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Original Article

DEVELOPMENT OF HYDROPHILIC MATRIX TABLET OF CARBAMAZEPINE USING 3^3 FULL FACTORIAL EXPERIMENTAL DESIGNS

SHASHIKANT BARHATE[1], MARIA HUSAIN[2]

[1]Department of Pharmaceutics, Shri Suresh Dada Jain Institute of Pharmaceutical Education and Research, Jamner, Maharashtra, [2]Department of Pharmaceutics, Dr. Rafiq Zakaria Campus, Y. B. Chavan College of Pharmacy, Aurangabad, Maharashtra.
Email: saifeemaria@gmail.com

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ABSTRACT

Objective: The study aims at developing the hydrophilic matrix tablet of carbamazepine (CBZ) using an optimization technique. The purpose of the study was to develop the hydrophilic matrix dosage form using the combination of different viscosity grades of hydroxypropyl methylcellulose (HPMC) to get the release within the desired target dissolution profile (TDP).

Methods: A full factorial design was employed to develop once a day matrix tablet using hydrophilic matrix polymers like HPMC K4M (X_1), HPMC K15M (X_2) and HPMC K100M (X_3) as independent variables and the percent drug release at 1h (Y_1), 8h (Y_2) and 20h (Y_3) was considered as dependent variables. The optimization and the design space were obtained using response surface methodology and multiple response optimization using the polynomial equation.

Results: The result indicates that concentration of all the three polymers plays an important role in the release of the drug for 24h. The formulated tablets have good physical properties and the optimized formulation prepared using design space showed the release within the target dissolution profile and followed zero order release pattern.

Conclusion: The results demonstrated that design of an experiment can be used to develop hydrophilic matrix dosage form with the desired drug release properties.

Keywords: Design of experiment, Hydroxypropyl methycellulose, Full factorial design, Design space, Targeted dissolution profile.

INTRODUCTION

Hydrophilic matrices are simple to formulate, easy to produce, in expensive and have valid invitro-invivo correlation beside that it has good regulatory acceptability [1]. HPMC is one of the most frequently used hydrophilic polymer for matrix dosage form because of its approval as an excipient by Food and Drug administration of United States [2-4]. It is a water-soluble polymer and study have shown that the drug release from the HPMC matrices occurs either by diffusion through the gel layer or through surface erosion of this gel layer [3, 5, 6]. Matrix dosage forms prepared using HPMC generally show pH-independent release profiles when the drug solubility is pH independent but may produce pH-dependent release profiles for drugs having pH dependent solubility [7-9]. CBZ a dibenzapine derivative with a structure resembling the tricyclic antidepressants [10], is an effective anti-epileptic drug and specific analgesic for trigeminal neuralgia. It is poorly water soluble drug belonging to BCS class II [11, 12] and its absorption is dissolution rate-limited. As CBZ shows the narrow therapeutic window and diurnal variations in plasma concentration, the conventional tablets needs to be administered 3-4 times a day [13]. Thus preparing sustained release matrix helps in reducing side effects and improving patient compliance [14]. Several studies have been done to prepare CBZ extended release tablets by using different techniques viz. using a combination of eudragit RS PO and RL PO [13], HPMC K4M [15], ethyl cellulose [16] and compritol 888ATO and HPMC K15M [17]. The purpose of the study was to examine the effect of combination of different viscosity grades of HPMC namely K4M, K15M and K100M on the release of CBZ from the hydrophilic matrices and to obtain a design space for formulation wherein the drug release from the hydrophilic matrix will always be within Targetted Dissolution Profile (TDP). To achieve this aim the design of experiment (DOE) was used. A full factorial design was proposed for the development of hydrophilic matrix tablet based on the combination of three polymers. The independent variables include the percentage amount of HPMC K4M (X_1). HPMC K15M (X_2) and HPMC K100M. The dependent variables were selected as percent release of drug at 1h (Y1), percent release of drug at 8h (Y2) and percent drug release at 20h (Y3). These responses were selected with the view that release at 1h is indicative whether dose dumping will occur from the formulation or not. The release of the drug at 8h from the matrix tablets indicates whether the drug release could be sustained until 12 h or 24h and release of the drug from the matrix tablets at 20h is indicative of the complete release of the drug from the dosage form. All the response variables were fitted to linear, cubic and quadratic model and regression analysis were carried out to get a quantitative relationship between dependent and independent variables.

