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Surface Response Methodology for Optimizing Combination of Hydrophilic Polymers for Controlled Release of Valsartan.

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ABSTRACT

Controlled release matrix tablets were developed to study the effect of combination of three grades of hydroxypropyl methyl cellulose (HPMC) on the *in vitro* release profile of the drug Valsartan. Tablet formulations F1 to F27 based on 3^3 full factorial design using different concentration of various grades of HPMC(HPMC K4M, HPMC k15M and HPMC K100M) were compacted by direct compression method. The prepared tablets were evaluated for their physicochemical performance and *in vitro* drug dissolution and the formulation and the optimum level of the polymers concentration was determined using design of experiment. Results: The formulated tablets were studied for *in vitro* drug release in phosphate buffer pH 6.8. The effect of independent variables (different concentration of combination of various grades of HPMC) on dependent variables that is % amount of drug release at first, eighth and twelfth hour was determined using design of experiment. The optimum levels of polymers determined from the contour plots was found to be between 10.3 % to 10.6% for HPMC K4M and HPMC K15M and between 10% to 10.25 % for HPMC K 100M which gave the targeted % amount of drug release of 3 to 7% per hour. The hydrophilic matrix tablets using combination of HPMC can be prepared for valsartan to obtain the drug release within a targeted dissolution profile.

Keywords: HydroxyPropyl Methyl Cellulose, 3^3 full factorial design, variables, responses, contour plots.

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INTRODUCTION

A simplest and most widely used method of controlling drug delivery is by incorporating drug in the polymer matrix [1]. Drug dissolution and drug diffusion through the polymer are important phenomena in controlling the release characteristics of the formulation [2].For many drugs, the optimal therapeutic response is observed only when the blood level of the drug is maintained within a narrow therapeutic window [3]. In the case of oral controlled release dosage forms, the most commonly used hydrophilic carrier materials hydroxypropyl methylcellulose (HPMC), has been used since the early 1960s [4]. It displays good compression characteristics, has adequate wetting properties (i.e. degree and time of swelling), can accommodate high levels of drug loading, and is considered non-toxic [5].

In the present work Valsartan was selected as a model practically water insoluble drug. Valsartan is an angiotensin II receptor blocker and is widely used in the therapy of essential hypertension [6] .In the preliminary study, the effect of individual viscosity grades of HPMC (i.e. is HMPC K4M. K15M and K100M) in different concentration was studied on the release of drug from hydrophilic matrix tablets of Valsartan. It was found from the study, lower concentration (10%) of each viscosity grade of the polymers were unable to control the drug release for 24 hrs. The reason could be lower concentration of each individual polymer was not able to form coherent matrix needed to control the release of drug. But as the concentration of the polymer was increased to 15% concentration only HPMC K15M was able to control release of the drug in the desired release profile for 24 hrs. HPMC K100M drastically retarded the release and HPMC K4M did not give the release in the desired release rate for 24hr. Hence it was decided to evaluate the effect of combination of three different viscosity grades of these polymers on the *in vitro* dissolution profile of Valsartan from hydrophilic matrix tablet so as to get the targeted drug release profile. Design of experiment was used to study the effect of combination of these polymers on the release of Valsartan from hydrophilic matrix tablets.

The response surface methodology (RSM) is an experimental design used for optimization, which helps develop model equations and carry out the analysis of experiments with the least number of experiments. Basically, this methodology is a collection of mathematical and statistical techniques that are useful for the modeling and analysis of problems [7] . Factorial design is an effective tool to obtain an apposite mathematical model with minimum experiments for optimization of formulation design. Factorial design allows all the factors to be varied simultaneously, thus enabling the evaluation of the effects of each variable at each level and showing inter-relationship among them. Most important variables which affect the system function are selected and systemic experiments are then performed. The number of independent variables selected decides the number of experiments that are to be performed [8].

