by using super disintegrants. Sustained release part can be design by using matrix type of system containing suitable polymers. Sodium starch glycolate is easily available and cheap. HPMC is a semisynthetic derivative of cellulose, which is swellable and hydrophilic in nature. It is very suitable to use as a retardant material in sustained release matrix formulations, as it is non-toxic and easy to handle. [5] Ethylcellulose is partially ethoxylated. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of b-anhydroglucose units joined by acetal linkages. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former [6, 7].

EXPERIMENTAL SECTION

Ambroxol hydrochloride obtained as gift sample from Ami Lifesciences Pvt. Ltd., Baroda. Roxithromycin obtained as gift sample from Blue Cross Laboratories Ltd., Nashik. Hydroxypropyl methyl cellulose K4M and ethyl cellulose were gifted by Colorcon, Goa. Microcrystalline cellulose (Avicel PH 101) and Sodium starch glycolate were procured form Signet Chemical Corporation, Mumbai. PVP K30 was procured from S.D. Fine chemicals, Mumbai. All other excipients used were of an analytical grade, and procured from commercial sources.

Calculation of theoretical release profile from dual release tablets:
The theoretical dissolution profile was calculated using available pharmacokinetic data from a design of one compartment model. This was calculating as described by Robison and Eriksen [8]. The zero-order drug release rate constant (K_0) was calculated using equation $K_0 = D_I \times K_e$, where D_I is the initial dose (i.e., conventional dose = 30 mg) and K_e is first-order rate constant for overall elimination ($K_e = 0.693/t_{1/2} = 0.1723$ hr^{-1}) and was found to be 5.19 mg/h. The maintenance dose can be calculated by $D_m = K_0 * T$, where T is the time for sustained action. The maintenance dose was to be founded 57.09 mg. The loading dose can be calculated by $D_L = D_I - K_0 * T_p$, where T_p is time to reach peak plasma concentration (for ambroxol hydrochloride T_p is 2 hr). The loading dose was to be founded 19.62 mg. Hence, the matrix tablet should contain a total dose of 76.51 mg ($\cong$ 75 mg) calculated by using the equation, $D_t = D_L + D_m$. It should release 30 – 10.38 = 19.62 mg (26.13%) in the 1st hr like conventional dosage form and the remaining dose (75 – 19.60) in remaining 11 h, i.e. 55.39 mg (73.86%) or 5.19 (6.9%) mg per hour up to 12 hr.

Preparation of dual release tablet (trial batch)
Dual release tablets were prepared by direct compression method. The ingredients were accurately weighed and mixed by triturating in a glass mortar & pestle. The quantity of powder for the fast release layer was compressed lightly using a rotary compression machine (Hardik engineering, India) equipped with 12 mm round and flat punches. Over this compressed layer, the required quantity of the sustained release layer was placed and compressed to obtain hardness in the range of 5–6 kg per cm^2 to form a bi-layer matrix tablet [9]. Formulation of preliminary trial batches of the immediate release layer and sustained release layer is shown in Table 1.

Table 1: Compositions of trial baches.

Ingredients	H1	H2	H3	E1	E2	E3
Immediate release layer						
Roxithromycin	300	300	300	300	300	300
Sodium starch glycolate	30	30	30	30	30	30
PVP K30	20	20	20	20	20	20
MCC	140	140	140	140	140	140
Talc	5	5	5	5	5	5
Mg. stearate	5	5	5	5	5	5
Sustained release layer						
Ambroxol hydrochloride	75	75	75	75	75	75
HPMC K4M	20	40	60	-	-	-
Ethyl cellulose	-	-	-	20	40	60
MCC	50	30	10	50	30	10
Talc	3	3	3	3	3	3
Mg. stearate	2	2	2	2	2	2

Physical Characterization of dual release Tablets [10]
The dual release tablets were characterized for weight variation using an analytical balance (Sartorius Weighing India Pvt. Ltd, new Delhi.), thickness using a vernier callipers, hardness using a Monsanto type hardness tester (Janki impex Pvt. Ltd, Ahmedabad) and friability using a Roche-type friabilator (Electrolab, India).

Drug content uniformity
Ten tablets were finely powdered and an amount equivalent to 75 mg of ambroxol hydrochloride was accurately weighed and transferred to a 100 mL volumetric flask; 70 mL of 0.1 N HCl was then added. The flask was shaken for 10 min. Finally, the volume was made up to the mark with 0.1 N HCl. The mixture was then filtered and measured by high-performance liquid chromatography (LC-2010 CHT), Shimadzu, Japan. The method to quantify ambroxol hydrochloride and roxithromycin was done by HPLC with Phenomenex C18 column. The mobile phase consisted of an Acetonitrile: Phosphate buffer pH 5 in the ratio of 65: 35. The liquid flow rate of HPLC was 1 ml/min. The wavelength of detection was 210 nm.