MATERIALS AND METHODS

Materials

CBZ (MW= 236.269 g/mol) was purchased from EMCO Industries Hyderabad Ltd. HPMC (K4M. K15M and K100M) were received as gift samples from Dow Chemicals, India. Microcrystalline cellulose (Avicel PH 102) was obtained from FMC. Magnesium stearate was procured from Ferro USA. Colloidal silicon dioxide (Aerosil 200 Pharma) was received as gift sample from Evonik Technical Centre India. All other reagents used for analysis were of analytical grade and procured from Merck India. Purified water IP was used wherever indicated.

Table 1: Variables in 3^3 Factorial design

Independent variable	Level		
	Low	Medium	High
X_1 Percentage of HPMC K4M	10	12.5	15
X_2 Percentage of K15M	10	12.5	15
X_3 Percentage of K100M	10	12.5	15
Transformed Value	-1	0	+1

Preparation of matrix tablets

3^3Full factorial design was employed to study the effect of combination of HPMC (K4M, K15M and K100M) polymer on the release of the CBZ from the matrix tablet. Higher and lower levels of each factor were coded as+1 and −1 respectively, and the mean value as 0. The selected factor levels are summarized in table 1.

Twenty seven batches (F1 to F27) were prepared as per full factorial design for optimization of HPMC (K4M, K15M and K100M) concentrations to obtain the drug release profile similar to targeted dissolution profile (TDP). Compositions of the factorial batches are shown in table 2. For each batch, tablets of 500 mg were prepared using direct compression method. In brief, the manufacturing process can be described as previously weighed CBZ was mixed with the weighed quantity of HPMC (HPMC K4M, K15M and K100M) and passed through 30# sieve. This mixture was mixed with Avicel PH102 formerly passed through 30# and finally the whole blend was mixed with aerosil and magnesium stearate earlier passed through 60 #. The mixed blend was directly compressed on 12.5 mm circular biconvex die/punch set using Rimex Mini Press rotary compression machine. The compression force was set in such a way that all formulations were having the hardness of 4 to 6 kg/cm^2.

Table 2: Composition of hydrophilic matrix tablet of CBZ

Formulations	HPMC K4M	HPMC K15M	HPMC K100M	Avicel PH 102
F1	75	75	75	155
F2	75	75	62.5	177.5
F3	75	75	50	190
F4	75	62.5	75	177.5
F5	75	62.5	50	202.5
F6	75	62.5	50	190
F7	75	50	75	190
F8	75	50	62.5	202.5
F9	75	50	50	215
F10	62.5	75	75	177.5
F11	62.5	75	62.5	190
F12	62.5	75	50	202.5
F13	62.5	62.5	75	190
F14	62.5	62.5	62.5	202.5
F15	62.5	62.5	50	215
F16	62.5	50	75	202.5
F17	62.5	50	62.5	215
F18	62.5	50	50	227.5
F19	50	75	75	190
F20	50	75	62.5	202.5
F21	50	75	50	215
F22	50	62.5	75	202.5
F23	50	62.5	62.5	215
F24	50	62.5	50	227.5
F25	50	50	75	215
F26	50	50	62.5	227.5
F27	50	50	50	240

Each tablets contained 100 mg of CBZ and proper amount of magnesium stearate and talc.