Thus the purpose of the study was to develop and evaluate the effect of combination of three different viscosity grades of HPMC on the *in vitro* dissolution profile of Valsartan using full factorial design of experiments. In the present study 3^3 full factorial design was employed to study the effect of HPMC K4M, K15M and K100M on the *in vitro* dissolution of Valsartan. The independent variables selected were concentration of HPMC K4M (X_1). HPMCK15M (X_2) and HPMC K100M (X_3) and their effect were evaluated on the amount of drug release at 1h (Y_1), 8h (Y_2) and 20 h (Y_3).

MATERIALS AND METHODS

Materials

The following materials were uses as received:

Valsartan was purchased from EMCO Industries, Hyderabad , India. Hydroxypropyl methylcellulose (HPMC K4M, K15M and K100M) were received as gift sample from Dow Chemicals,USA. Microcrystalline cellulose (Avicel PH102) was obtained from FMC. Magnesium stearate was procured from, Ferro USA. Colloidal silicon dioxide (Aerosil 200 Pharma) was received as gift from Evonik Technical Center, India. All other materials used were of reagent grades. Purified water USP from Milipore water purification system was used where ever required.

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Methods

Preparation of matrix tablet of Valsartan

Valsartan was blended with HPMC (K4M, K15M and K100M) for 10 minutes. The diluents Avicel PH102 was added and further blended for 5 min. And finally Magnesium stearate and Aerosil were added to the blend and mixed for 3 minutes. The final blend containing 80mg of Valsartan was compressed on Cadmach single station machine (Cadmach Machinery, Ahmedabad, India) with 10.5 mm flat shaped circular punches. The hardness of tablets were kept constant between 50 to 70 N for all the factorial batches. Tests such as weight variation, hardness, friability, thickness, and *in vitro* dissolution were performed on the compressed tablets.

3^3 Factorial Experimental design

A 3^3full factorial statistical design of 27 runs was selected for optimization. The polynomial equation generated by this experimental design is as follows

$$Yi = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 \quad \text{Eq. 1}$$

where Yi is the dependent variable, b_0 is the intercept, b_1 to $b_{33}$are the regression coefficients, and X_1, X_2 and $X_3$are the independent variables.The main effects, X_1, X_2, and X_3, represent the average value of changing factor one at a time; X_1X_2, X_1X_3, and X_2X_3 represents the interaction terms and the polynomial terms (X_1^2,X_2^3 , and X_3^2) are used to assess nonlinearity. Independent and dependent variables are listed in Table1 and the experimental design is summarized in Table 2. The thickness of compressed matrix tablets was measured using a Monsanto vernier caliper. The hardness and friability of the compressed matrix tablets were measured using hardness tester (Monsanto Tablet Hardness Tester, Mht-20,Campbell Electronics, India) and the Roche Friabilator (Type EF2, Eletrolab, India), respectively. The weight variation test was done on 20 tablets , each tablet was weighed individually , the average weight was calculated and individual tablet weight was compared to the average weight [9].

In vitro drug release

The *in vitro* dissolution study of the compressed matrix tablet of Valsartan was carried out in 900ml of pH 6.8 phosphate buffer maintained at 37 ± 0.5°C in USP Type II as per USP. The drug release at various time intervals was analyzed spectrophotometrically at 250 nm (Shimadzu-1700 UV/Visible spectrophotometer,Japan). Aliquots of 5 ml was withdrawn at specified time interval and filtered through the cellulose acetate membrane (0.45µ) and the content of Valsartan was determined at 250nm spectrophotometrically. An equal volume of fresh dissolution medium, maintained atthe same temperature, was added after withdrawing each sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally (r^2 values in all the buffer was 0.99). The dissolution studies was performed in triplicate and mean values were plotted versus time. The target dissolution profile parameters of a sustained-release product were set as follows: After 1 h: 0-10 %; After 2 h: 5to15%; After4 h: 15to 35%; After 8h:40 to 70%; After 12h: 65 to 85% and After 20h: 80 to 100%.

Optimum Formula

After developing the polynomial equation for responses Y1 at 1h , Y2 at 8h and Y_3 at 20 h with the independent variables, the formulation was optimized for these responses. Optimization was done to find out the levels of independent variables (X_1,X_2 and X_3) that would yield the value of responses within the target release profile.

