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Research Article

IN VITRO RELEASE KINETICS STUDY AND OPTIMIZATION OF AMBROXOL HCl 75 MG MATRIX TABLETS USING RESPONSE SURFACE METHODOLOGY

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ABSTRACT
The aim of the present study was the in vitro evaluation and optimization of Ambroxol HCl sustained release matrix tablets by response surface methodology. The amounts of Methocel K4M and PVP K30 at three levels (-1, 0, +1) were selected as casual factors. *In vitro* dissolution time profiles at three different sampling times (1h, 4h, 8h) mean dissolution time (MDT) and time required for 50% drug release were selected as output variables . Thirteen kinds of Ambroxol HCl matrix tablets were prepared according to a 2^3 factorial design with five extra center points. The optimal tablet formulation based on some predetermined release criteria predicted by RSM was 80.28mg of Methocel K4M and 18.36mg of PVP K30. Dissolution studies were carried out in 900ml 0.1 N HCl for 2 hours followed by 900 ml phosphate buffer (pH6.8) for subsequent 6 hours. Polynomial mathematical models, generated for various response variables using multiple linear regression analysis, were found to be statistically significant ($p<0.05$). The release mechanism was explored and explained by zero order, first order, Higuchi's and Korsmeyers's equation. The drug release followed both diffusion and erosion mechanism in all cases. Calculated difference (f_1 5) and similarity (f_2 86) factors indicated that there was no difference between predicted and experimentally observed drug release profiles for the optimal formulation. It was concluded that optimization of Ambroxol HCl by Response Surface Methodology is quite efficient.
Keywords: Response Surface Methodology, Sustained Release, Methocel, Ambroxol HCl

INTRODUCTION

The research of sustained-release dosage forms is an important field in pharmaceutics. In the last few decades, sustained-release dosage forms have made significant progress in terms of clinical efficacy and patient compliance[1-4]. Oral sustained release dosage form by direct compression technique is a very simple approach of drug delivery systems that proved rational demand in the pharmaceutical arena as its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms . Sustained or controlled drug delivery occurs while embedded with a polymer that may be natural or semisynthtic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predesigned fashion and released the drug at constant rate for desired period[5]. There are a number of techniques applied in the formulation as well as in the manufacturing of sustained release dosage form however the matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. Direct compression method has been applied for preparation of tablet matrix that involved simple blending of all ingredients used in the formulations and then under went direct compression. It required fewer unit operations, less machinery, reduced number of personnel and reduced processing time, increased product stability and faster production rate[6]. A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, does not disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier which controls the drug release from and the liquid penetration into the centre of the matrix system[7].

Ambroxol is a metabolite of bromhexine[8]. It is an expectoration improver and mucolytic agent used in the treatment of acute and chronic disorders characterized by the production of excess or thick mucus. It works to decrease mucus viscosity by altering its structure. Expectoration of mucus is facilitated and breathing is eased considerably. Long-term use is possible because of the good tolerability of the preparation. It is chemically described as trans-4-((2-Amino-3, 5-dibromobenzyl) amino) cyclohexanol. It is a white to yellowish crystalline powder; slightly soluble in water, ethanol; soluble in dimethylformamide, methanol; insoluble in chloroform and benzene; melting point 240 C; administered orally. Its short biological half life (4 hours)[9] that calls for frequent daily dosing (2 to 3 times) and therapeutic use in chronic respiratory diseases necessitates its formulation into sustained release dosage form. So, the development of sustained release dosage form of Ambroxol hydrochloride is of therapeutic relevance and can be used to provide a consistent dosage through sustaining an appropriate level of the drug over time.

For developing a sustained release tablet dosage form, an important issue is to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum number of trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. For this purpose, a computer based optimization technique with a response surface methodology (RSM) utilizing a polynomial equation has been widely used. Different types of RSM designs include 3-level factorial design, central composite design (CCD), Box-Behnken design and D-optimal design. Response surface methodology (RSM) is use when only a few significant factors are involved in optimization. The technique requires minimum experimentation and time, thus proving to be far more effective and cost effective than the conventional methods of formulating sustained release dosage forms.