In vitro drug release studies:
The in vitro dissolution studies were carried out using USP 6 dissolution apparatus type II (paddle method) at 100 rpm. Dissolution test was carried out for a total period of 12 h using 0.1N HCl (pH 1.2) solution (750 ml) as dissolution medium at $37 \pm 0.5°$ for first 2 h, and then addition of 0.2 M tribasic sodium phosphate to achieve pH 6.8 (1000 ml) for the rest of the period. Ten millilitres of the sample was withdrawn at regular intervals and replaced with the same volume pre warmed ($37 \pm 0.5°$) fresh dissolution medium [11]. The samples withdrawn were filtered through 0.45 μ membrane filter, and drug content in each sample was analyzed by high-performance liquid chromatography (LC-2010 CHT), Shimadzu, Japan. The wavelength of detection was 210 nm.

Optimization of dual release tablets by experimental design [12]
The statistical optimization was carried out using Design Expert 7 software. The factorial design is an effective method of indicating the relative significance of a number of variables and their interactions. The number of experiments required for these studies is dependent on the number of independent variables selected. The response (Y) was measured for each trial.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y is the dependent variable
b_0 is the arithmetic mean response of the nine runs
X_1 and X_2 is the independent variable
b_1 and b_2 is the co-efficient of X_1 and X_2 variable, b_{12} is the co-efficient of interaction, b_{11} and b_{22} is the co-efficient of quadratic terms

A 3^2 full factorial design was adopted in the study. In this design, two factors were evaluated. Three levels study and experimental trials were carried out using total nine possible combinations. The design layout and coded value of independent factor is shown in table 2 and 3 respectively. The factors were selected based on preliminary trial batches.

The dual release bi-layer tablets were formulated as above mentioned procedure. The amount of HPMC K4M and amount of ethyl cellulose were selected as independent variable. The similarity factor with theoretical dissolution profile and percentage drug release at 10th hr was selected as dependent variables.

Table 2: Formulation of various batches according to factorial design

Ingredients	HE1	HE2	HE3	HE4	HE5	HE6	HE7	HE8	HE9
Immediate release layer									
Roxithromycin	300	300	300	300	300	300	300	300	300
Sodium starch glycolate	30	30	30	30	30	30	30	30	30
PVP K30	20	20	20	20	20	20	20	20	20
MCC	140	140	140	140	140	140	140	140	140
Talc	5	5	5	5	5	5	5	5	5
Mg. stearate	5	5	5	5	5	5	5	5	5
Sustained release layer									
Ambroxol hydrochloride	75	75	75	75	75	75	75	75	75
HPMC K4M	10	10	10	20	20	20	30	30	30
Ethyl cellulose	20	30	40	20	30	40	20	30	40
MCC	60	50	40	50	40	30	40	30	20
Talc	3	3	3	3	3	3	3	3	3
Mg. stearate	2	2	2	2	2	2	2	2	2
TOTAL WEIGHT	670	670	670	670	670	670	670	670	670

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Table 3: Coded values and actual values for the independent variables (factors)

Factor level	Coded Values	Actual values (mg)	
		HPMC K4M (X_1)	Ethyl cellulose (X_2)
Low	-1	10	20
Medium	0	20	30
High	+1	30	40

Mechanism of drug release from prepared tablets [13]
Drug release mechanisms and kinetics are two important characteristics of delivery system in the dissolution system. The mechanism of drug release from prepared dual release tablets was carried out by mathematical models. The data was taken from dissolution of optimised batch.

Zero order: In zero order release study, percentage drug release versus time graph is plotted.

$$f_t = K_0t$$

Where, f_t is fraction of dose release at time t. K_0 is zero order rate constant expressed in units of concentration/time.

First order: In first order release study, log percent drug remaining versus time graph is plotted.

$$\text{Log } Q_t = \text{Log } Q_o - Kt/2.303$$

Where, Q_0 is the drug amounts remaining to be released at zero hour. K is the first-order constant. Q_t is the drug amounts remaining to be released at time t.

Higuchi's model: In Higuchi's model, percentage of drug released versus square root of time graph is plotted.

$$f_t = K_H t^{1/2}$$

Where, f_t is fraction of dose release at time t. K_H is the constant for higuchi's model.