RESULT AND DISCUSSION

In the present study an attempt was made to control the drug release of Valsartan by using combination of various viscosity grades of Hydroxypropyl Methylcellulose. The physical parameters of all the formulated batches showed uniformity of weight, hardness, drug content and the results are shown in table 3.

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From table 2, it was found that when the concentration of all the three polymers were low (10%) the matrix system was not able to control the drug release for 24 hrs.

DATA ANALYSIS

All the batches of matrix release drug delivery system of valsartan were evaluated for Y_1, Y_2 and Y_3.Transformed values of all the batches, along with their results are shown in Table 2.

The Y1 (dependent variable) obtained at various levels of three independent variables (X1,X2 and X3) was subjected to multiple regression to yield a polynomial equation (Full Model)

$$Y_1= 6.420+0.0722X_1+0.6711X_2+0.1100X_3+0.99083X_1X_2+1.161X_2X_3+1.73X_2X_3 -1.608X_1X_2X_3 -0.380X_1^2-0.1833X_2^2+1.442X_3^2 \quad \text{Eq.2}$$

The value of the coefficient of determination (R^2) was found to be 0.8758. The value of Y1 measured for various batches showed wide variation (that is values ranged from 3.1to 20.5).The values of Y1 is strongly affected by the variables selected in the study. This is clearly indicated from the wide range of values of coefficients of the terms in Eq.(2). The main effects of the term X_1, X_2 and X_3 indicate the average changes in 1 variable at time when it changes from its low level to high level. The interaction term X_1X_2, X_1X_3, X_2X_3 , X_1^2,X_2^2 andX_3^2 indicates how Y1 changes if two variables are changing simultaneously. The positive coefficient for three independent varables indicates favorable effect on Y1 ,whereas negative coefficient for interaction term between 3 independent variables $X_1X_2X_3$ indicated an unfavourable effect on response Y1. The significance level of coefficient of b_1, b_2, b_3,b_{12}, b_{11},b_{22} and $b_{33}$was found to be more than 0.05 hence it was omitted from the model. Coefficients of b_{13}, b_{23},b_{123} was found to be significant at $p < 0.05$, hence a reduced equation can be written as

$$Y_1= 6.420 +1.61X_2X_3+1.73X_2X_3 -1.608X_1X_2X_3 \quad \text{Eq.3}$$

The Eq (3) indicates that release of drug at 1hr from matrix tablet is controlled mainly by combination of polymer HPMC K15 M and K100M as they have positive coefficient values and they will give the release within target release profile whereas combination of all the three polymers that is HPMC K4M, K15M and K100M have negative effect on the release of drug at 1hr where they drastically reduce the release of the drug from polymer matrix.

The valsartan release from hydrophilic matrix tablet at 8hr (Y_2) was found to be in range of 20.43% to 95.26%. a polynomial equation developed for % valsartan release at 8 h can be written as

$$Y_2 = 34.091 – 1.783X_1 +0.92556X_2 – 1.058 X_3 + 5.948X_1X_2 +4.890X_1X_3 + 6.848 X_2X_3 -10.290X_1X_2X_3- 0.4611X_1^2 -1.726 X_2^2 + 1.067 X_3^2 \quad \text{Eq.4}$$

The value of the coefficient of determination (R^2) was found to be 0.9145 which indicates good fit.Depending upon the p value <0.05 , it was found that all three independent variables are having an influence on the response Y_2. The coefficients b_1, b_2 b_3 and b_4 were found to be significant hence reduced equation for respone Y_2 can be written as

$$Y_2 = 34.091 + 5.948 X_1X_2 + 4.890 X_1X_3 +6.848X_2X_3 -10.290X_1X_2X_3 \quad \text{Eq.5}$$

From equation 3 it is found that combination of three polymers have negative effect on the release of the drug at 8th hour. That is HPMC K4M, K15M and K100M in higher concentrations (i.e is 15%) drastically reduces the release of the drug at 8h as can be seen in formulation 1.And HPMC K4M, K15M and K100M in lower concentration(i.e is 10%) is unable to control the drug release at 8 hr and release almost 95%of drug at 8h (formulation 27).