MATERIALS AND METHODS

Materials

Ambroxol hydrochloride was obtained from Alchymars ICM SM Pvt.Ltd., India, Hydroxy propyl methylcellulose (Methocel K4M) was a gift sample received from colorcon Asia Pvt.Limited. Microcrystalline Cellulose (MCC) and PVP K30 (polyvinyl pyrrolidone K30) were purchased from Ming Tai Chemical Co.Ltd., Taiwan. Magnesium stearate was procured from Hanua Chemicals Limited, Japan.

Preparation of matrix tablets

This method of tablet production has previously been described by several authors[10,11] that provided reproducible experimental results in terms of *in vitro* release. Drug, polymer and other excipients were weighed separately for 20 tablets per formulation as per proposed formulations (table: 1). The proposed formulations were coded as K4M1, K4M2, K4M3, K4M4, K4M5, K4M6, K4M7, K4M 8, K4M9, K4M10, K4M11, K4M12 and K4M13. The amounts of drug and excipients are expressed in milligram. Then active ingredient, microcrystalline cellulose (MCC), PVP K-30, and polymer were blended for 20 minutes and then magnesium stearate was added and further blended for another 2 minutes. Blended mass was taken in the hopper and then die and punch were adjusted to get the desired weight of the tablet (600 mg). The tablets were prepared by direct compression using a Perkin-Elmer laboratory hydraulic press equipped with a 11.7 mm flat faced punch and die set.

Tablet assay and physical evaluation

The tablets of the proposed formulations (K4M1 to K4M13) were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a hand operated Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai). The thickness of the tablets was measured by vernier calipers. Weight variation test was performed according to the official method. Drug content for Ambroxol hydrochloride was carried out by measuring the absorbance of the sample at 244.5 nm using Shimadzu 1240 UV spectrophotometer and comparing the content from a calibration curve prepared with standard Ambroxol hydrochloride in the same medium.

Design of experiment

A 2^3 factorial (central composite) design with α=1 was employed as per the standard protocol[12, 13]. The amounts of HPMC K15M (X_1) and PVP K 30 (X_2) were selected as the factors, studied at 3 levels each. The central point (0, 0) was studied in quintuplicate. The range of HMPC K4M (30-90 mg) and PVPK30 (0-30 mg) was selected based on preformulation trial to prepare 600 mg ambroxol HCl sustained release tablet. All other formulation and processing variables were kept invariant throughout the study. Tables (2-3) summarize an account of the 13 experimental runs studied, their factor combinations and the translation of the coded levels to the experimental units employed during the study. Amount of drug released in 1 hour (rel_{1hr}) (Y_1), % of drug released in 4 hour (rel_{4hr}) (Y_2), % of drug released in 8 hour (rel_{8hr}) (Y_3), time to 50% drug release ($t_{50\%}$) (Y_4) and MDT (Y_5) were taken as the response variables. The response surface graphs and mathematical models were obtained by Design Expert® 7.0 (Statease, USA) software.

In vitro dissolution study of tablets

Dissolution studies were conducted for a period of 8 hours according to USP method (USP XXII) using apparatus II at a speed of 100rpm and the temperature was maintained at *37 ± 0.5° C.* The dissolution studies were carried out in triplicate in 900 ml 0.1 N HCl for 2 hours followed by 900 ml phosphate buffer (pH 6.8) for subsequent 6 hours. At every 1-hour interval samples of 10 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 244.5 nm by a UV spectrophotometer (UV-1601, Shimadzu, Japan). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time (hours) curve.

Kinetic analysis of release data

Different kinetic models (zero-order, first-order, Higuchi's and korsmeyer's) were applied to interpret the release profile from matrix system. The best fit with higher correlation (R^2>0.99) was found with the Higuchi's equation. However, two factors diminish the applicability of Higuchi's equation to matrix systems. This model fails to allow the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential equation (Korsmeyer equation), Eq. (1), which is often used to describe the drug release behavior from polymeric systems[14].

$$\text{Log}\,(Mt / Mf) = \text{Log}\,k + n\,\text{Log}\,t \quad \ldots\ldots\ldots\ldots (1)$$

Where, Mt is the amount of drug release at time t; Mf is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release. Talukder et al applied this equation to evaluate the drug release mechanism from xanthan gum matrix tablets[15].