***In vitro* release of CBZ from prepared hydrophilic matrix tablets**

The *in vitro* drug release from CBZ matrix tablets was evaluated using USP type I dissolution test apparatus. The dissolution test was carried out for a total period of 24 hours. The dissolution medium comprised of 900 ml of distilled water maintained at 37°±0.5 °C. The dissolution test was carried out at 100 revolutions per minute. Aliquot samples (10 ml) were withdrawn and replaced by fresh medium to maintain constant volume at 1,2,4,8, 12 and 20 h. The samples were filtered and analyzed at 285.5 nm by UV Spectrophotometer. The drug concentration was calculated using the standard calibration curve. The percent drug releases were compared to the target dissolution profile (TDP). The values of the TDP were based on an average dissolution rate of 4% to 6.5 % per hour in order to achieve a 24h in-vitro release profile.

Drug release kinetic studies

The drug release mechanism from CBZ hyrdrophilic matrix tablets was determined using zero order (Eq. 1) [18], First order (Eq2), Korsmeyer Peppas (Eq. 3) [19], and Higuchi release models (Eq. 40) [20].

$$Mt = M0 + k0t \quad \text{Eq. 1}$$

M_t = amount of drug released at time 't', M_0 = amount of drug in the solution at t= 0, k_0 = zero-order release constant

$$\ln Mt = \ln M0 + k1t \quad \text{Eq. 2}$$

Where M_t and M_0 are described as above and k_1 is first order release rate constant.

$$\frac{Mt}{M\infty} = kKP\, tn \quad \text{Eq. 3}$$

Where M_t/M_∞ = Fraction of drug released at time t, k_{KP} is the release constant and n = is the release exponent.

$$Mt = kH\sqrt{t} \quad \text{Eq. 4}$$

Mt = is amount of drug release at time t '$\sqrt{t}$ ', kH = Higuchi release constant.

Data analysis

All responses were fitted to linear, interaction or quadratic models using Design Expert 9.0.3.1 Stat-Ease Minneapollis USA trial version and analyzed statistically using analysis of variance (ANOVA) and those having p-value<0.05 was included in the analysis. The data were also subjected to 3-D response surface methodology to study the interaction of polymers and their effect on dependent variables. Thus from the DOE data the design space was constructed within which the dissolution profile for formulation shall always be within the TDP.

RESULTS AND DISCUSSION

Initially, the preliminary formulation trials were done to evaluate the effect of individual polymer on the release of CBZ from hydrophilic matrix tablets prepared using different viscosity grades of HPMC. Initial studies indicated that to control the percent drug release of CBZ from the matrix tablet, the minimum concentration of HPMC K4M individually required was 30% of the tablet weight and

15% of HPMC K100M was required for controlling the drug release when used alone. However, the drug release was within the TDP only for the formulations containing 45% of HPMC K4M and 30% of HPMC K15M individually. Rest of the formulations failed to meet the TDP. Thus based on these early experiments, the overall level of the three polymers in combination for the DOE experiment was finalized as 30% low, 37.5% middle and 45% of the tablet weight as the highest level. The preliminary study indicated that for each polymer, the level of polymer in DOE study should be+1 =15%, 0= 12.5% and-1 should be equal to 10% of the tablet weight.

The factorial batches prepared using DOE was evaluated for tablet characteristics, and all batches showed uniformity in tablet weight. The weights of matrix tablet for all 27 batches were found to be in between 500±15 mg indicating good uniformity in weight and less variation in the filling of the powder in the die cavity. Thickness for all the factorial batches was found to 7.6±0.39 mm, the hardness of the tablets of all the factroial batches were between 6 to 8 kg/cm^2 and the friability all the batches were within the pharmacopoeial limits and have friability less than 0.5 % w/w. The drug contents of each formulation batch were determined using the UV spectroscopic method, and all formulations complies the official requirement of the pharmacopoeia and showed % assay between 97.52 to 98.64%.

***In vitro* release of CBZ from the hydrophilic matrix tablet**

The TDP of the drug release from 24 h matrix tablets based on the average dissolution rate of 4 to 6.5% per hour is shown in table 3.