Y_3 (release at 20hr) was found in the range of 44.9 % to 100 %. The polynomial equation for the response was

$$Y_3= 91.670-11.319X_1-4.618X_2-9.777X_3+2.00X_1X_2-2.357X_1X_3+7.902X_2X_3-5.253X_1X_2X_3$$

$-7.186X_1^2-8.319X_2^2-8.449X_3^2$ Eq.6

The value of coefficient of determination (R^2) was found 0.9172 indicating good fit. Depending upon p value < 0.05 it was found that coeffcients b_1, b_3, b_{23}, b_{11},b_{22} and b_{33} are only significant and reduced equation can be written as

$Y_3= 91.670 – 11.319X_1 – 9.77 X_3 + 7.902 X_2X_3 -7.186 X_1^2– 8.319 X_2^2 – 8.449 X_3^2$ Eq.7

Equation 7 suggests that independent variable X_1 and X_3 and X_1^2, X_2^2 and X_3^2 has negative effect on the response Y_3 where as combination of independent variable $X_2$and X_3 has a positive effect on response Y_3. The equation suggests that interaction of HPMC K15M and K100M is playing a major role in controlling the release of the valsartan at 20h. The results of testing the model are shown in table 4.

As can be seen from Table 2, at higher concentration (15%) of all the three polymers the drug release at 1hr was within the target release profile but release at 8h and 20 h was very slow and at 20h only 48.30% of the drug was release. When the concentration of the three polymers was medium (i.e 12.5%) the release of the valsartan and 1h and 20h was similar to target product profile but the release was a bit slow at 8h. And when the concentration of the three polymers were kept low (10%) in formulation the release of valsartan was very fast and was not within the TPP at any of the time point.

The effect of independent variables on dependent variable was further studied by plotting contour plots. The contour plot, showing the effect of X1 and X3 when X2 (middle level) was kept constant on response Y1 is shown in the figure 1. The contour plot depicts that lines are not linear indicating a nonlinear interaction between X_1 and X_3. To get the minimum release of valsartan between 5% to 7% at 1h, the HPMC K100M should be kept between 12.2 to 12.7% and HPMC K4M should be kept between 10% to 15%. Figure 2 depict the contour plot showing the effect of HPMC K4M and K100M when K15M (middle level) was kept constant on response Y2 (release at 8 h). The lines are not linear in contour plot indicating a non-linear interaction between the independent variables. To get release of Valsartan between 50% to 55% from the hydrophilic matrix tablets the polymer concentration of HPMC K4M should be kept between 10 to 10.5% and HPMC K100M concentration should also be kept between 10 to 10.5%.

The contour plot showing the effect of HPMC K4M (X1) and HPMC K100M (X3) when HPMC K15M (X4, Middle level) was kept constant on response Y3 is shown in figure 3.The plot indicate the nonlinear interactions between the independent variables.

Table1: Variables in 3^3 factorial design

Independent Variable	**Level**		
	Low	Medium	High
X1 Percentage of HPMC K4M	10	12.5	15
X2 Percentage of K15M	10	12.5	15
X3 Percentage of K100M	10	12.5	15
Transformed Value	-1	0	+1
Dependent Variables			
Y_1 amount of drug release at 1h			
Y_2 Amount of drug release at 8 h			
Y_3 Amount of drug release at 20 h			

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Table 2: Full factorial design with responses