To clarify the release exponent for different batches of matrix tablets, the log value of percentage drug dissolved was plotted against log time for each batch according to the equation 1. A value of n = 0.45 indicates Fickian (case I) release; >0.45 but <0.89 for non-Fickian (anomalous) release; and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release[16].

Mean dissolution time (MDT) was calculated from dissolution data using the following equation (Mockel and Lippold)[17].

$$MDT = (n / n+1).k\ -1/n \quad \ldots\ldots\ldots\ldots\ldots (2)$$

Analysis of similarity

For every point of observed/predicted drug release profiles for optimal formulation, difference (f_1) and similarity (f_2) factors were calculated. According to the US Food and Drug Administration's guide for industry[18]generally f_1 values up to 15 (0-15) and f_2 values greater than 50 ensures sameness of the two curves. The value is determined by the following equation:

$$f_2 = 50 \cdot \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \cdot 100\right\} \quad (6)$$

Where n is the number of dissolution sample times, and R_t and T_t are the individual percentages dissolved at each time point t for the reference and test dissolution profiles respectively.

RESULTS AND DISCUSSION

Physical Evaluation of Ambroxol HCl matrix tablets

The tablets of the proposed formulations (K4M1 to K4M13) were subjected to various evaluation tests such as thickness, hardness, uniformity of weight, drug content, and friability.

The thickness of the tablets ranged from 3.41 to 3.54 mm. The hardness and percentage friability of the tablets of all batches ranged from 7.21 to 7.98 kg/cm^2 and 0.01 to 0.03%, respectively. The average percentage deviation of 20 tablets of each formula was less than ±5%. Drug content among different batches of tablets ranged from 97.13 to 100.03%. Thus, all the physical parameters of the matrices were practically within control.

Effect of Methocel K4M on release pattern of Ambroxol Hydrochloride matrix tablets

For this experiment, different Methocel K4M matrix tablets containing ambroxol hydrochloride as active ingredient were prepared according to formulation shown in table 1. The prepared tablets were subjected to *in vitro* dissolution studies in paddle method at 100 rpm in 900ml, 0.1N HCl medium at 37^0 c (± 0.5^{0}c) for 2 hours followed by 900 ml, phosphate buffer (pH 6.8) medium for another 6 hours at 37^{0}c (±0.5^{0}c). Three tablets from each formulation were used for the dissolution study. The release profile of Ambroxol HCl was monitored up to 8 hours. To determine the effects of polymers on drug release, different kinetic models such as Zero order, First order, Korsmeyer, Higuchi were investigated. The zero order, First order, Higuchi and Korsmeyer release patterns are shown in figure 1(A-D). The percent of drug release from these 13 formulations at different time intervals is shown in the table 4.

From the graphs, a release profile of ambroxol HCl containing Methocel K4M matrix tablet of 13 formulations was obtained. The total % of ambroxol HCl release from the formulation K4M1, K4M2, K4M3, K4M4, K4M5, K4M6, K4M7, K4M 8, K4M9, K4M10, K4M11, K4M12 and K4M13 were 94.35%, 92.14%,90.22% 88.24%, 85.41%, 84.26%,81.85%, 80.53%, 77.99%, 87.06%, 86.42%, 85.89%, 86.14% respectively. It has been observed that the release rate has been declined with the increase of polymer content. The highest percent of drug release within 8 hours is obtained from K4M1 where polymer content is 5%. But in K4M9, the polymer content is 15% , the release of drug is minimum 77.99 % within 8 hours. The rate of drug release was found to be inversely related to the amount of Methocel K4M present in the matrix structure, i.e. the drug release increased with decrease in the polymer content of the matrix tablet. This is due to the formation of gel barrier of the hydrophilic HPMC polymer. Elevating the concentration of HPMC may result increased tortuosity or gel strength of the polymer. When HPMC polymer is exposed to aqueous medium, it undergoes rapid hydration and chain relaxation to form viscous gelatinous layer (gel layer). This is an agreement with the literature[19,20] findings that the viscosity of the gel layer around the tablet increases with increase in the hydrogel concentration, thus limiting the release of the active ingredient**.** Failure to generate a uniform and coherent gel may cause rapid drug release.