Table 3: Target dissolution profile for 24h drug release

Time (h)	TDP low (%)	TDP high (%)
0	0	0
1	0	10
2	5	15
4	15	35
8	40	70
12	65	85
20	80	100

The percent drug releases of factorial batches of hydrophilic matrix tablets of CBZ were compared with the TDP, and it was found that except formulation F15, F24 and F26 none of the formulations showed the percent drug release within the TDP. The graphs of percent drug release of CBZ at various time intervals are shown in fig. 1,2 and 3. The factorial batch F27 containing low levels of the three polymers that is HPMC K4M, K15 M and K100M, showed the faster drug release than the TDP. In this formulation, almost 20.52% of drug got released in 1st hour and more than 95% of the drug got released in the 8 h. This formulation was not able to control the release of the drug for 24 h. The reason for higher drug release from the formulation could be the low levels of hydrophilic polymer, which was not able to form a strong coherent matrix. Moreover, the presence of high amount of microcrystalline cellulose (Avicel PH 102) could be acting as channeling agent by absorbing water to some extent, and allowing faster permeation of the drug from the weak matrices [16].

Rest of all the formulations except F15, F24 and F26 showed a less percent drug release when compared with target dissolution profile. The reason of the slow drug release from the maximum formulations could be because of low solubility of carbamazepine in the dissolution medium [21]. The percent drug release of CBZ was found to be minimum with the formulation F1 containing the highest concentration of the total polymer that is 45% w/w. The reason of slower drug release from the formulation could be that with an increase in concentration and viscosity of HPMC could have led to increase tortuosity or gel strength of polymer. Literature has reported that use of hydrophilic polymer like HPMC is preferred in formulation of CBZ matrix tablets because they inhibit the polymorphic transition of carbamazepine to carbamzepine dihydrate. This result in the more amorphous and less crystalline form of carbamazepine present in the polymeric matrix. The literature indicates that such hydrophilic polymers like HPMC serves as templates or micro substrate for nucleation in the crystallization process. The interaction between the drug and polymer appears to occur by hydrogen bonding. The hydroxyl groups of the polymer apparently attach to the drug at the site of water binding, and thus its transformation to the dihydrate form, is inhibited [22].

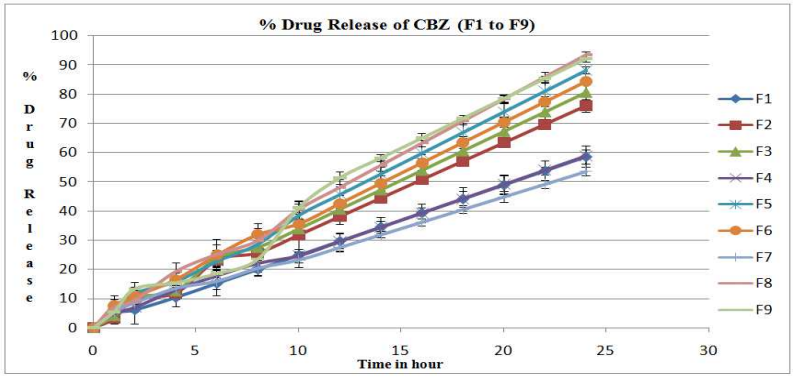

Fig. 1: Release of CBZ from factorial batches (F1-F9) (n=3)

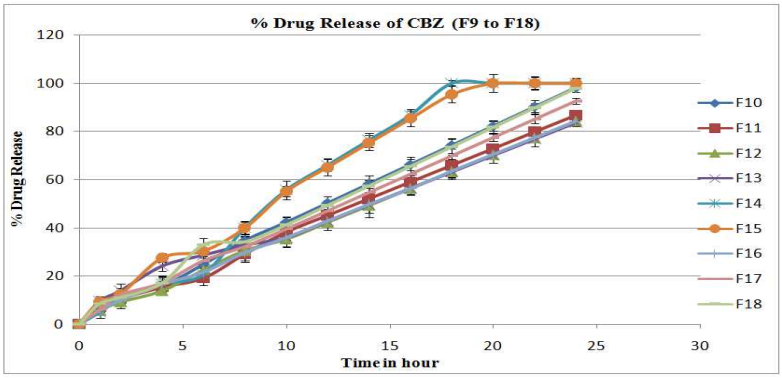

Fig. 2: Release of CBZ from factorial batches (F10-F18) (n=3)