Batch No.	X1	X2	X3	Y_1(h)	Y_2 (h)	Y_3 (h)
1	+1	+1	+1	4.9	20.00	48.30
2	+1	+1	0	3.1	25.62	63.30
3	+1	+1	-1	4.1	27.51	67.20
4	+1	0	+1	4.8	22.01	49.00
5	+1	0	0	5.8	28.66	74.00
6	+1	0	-1	7.5	31.95	70.52
7	+1	-1	+1	5.3	20.43	44.9
8	+1	-1	0	7.0	29.86	78.2
9	+1	-1	-1	5.5	23.53	78.58
10	0	+1	+1	8.7	34.67	82.10
11	0	+1	0	7.0	29.1	72.90
12	0	+1	-1	5.6	30.49	70.24
13	0	0	+1	9.5	32.77	69.80
14	0	0	0	4.9	39.96	100
15	0	0	-1	9.4	39.85	100
16	0	-1	+1	5.7	29.67	70.30
17	0	-1	0	6.0	32.2	77.40
18	0	-1	-1	8.5	34.16	81.68
19	-1	+1	+1	6.0	33.53	81.60
20	-1	+1	0	6.4	31.38	71.20
21	-1	+1	-1	5.56	25.36	62.56
22	-1	0	+1	6.5	31.12	72.9
23	-1	0	0	6.2	35.36	95.00
24	-1	0	-1	9.55	48.78	100
25	-1	-1	+1	7.08	25.52	62.24
26	-1	-1	0	7.97	41.56	100
27	-1	-1	-1	20.5	95.26	100

Table 3: Result of physical parameters of formulated tablets

Sr.No.	Physical Parameters	Results
1	Average weight of tablets	505mg
2	Weight variation	500 mg ± 1.5%
3	Hardness	50 N to 70 N
4	% Friability	Below 0.5% w/w ± 0.45
5	Assay	Between 96.5% to 98.5%

Table 4: Testing the Model

		For Y1			
Regression	Df	SS	MS	R2	F
FM	16	227.6	14.2	0.8758	4.4062
		For Y2			
Regression	Df	SS	MS	R2	F
FM	16	4669.6	291.9	0.9145	6.6827
		For Y3			
Regression	Df	SS	MS	R2	F
FM	16	6058.7	378.7	0.0.9172	6.9254

Table 5: Levels of Independent Variables of optimum formula

HPMC GRADE	Low Level (%)	High Level (%)
K4M (X1)	10.3	10.6
K15M (X2)	10.3	10.6
K100M (X3)	10	10.25

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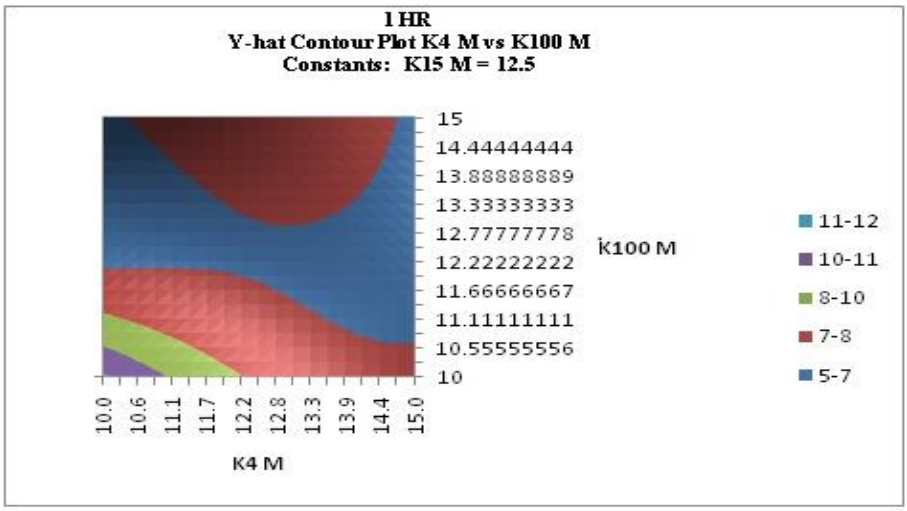

Figure 1: Contour Plot showing the effect of HPMC K15 M in HPMC K4M and K100M on percent drug release at 1hr