In this experiment, the release kinetics data (table 5) were treated according to Higuchi's and Korsmeyer et al.'s equations. The *in vitro* release profiles of drug from all these formulations could be best expressed by Higuchi's equation, as the plots showed high linearity (R^2: 0.992~0.997). From Higuchi model, it is evident that Ambroxol hydrochloride is released by diffusion process. To confirm the diffusion mechanism, the data were fitted into Korsmeyer's equation. The formulations showed good linearity (R^2: 0.990~0.998), with slope (n) values ranging from 0.546-0.615. This n value appears to indicate a coupling of diffusion and erosion mechanism (known as anomalous non-Fickian diffusion).

The drug release also fitted first order kinetic model to high extent. It indicates the drug release is dependent on the concentration of Ambroxol hydrochloride.

The mean dissolution time (MDT) of K4M9 formulation figure 1(E) is highest (4.38 hrs), which means it can retard drug release most effectively.The values of $t_{50\%}$ figure 1(F) enhanced markedly from 2.55 hrs, observed at low levels of both the variables, to as high as 3.82 hrs, observed at high levels of both the variables. This finding indicated considerable release retarding potential of the polymer and binder.

To determine possible interaction of two polymers a response surface study was also done. The drug release percentages at 1hr, 4hrs, 8 hrs, $t_{50\%}$ and MDT were selected as responses(table 4). These time periods are selected to detect any initial burst effect, $t_{50\%}$ and $t_{90\%}$. From multiple regression analysis (table 6), it was found that Methocel K4M (X_1) was responsible for reducing drug release significantly ($p<0.05$) at 1, 4 and 8 hours. No Interaction between Methocel K4M and PVP K 30 was found regarding drug release. It was also found that PVP K 30 (X_2) was responsible for reducing drug release significantly ($p<0.05$) at 1, 4 and 8 hours.

Optimization

Figure 2 (A to E) shows the three-dimensional diagrams of each response variable as a function of HPMC K4M and PVP K30 obtained by using RSM. The model was optimized by choosing optimum formulation based on predetermined criteria of release profile. The target release profile was selected as 24%, 54% and 76% in 1h, 4h and 8 h respectively. The range of Methocel K4 M and PVP K 30 was set at 5-15% and 0-5% respectively. The optimization was carried out in Design Expert® 7.0 software. Out of 39 solutions suggested by the software, the solution having highest desirability was selected. Tablets were prepared using 13.38% w/w Methocel K4M and 3.06% w/w PVP K 30 respectively. Other excipients used were same as table-1. Tablets were prepared by direct compression method. The dissolution of optimized formulation was carried out by the method described in "Materials and Method" section. The f_1 and f_2 values were also calculated for each time point. The predicted and actual release were almost same ($f_1 \geq 5$ and $f_2 \geq 86$, Fig.:3).

Table1: Different formulations of Ambroxol Hydrochloride tablet containing K4M formulations

Formulation code	Weight (mg)/ Tablet					
	Ambroxol HCl	Methocel K4M CR	PVP K 30	Magnesium Stearate	MCC 101	Total
K4M1	75	30	00	3	492	600
K4M2	75	30	15	3	477	600
K4M3	75	30	30	3	462	600
K4M4	75	60	00	3	462	600
K4M5	75	60	15	3	447	600
K4M6	75	60	30	3	432	600
K4M7	75	90	00	3	432	600
K4M8	75	90	15	3	417	600
K4M9	75	90	30	3	402	600
K4M10	75	60	15	3	447	600
K4M11	75	60	15	3	447	600
K4M12	75	60	15	3	447	600
K4M13	75	60	15	3	447	600