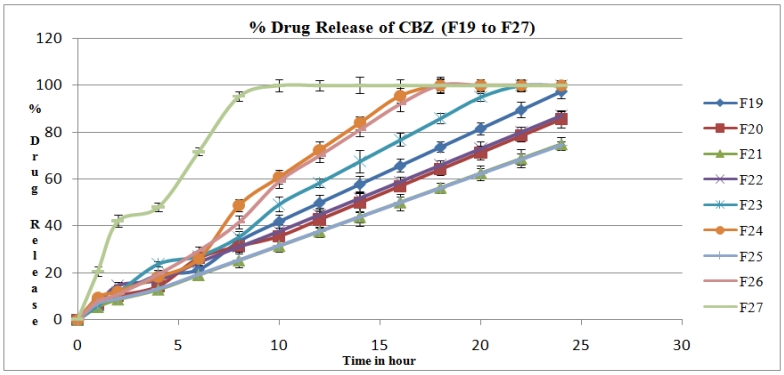

Fig. 3: Release of CBZ from factorial batches (F19-F27) (n=3)

Drug release kinetic studies

In this study, different mathematical models like zero order, first order, Higuchi, Hixon Crowell and Korsmeyer Peppas model were applied to understand the dissolution profile of CBZ from the hydrophilic matrix prepared using different viscosity grades of HPMC. The R^2 values obtained from different mathematical models were evaluated. According to Korsmeyer Peppas model, CBZ release during 24 h of the test was mainly by anomalous transport. The n value obtained for formulations F1 to F27 was 0.0.453<n<0.85 in which both Fickian diffusion and non-Fickian mechanism occur. Anomalous diffusion of drug release mechanism signifies a coupling of the diffusion and erosion mechanism which indicate that the drug release is controlled by more than one process [23]. During first 2 h of dissolution differences in drug release was observed for formulations F15, F24 and F26, which fitted the targeted dissolution profile. The R^2 values obtained for these formulations are listed in table 4. The drug release during first, 2h in all the three formulations was predominantly by diffusion (n values were between 0.362-0.457). During the remaining 22h the drug release was mainly by zero order release. The formulations did not have good fit for first order release mechanism, indicating that the CBZ release from the hydrophilic matrix tablets was not dependent on the drug remaining in the HPMC matrix tablet.

Statistical analysis of the data

All responses were fitted to linear, interaction or quadratic models using Design Expert 9.0.3.1. The regression coefficients for each term to the regression model are summarized in table 5 and table 6, describing the model parameters affecting the response variable's Y_1, Y_2 and Y_3.

Table 4: Mathematical fit for drug release model for CBZ hydrophilic matrix tablets

Formula-tion	Zero Order R^2			First order R^2			Higuchi			Korsmeyer-peppas R^2n					
	0-2h	2-24h	0-24h	0-2h	2-24h	0-24h	0-2h	2-24h	0-24h	0-2h	2-24h	0-24h	0-2h	2-24h	0-24h
F15	0.9175	0.9847	0.9898	0.9246	0.9483	0.9525	0.9968	0.9584	0.9254	1	0.9644	0,970	0.397	0.859	0.763
F24	0.9064	0.9805	0.9815	0.9133	0.9372	0.9204	0.9942	0.9468	0.8796	1	0.9318	0.911	0.362	1.013	0.803
F26	0.9349	0.9921	0.9914	0.9410	0.9596	0.9304	0.9995	0.9430	0.8920	1	0.9856	0.967	0.457	1.027	0.863