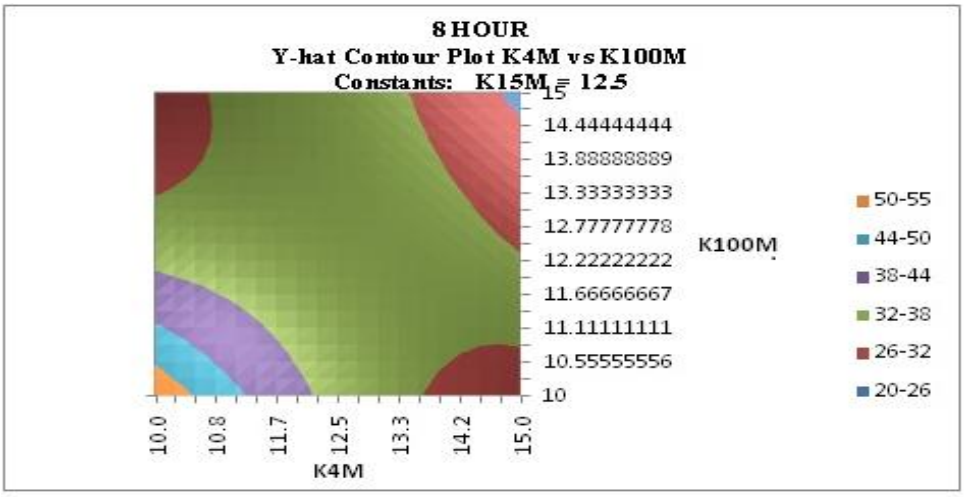

Figure 2: Contour Plot showing the effect of HPMC K15M , HPMC K4M and K100M on percent drug release at 8hr

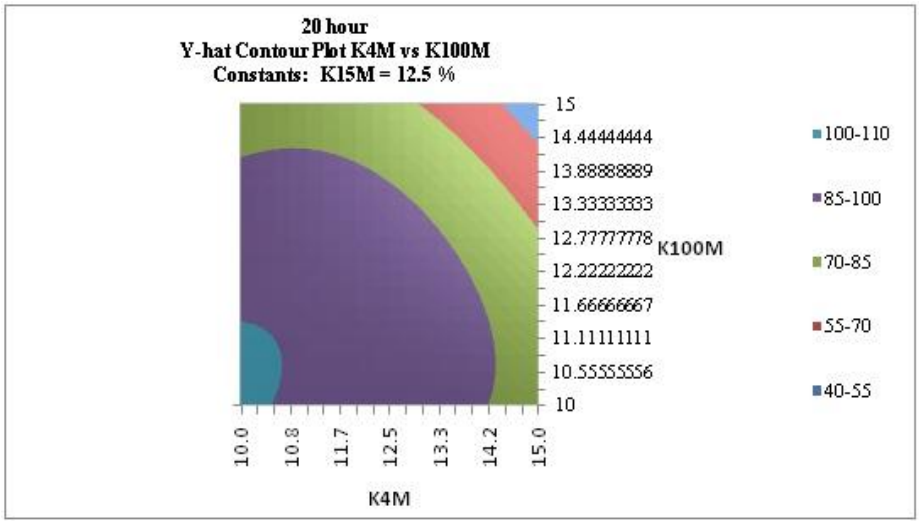

Figure 3: Contour Plot showing the effect of HPMC K15M , HPMC K4M and K100M on percent drug release at 20hr

Optimum Formula

The levels of variables that give the optimum response were determined after studying the effect of independent variables on various responses. It was evident from polynomial equations and contour plots that high levels of independent variables(X1,X2,X3) could not target the release of valsartan in target dissolution profile. The optimum formulation is one which target the release of valsartan in target dissolution profile. Using contour plots and a computer optimization process we have selected the levels of independent variables as shown in Table 5 which gave the % amount release of valsartan as per targeted dissolution profile.

CONCLUSION

Results from the studies indicates that valsartan matrix tablet can be formulated using hydrophilic polymer HPMC of different viscosity grades. The effects of variables on the release of valsartan from hydrophilic matrix tablet was well studied using Factorial design. The design of experiment has become a rapid, systematic and reliable screening tool to identify and quantitatively define the significant factors influencing the drug release. The derived polynomial equations and contour plots aids in predicting the values of independent variables for preparation of optimum controlled release matrix tablet of Valsartan with the desired release profile matching the targeted dissolution profile.

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