Table 2: Factor combinations as per the chosen experimental design

Trial no.	Formulation code	Coded Factor levels	
		X_1	
1	K4M1	-1	-1
2	K4M2	-1	0
3	K4M3	-1	1
4	K4M4	0	-1
5	K4M5	0	0
6	K4M6	0	1
7	K4M7	1	-1
8	K4M8	1	0
9	K4M9	1	1
10	K4M10	0	0
11	K4M11	0	0
12	K4M12	0	0
13	K4M13	0	0

Table 3: Translation of coded levels for Methocel K4M Formulations

Coded level	-1	0	1
X_1(Methocel K4M)	5%	10%	15%
X_2 (PVPK30)	0%	2.5%	5%

Table 4: The casual factor and responses of model formulations of Ambroxol HCl sustained release tablets of K4M formulations

Trial	**Formulation**	**X_1**	**X_2**	**Y_1**	**Y_2**	**Y_3**	**Y_4**	**Y_5**
01	K4M1	-1	-1	28.44	66.15	94.35	2.55	3.11
02	K4M2	-1	0	27.02	65.83	92.14	2.66	3.20
03	K4M3	-1	1	26.91	63.73	90.22	2.75	3.35
04	K4M4	0	-1	25.39	60.05	88.24	2.92	3.49
05	K4M5	0	0	24.32	58.93	85.41	3.10	3.69
06	K4M6	0	1	24.13	57.99	84.26	3.16	3.76
07	K4M7	1	-1	22.88	54.53	81.85	3.44	4.07
08	K4M8	1	0	22.15	54.14	80.53	3.54	4.19
09	K4M9	1	1	19.54	52.38	77.99	3.82	4.38
10	K4M10	0	0	25.05	59.31	87.06	3.10	3.70
11	K4M11	0	0	24.15	58.44	86.42	3.11	3.68
12	K4M12	0	0	23.99	59.05	85.89	3.16	3.72
13	K4M13	0	0	24.31	57.89	86.14	3.14	3.72

X_1 and X_2 are the amount of Mehocel K4M and PVP K 30 respectively. The formulations are according to table 1. Y: responses, the release percent at 1 h(Y_1), 4 h (Y_2), 8 h (Y_3), T 50%(Y4) and MDT (Y_5).

Table 5: Release kinetics of Ambroxol HCl matrix tablets of K4M formulations

Code	Zero Order		First Order		Higuchi		Korsmeyer	
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
K4M1	0.933	10.818	0.964	-0.142	0.997	34.091	0.998	0.574
K4M2	0.931	10.676	0.984	-0.130	0.996	33.652	0.995	0.588
K4M3	0.930	10.343	0.987	-0.118	0.994	31.304	0.996	0.577
K4M4	0.933	10.220	0.992	-0.110	0.994	32.157	0.994	0.596
K4M5	0.937	9.921	0.996	-0.100	0.995	31.167	0.995	0.599
K4M6	0.938	9.844	0.998	-0.097	0.995	30.904	0.996	0.600
K4M7	0.946	9.487	0.996	-0.088	0.994	29.654	0.997	0.606
K4M8	0.944	9.306	0.994	-0.084	0.994	29.109	0.995	0.609
K4M9	0.947	9.104	0.997	-0.079	0.992	28.401	0.990	0.646
K4M10	0.944	10.012	0.987	-0.103	0.994	31.324	0.998	0.596
K4M11	0.944	10.012	0.993	-0.103	0.994	31.494	0.996	0.609
K4M12	0.947	10.084	0.995	-0.103	0.993	31.479	0.997	0.615
K4M13	0.943	10.006	0.993	-0.102	0.994	31.304	0.996	0.605

Table 6: Regression equation for each response variable determined by Multiple regression analysis for K4M formulations

Regression coefficient	Independent variables	Y_1	Y_2	Y_3	Y_4	Y_5
b_0		24.48308	59.10923	86.19231	3.111863	3.697534
b_1	X_1	-2.96667	-5.77667	-6.05667	0.472107	0.495881
b_2	X_2	-1.02167	-1.105	-1.995	0.136013	0.135654

X_1 and X_2 are the amount of Mehocel K4M and PVP K 30 respectively. The formulations are according to table 1. Y: responses, the release percent at 1 h(Y_1), 4 h (Y_2), 8 h (Y_3), T 50%(Y4) and MDT (Y_5).