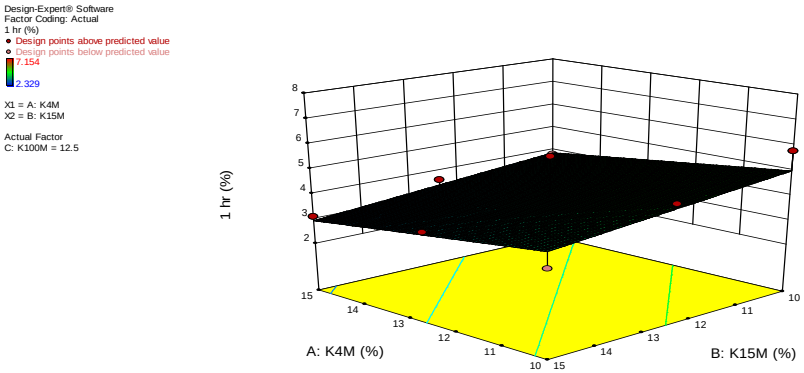

Fig. 4: Surface response plot showing the effect of X1 and on drug release at 1h

Table 5: Regression coefficient for the response variables

$Y1= 3.97-0.56\ X_1-0.47X_2-0.57X_3$

$Y2 = 33.34-7.68\ X_1-4.14\ X_2-5.95X_3+5.95\ X_1X_2+4.89\ X_1X_3+6.85\ X_2X_3$

$Y3= 91.66-9.49X_1-4.07X_2-8.28X_3+2.05X_1X_2-2.32\ X_1X_3+7.95X_2X_3-7.14\ X_1^2 -8.30X_2^2-8.44\ X_3^2$

The release of drug at 1h was affected by the concentrations of X_1, X2 and X_3 as the concentrations of HPMC K4M, K15M and K100M increased in the matrix tablets the percent drug release decreased as was evident in formulation F1, F2, F3 and F4. They showed the percent release between 3.16 to 4.92% and with the lowest concentration of all the formulations in matrix tablet that is F27 the release was 20.52% at 1h. There was no significant interaction between X_1, X_2 and X_3 polymer, which would influence the drug release at 1h, which was evident from surface response plot shown in fig. 5.

The concentration of HPMC K4M, K15M and K100M has the negative influence on the percent release of drug at 8 h as seen from the equation listed in table 5. The interaction between HPMC K4M, K15M and K100M can be elucidated by using surface response and interaction plots shown in fig. 4. When HPMC K100M was kept constant at mid level and HPMC K4M and K15M was kept to the lowest level the percent drug release was 41.56% but when the concentration

of HPMC K4M and K15M was increased to the high level (+1) the percent drug release of CBZ drastically decreased to 25.62% indicating a stronger matrix formation which retarded the release of already poorly soluble drug due to more hindrances for drug diffusion.

Table 6: Model parameters for the studied response variables

Source	df	SS	MS	F value	p
Release at 1h (%)					
X_1	1	5.62	5.62	7.55	0.0115
X_2	1	4.04	4.04	5.43	0.0290
X_3	1	5.86	5.86	7.87	0.0101
Release at 8h (%)					
X_1	1	1062.1	1062.1	11.66	0.0027
X_2	1	308.60	308.60	3.39	0.0807
X_3	1	638.08	638.08	7	0.0155
X_1X_2	1	424.59	424.59	4.66	0.0432
X_1X_3	1	286.95	286.95	3.15	0.0912
X_2X_3	1	562.66	562.66	6.17	0.0219
Release at 20h (%)					
X_1	1	1620.51	1620.51	6.98	0.0003
X_2	1	297.84	297.84	3.62	0.0004
X_3	1	1233.06	1233.06	14.98	0.0742
X_1X_2	1	50.51	50.51	0.61	0.4442
X_1X_3	1	64.36	64.36	0.78	0.3889
X_2X_3	1	64.36	64.36	0.78	0.3889
$X1^2$	1	305.54	305.54	3.71	0.0709
X_2^2	1	413.12	413.12	5.02	0.0387
X_3^2	1	427.85	427.85	5.20	0.0358