Korsmeyer–Peppas model:

$$M_t/ M_\infty = K t^n$$

Where, M_t/M_∞ is fraction of drug released at time t. K is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms. The value of n is given in table 4 for characterize of release mechanism.

Table 4: Various drug transport mechanisms

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.45 < n = 0.89	Non –Fickian transport
0.89	Case II trasport
Higher than 0.89	Super Case II trasport

Comparison of dissolution profile of optimized batch with marketed formulation
The dissolution study of marketed formulation Acocontin CR containing 75 mg of ambroxol hydrochloride were carried out using same procedure as mention above. The comparison of dissolution profile of optimised batch with this marketed formulation was carried out. The similarity and dissimilarity factors ware calculated by following equation.

Similarity factor, $f_2 = 50*\log\{[1+(1/n)\sum_{t=1}^{n} (R_t\text{-}T_t)^2]^{-0.5}*100\}$

Dissimilarity factor, $f_1 =\{[\sum_{t=1}^{n} |R_t\text{-}T_t|]/[\sum_{t=1}^{n} R_t]\}*100$

RESULT AND DISSCUSION

Physical Characterization of dual release Tablets
The evaluation parameters of trial batches are show in table 5. The weight variation of prepared tablets is between 644.6 and 663.2, which is acceptance in range as per standard limit. Hardness and Friability data shows that good

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mechanical properties because the hardness of tablets is near to 5 kg/cm^2 and friability is less than 1%. The thickness of tablets is uniform and between 5.9 to 6.3 mm. Drug content shows the uniformity of drug in individual dosage forms. The roxithromycin is found to be in the range of 98.3 to 103.1%. The ambroxol hydrochloride is found to be in the range of 97.2 to 102.4. The drug content is found to be uniform and acceptable range.

Table 5: Evaluation of prepared tablets

Parameter	H1	H2	H3	E1	E2	E3
Weight variation	644.6±6.3	663.2±8.8	655.1±7.9	646.5±5.7	660.2±3.6	654.9±4.3
Assay of roxithromycin (%)	98.3	99.2	103.1	99.4	100.4	98.5
Assay of ambroxol (%)	97.2	99.6	100.3	100.8	102.4	99.7
Friability (%)	0.74	0.45	0.66	0.70	0.46	0.54
Hardness (kg/cm^2)	5	5.5	5	4.5	5	5
Thickness (mm)	6.3	6.2	6.3	5.9	6.0	5.9

In-vitro **drug release study:**
The drug relese of roxithromycin and ambroxol hydrochloride from prepared dual release tablet are show in figure 1 and 2. The roxithromycin was almost (> 95%) released at 15 min. which shows the quick drug release. The ambroxol hydrochloride is released from prepared matrix of HPMC K4M or ethyl cellulose. The dissolution study was carried out up to 12 hr. As the concentration of HPMC K4M or ethyl cellulose increases than the release of ambroxol hydrochloride from tablets is decreses. In the H3 batch, HPMC K4M is used in 60 mg quantity so the drug release is very slow and only 48% drug was released at 12 hr. Release of drug in H1 batch containg 20 mg of HPMC K4M have good release up to 12 hr. Fast drug release found in E1 batch containing 20 mg of ethyl cellulose, almost drug was released at 8 hr. Slow drug release found in E3 batch containig 60 mg of ethyl cellulose. For optimisation study the amount of HPMC K4M was selected 10 to 30 mg and ethyl cellulose was selected 20 to 30 mg.
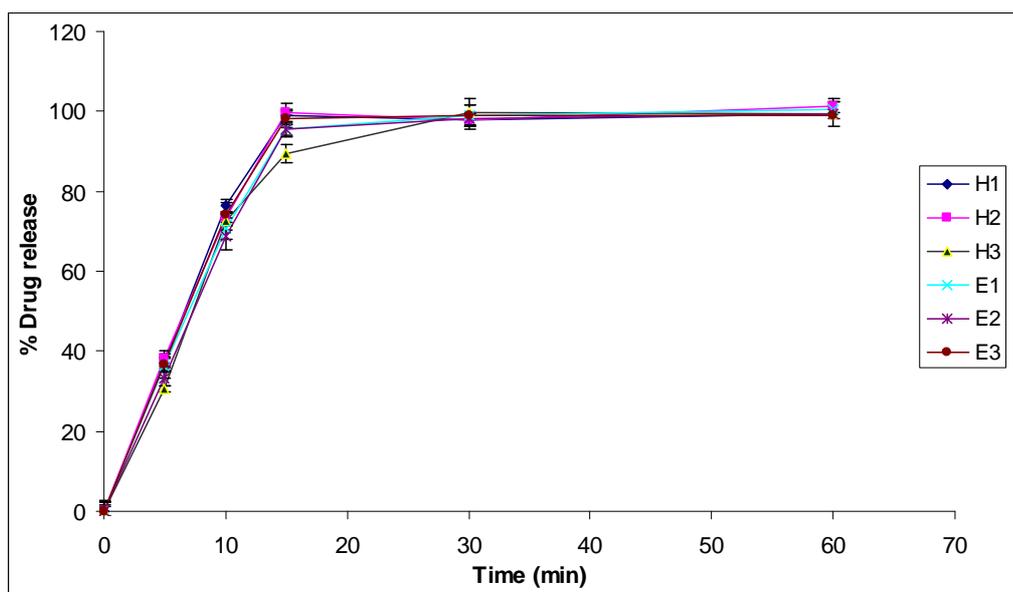