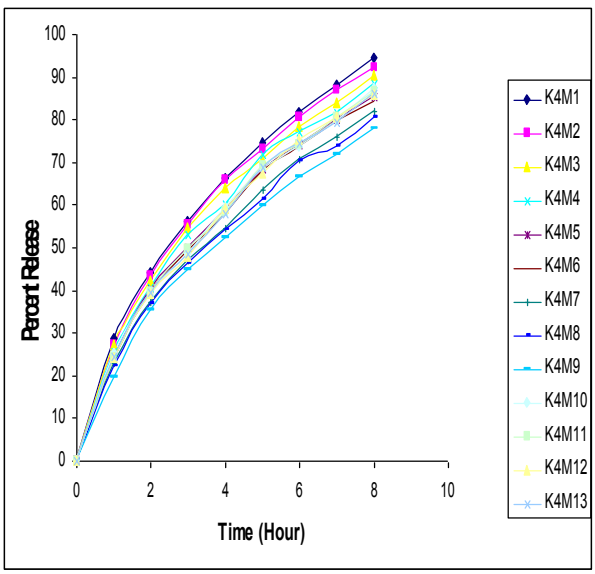

Fig. 1A: Zero order plot of release kinetics of ambroxol HCl matrix tablets

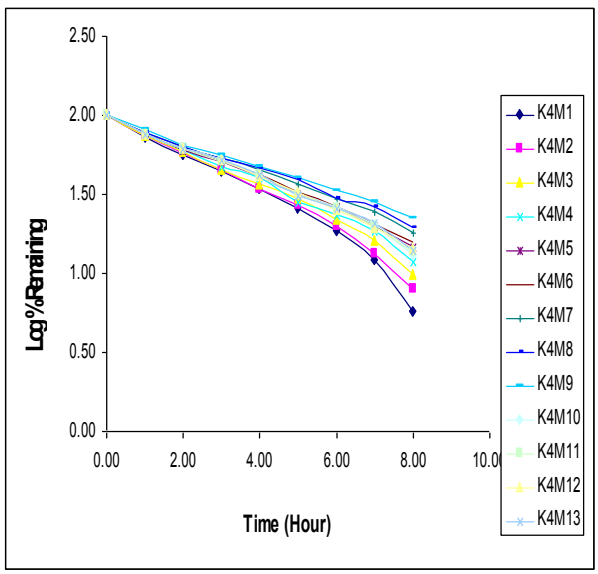

Fig. 1B: First order plot of release kinetics of ambroxol HCl matrix tablets

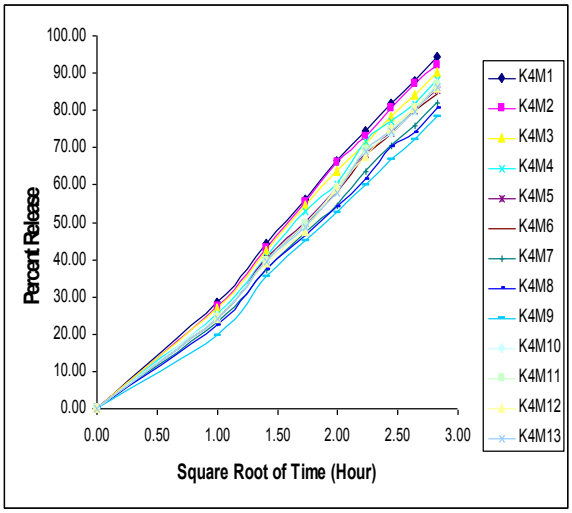

Fig. 1C: Higuchi plot of release kinetics of ambroxol HCl matrix tablets

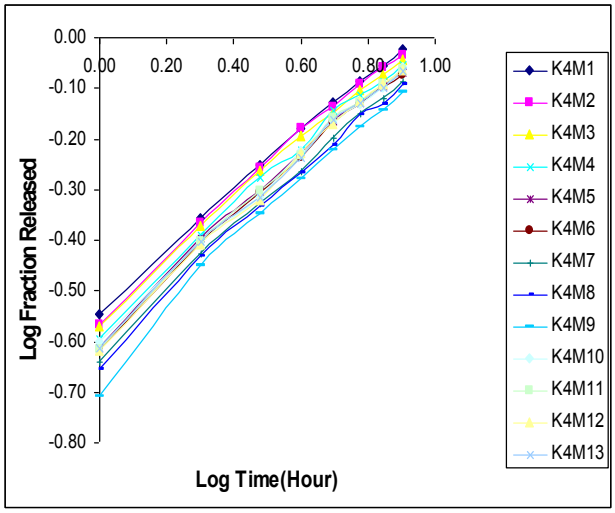