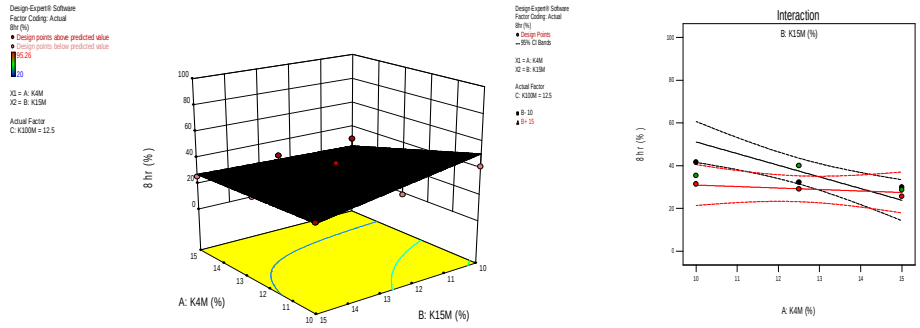

Fig. 5: Surface response plot showing the effect of X1 and X2 on drug release at 8h. and the interaction plots between the three polymers

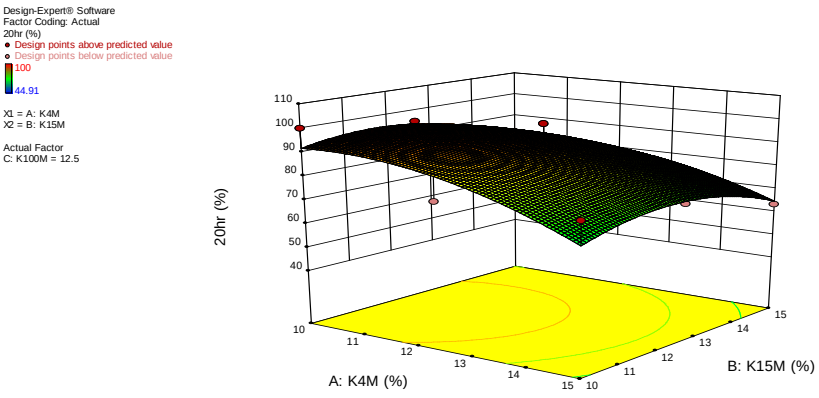

Fig. 6: Surface Response Plot showing the effect of X1 and X2 on drug release at 20h

In case of percent drug release at 20h (Y3) the factor X_1, X_2, X_3 and its quadratic effect were found to be significant as the concentrations of all the three polymers in the matrix tablet increases the percent drug release decreases. The interaction between the three polymers can be elucidated using surface response plot shown in fig. 6. The result indicates that when X_1 is kept at the high level (+1) and the concentration of X_2 is varied from lower level to higher level (i.e. from-1 to+1) the percent drug release decreased from 78.29% to 63.36%. Similarly when X1 was kept at the lowest level (-1), and the X_2 was varied from the lowest level (-1) to highest level (+1) the drug release decreased from 100% to 74.03%. The probable explanation of this behavior could be due to polymer relaxation and disentanglement leading to erosion of the polymer at 20h of dissolution study.

From the DOE data, the design space was created with the help of the contour plots of Y1, Y8 and Y20. The contour plots are shown in the fig. 7 and 8 for the various responses. The design space constructed within which the dissolution profile for formulation shall always be within the Target Dissolution profile (TDP). The optimized levels low and high for the three grades of HPMC are given in table 7.