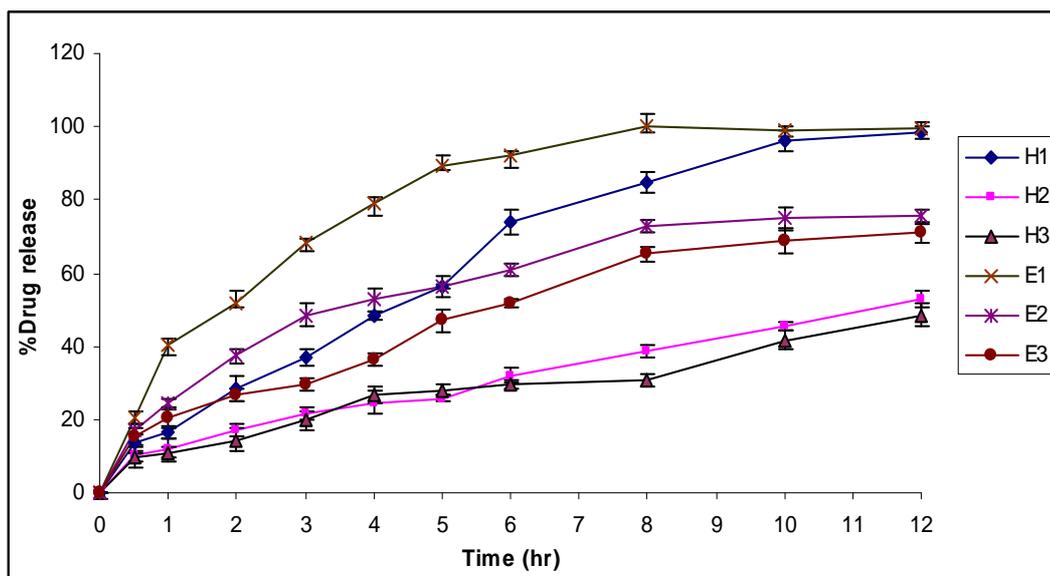**Fig.1: in-vitro drug release of roxithromycin from prepared tablets**

Fig.2: in-vitro drug release of ambroxol hydrochloride from prepared tablets

Experimental design

In order to achieve desire drug release the experimental design was adopted for optimization. A quadratic model was obtained after analysing data. Values of p are less than 0.05 indicate model terms are significant. The statistical model comprising incorporated interactive and polynomial terms was utilized to evaluate the response. Once the uncoded values of factor levels were applied and response quadratic model was performed using DESIGN EXPERT. Values of coefficients are mention in table 6.

Table 6: Summary of regression output of significant factors for the measured responses

Parameters	Co-efficient of regression parameters							
	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}	r^2	P
% Drug Release at 10 hrs	87.48	- 5.43	- 2.25	-1.3	3.56	0.42	0.9923	0.0023
Similarity factor	83.25	10.38	4.04	- 3.07	-14.905	- 8.34	0.9682	0.0187

A positive value indicates a synergistic effect that favours optimization, while a negative sign represents an antagonistic effect or inverse effect of the factor on the selected response.

The result of ANOVA is show in table 7. For drug release at 10 hr, the model f- value of 77.81 implies the model is significant. The p value is only a 0.0023, which shows that the model is significant. Values of p less than 0.05 indicate model terms are significant. For similarity factor, the model f- value of 18.29 implies the model is significant. The value of p is 0.0187, which is less than the 0.05 that indicate the model is significant.