Fig. 1D: Korsmeyer plot of release kinetics of ambroxol HCl matrix tablets

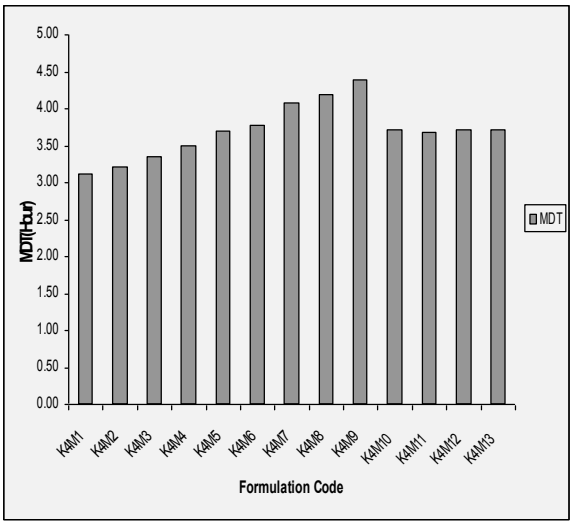

Fig.1E: MDT values of Methocel K4M based matrix tablets

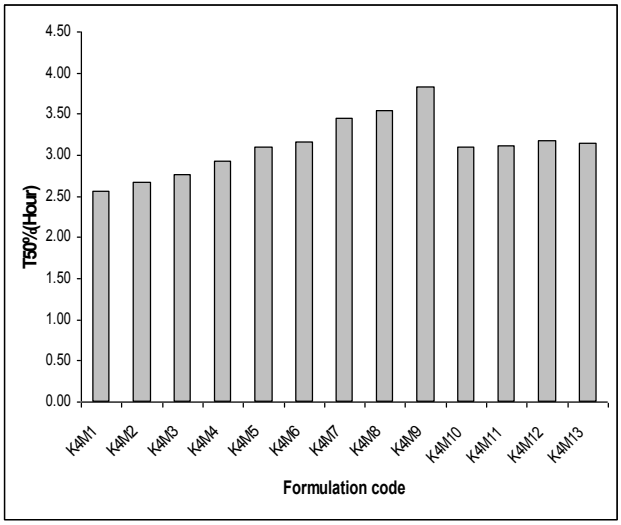

Fig. 1F: $T_{50\%}$ values of Methocel K4M based matrix tablets

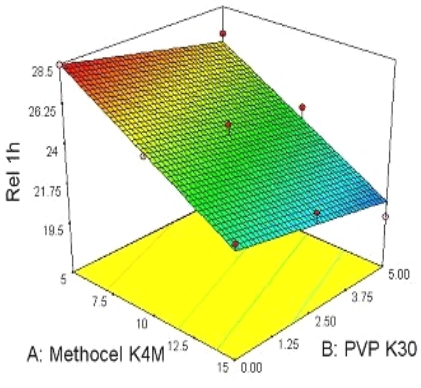

Fig. 2A: Response surface plot of tablet dissolution formulations after 4 hours dissolution