Table 7: Optimized range of polymer concentrations for Carbamazepine hydrophilic matrix tablets

HPMC grade	Low level (%)	High level (%)
K4M	10	10.6
K15M	10.2	10.6
K100M	10	10.27

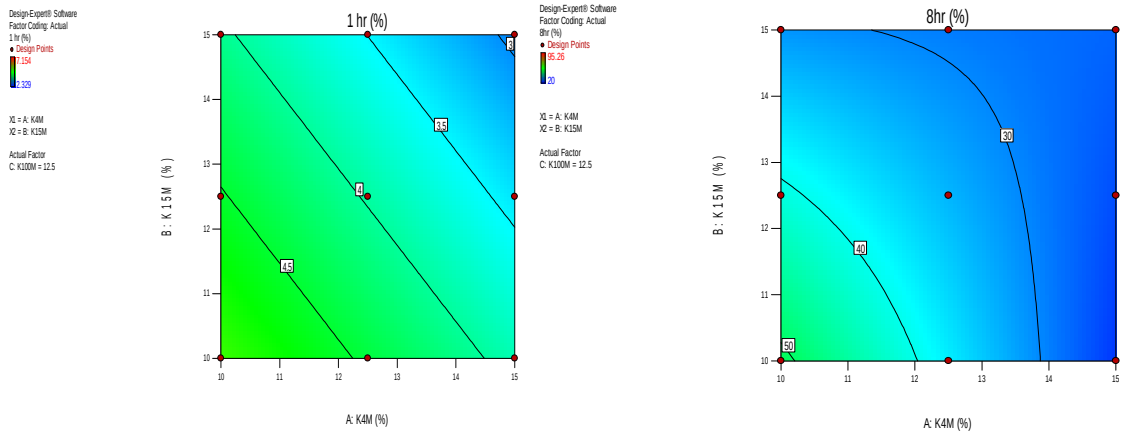

Fig. 7: Contour plot showing the effect of HPMC K4M, K15M and K100M on the percent drug release at 1h and 8h

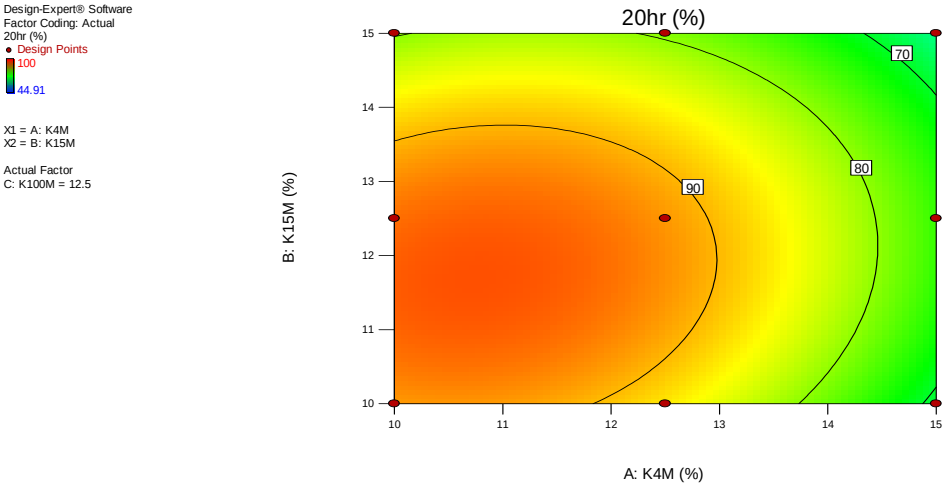

Fig. 8: Contour plot showing the effect of HPMC K4M, K15M and K100M on the percent drug release at 20h

The optimized formulation was prepared by keeping the levels of different viscosity grades of HPMC as obtained in design space mentioned in table 7. The formulation was compressed and all compression parameters were kept same as that of factorial batches and the formulation obtained showed the dissolution profile within TDP and the release of CBZ from the matrix followed zero order release kinetic.

CONCLUSION

CBZ hydrophilic matrix tablets were successfully prepared using a combination of different viscosity grades of HPMC. A full factorial design was employed to study the effect of polymer concentrations on the release of the drug at various time points. Amount of HPMC K4M, K15M and K100M was significant in maintaining the drug release within TDP. The DOE approach for formulation optimization is a useful tool in obtaining a design space within which the formulations will always show the desired dissolution profile.

CONFLICT OF INTERESTS

Declared None

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