Table 7: Result of two way ANOVA for dependent variables

Response model	% drug release at 10 hrs	similarity factor
Sum of Squares	240.05	1366.85
Degree of Freedom	5	5
Mean Square	48.01	273.37
Model F Value	77.81	18.29
P value	0.0023	0.0187

The graphical representation was generated for influence of factors on dependent variables. The 3D plot and contour plot for % drug release at 10 hr and similarity factor shows in figure 3. As the concentration of HPMC K4M is increase, the % drug release at 10 hr is decrease and also p value indicating significant effect. The effect of ethyl cellulose is less compare to HPMC K4M. Aim of this study is to achieve drug release as per theoretical dissolution profile and value of % drug release at 10 hr equal to 88.1 with highest value of similarity profile. The effect of the HPMC K4M and ethyl cellulose on similarity factor is significant. As the concentration of polymer increase, the similarity factor also increase up to certain level than it is decrease gradually.
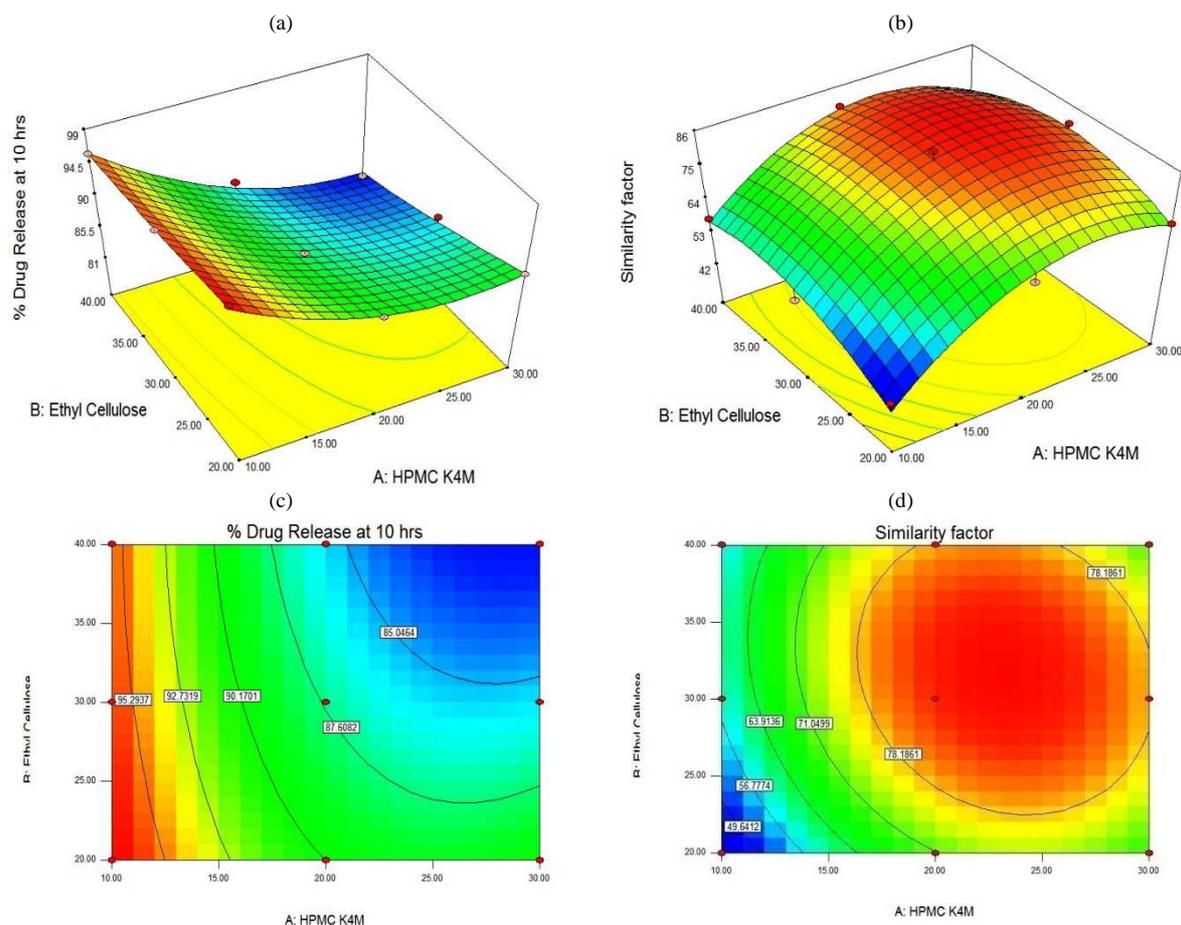
Fig. 3: Response surface plot for influence of concentration of HPMC K4M and ethyl cellulose (a) 3D plot for % drug release at 10 hr, (b) 3D plot for similarity factor, (c) contour plot for % drug release at 10 hr and (d) contour plot for similarity factor

One optimised formulation was obtained at two different target values for % drug release at 10 hr and similarity factor (table 8). The predicted and observed responses for the optimized tablet formulations showed no significant difference.