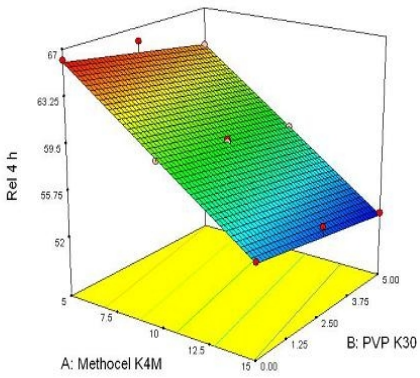

Fig. 2B: Response surface plot of tablet formulations after 1 hours

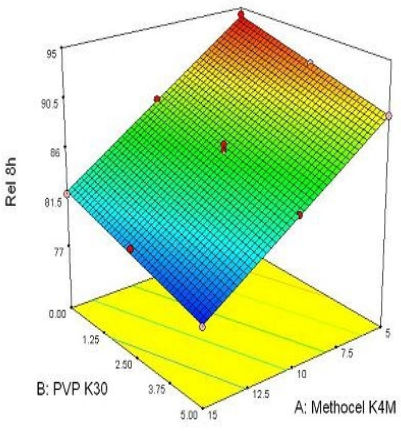

Fig. 2C: Response surface plot of tablet showing the effect of polymer on $T_{50\%}$

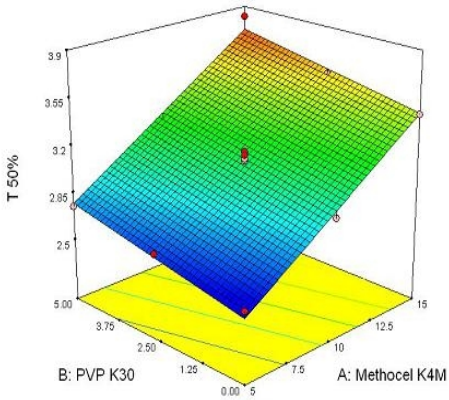

Fig. 2D: Response surface plot of tablet formulations after 8 hours dissolution

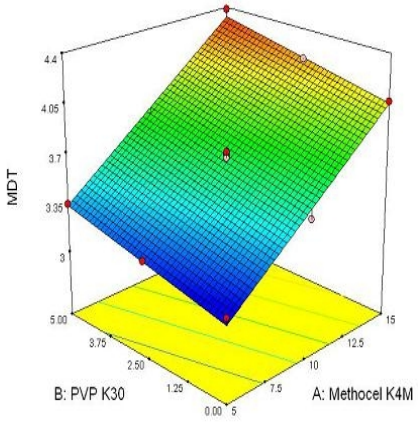

Fig.2E: Response surface plot of tablet formulations showing the effect of polymer on MDT

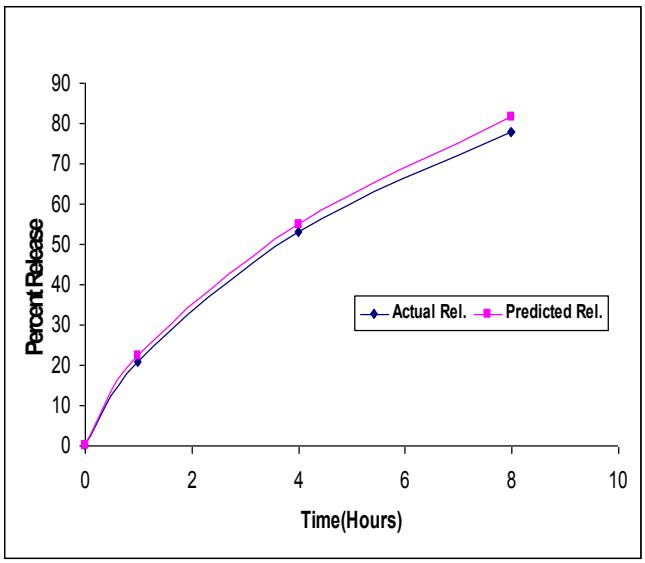

Fig. 3: Predicted and actual drug release from optimized formulation

CONCLUSION

It may be concluded from the present study that the hydrophilic matrix tablets of Ambroxol hydrochloride, prepared using Methocel K4M and PVP K 30, can successfully be employed as twice-a-day oral sustained release drug delivery system. Both the polymer and binder plays major role for the sustained release of Ambroxol hydrochloride. However, appropriate balancing between various levels of the polymer and binder may contribute better results. High degree of prognosis obtained using Response Surface Methodology. So, optimization of Ambroxol hydrochloride by Response Surface Methodology is quite efficient.

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