Table 8: Optimised values of HPMC K4M and ethyl cellulose with their predicted and observed response values

Response	HPMC K4M (mg)	Ethyl cellulose (mg)	Predicted value	Observed value	% error
Similarity factor	19.0	29.8	82.00	85.70	4.51
% Drug Release at 10 hrs			88.1	87.3	0.91

Kinetic modeling of drug release

The coefficient (R^2) was calculated for optimized batch using MS-excel and graphs were plotted. The value of rate constant and coefficient are show in Table 9. Based upon the regression coefficient, zero order drug release of ambroxol observed. The drug release of ambroxol also follows the higuchi model (R^2 is 0.986). The drug release exponent was found to be 0.55 in korsmeyer peppas plot which indicated that the drug transport system is non – fickian type due to HPMC and ethyl cellulose.

Table 9: Kinetic modeling for optimised batch

Zero order		First order		Higuchi plot		Korsmeyer peppas plot	
R^2	K_0	R^2	K_1	R^2	K_H	R^2	N
0.956	7.344	0.897	0.109	0.986	28.01	0.987	0.55

Comparison of dissolution profile

The comparison of dissolution profile of ambroxol HCl is show in figure 4. The identical dissolution profile found with the marketed formulation. There is no more change of dissolution profile. The similarity and dissimilarity factor found to be 81.27 and 3.41 respectively.
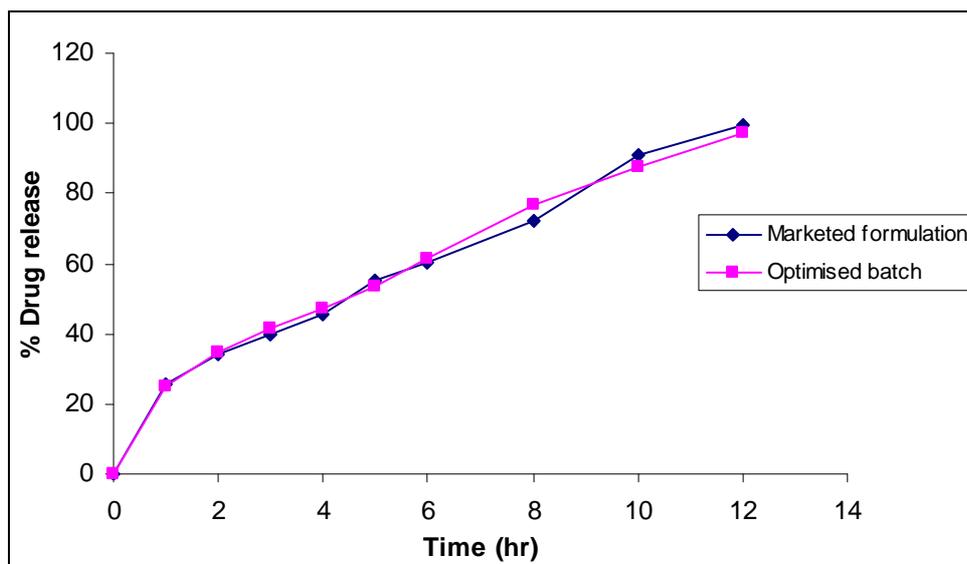
Figure 4: Comparison of dissolution profile of ambroxol HCl to optimised batch with marketed formulation

CONCLUSION

The dual release formulation of roxythromycin and ambroxol HCl can successfully formulate by using bi-layer tablet approach. Fast release of roxythromycin was incorporated with disintegrants. The matrix layer of ambroxol HCl with HPMC K4M and ethyl cellulose formulated to achieve the slow release of drug. The factorial design was adopted to obtain the drug release of ambroxol HCl identical to theoretical dissolution profile. The prepared dual release tablets of ambroxol HCl and roxithromycin shows acceptability after evaluated for various parameters.

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