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Research Article

Understanding the Impact of Polymer Ratio and its Concentration on Omeprazole Release from Matrix Tablets: Response Optimization Study

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ABSTRACT

In present study, matrix tablets of Omeprazole (OPZ) were formulated by wet granulation technique using a combination of hydroxyl propyl methyl cellulose (HPMC K15M) and ethyl cellulose (EC) in varying ratios and the effect of polymer ratio as well as their concentration on drug release profile was investigated. Response surface methodology (RSM) was conducted to optimize matrix tablets. Compressed tablets were evaluated for hardness, friability, weight variation, drug content and *in vitro* dissolution studies. The dissolution study was performed in pH1.2 for the first 2 h and in phosphate buffer (pH 7.4) for another 5 h. The optimized formulation was compared with other formulations using similarity ($f2$) and dissimilarity factor ($f1$) test. The results of RSM indicated that both X1 (the blending ratio of HPMC K15M K15M and Carbopol 934P 934P) and X2 (polymer blend concentration)have significant effect on *in-vitro* drug release profile. Hardness, friability, weight variation and drug content were found to be in desired range. Among different formulations, matrix tablets prepared by HPMC K15M and Carbopol 934P 934P (7:3) with 15% polymer blend concentration displayed 98.85% OPZ release in 7 hr. and release kinetic was higuchi (r^2= 0.9884). Similarity (*f2*) and dissimilarity (*f1*) factors demonstrated that the *in vitro* profiles were not similar. Finally, it was concluded that release rate of OPZ decreased proportionally with increasing polymer ratio (HPMC K15M: Carbopol 934P 934P) and decreasing polymer blend concentration.

Keywords: Omeprazole, matrix tablets, Response surface methodology, *in vitro* release.

INTRODUCTION

For orally administered dosage forms, extended drug action is achieved by modifying the rate at which drug is released from the dosage form and/or by slowing the transit time of dosage form through the gastrointestinal tract (g.i.t.)[1]. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration[2]. This deliberate control of drug release is achieved in sustained release dosage form as it prolongs the therapeutic effect by continuously releasing the drug over an extended period of time after administration of a single dose[3]. In spite of advances in injectable, transdermal, nasal, and inhalable routes of administration, oral delivery of drugs is preferred delivery route due to ease of administration, patient compliance and flexibility in formulation development[4]. The most employed and cost effective method is matrix system. An inert matrix system is one in which a drug is embedded in an inert polymer which is not soluble in the gastrointestinal fluids. Drug release from inert matrices has been compared to the leaching from a sponge. The release rate depends on the drug molecules in aqueous solution diffusing through a network of capillaries formed between compacted polymer particles[6]. For a successful hydrophilic matrix system, the polymer must form a gelatinous layer rapidly enough to protect the inner core of the tablet from disintegrating too rapidly after ingestion. In present study Carbopol 934P and HPMC K15M (hydrophilic polymers) have been used because of their highly cross linked structure which makes them suitable candidate for sustained release formulations. These polymers can be easily utilised to form matrix tablets by direct blending or granulation[4,5].In consequence, the drug release from this polymeric matrix is achieved by diffusion, erosion or a combination of both processes[7,8].

Omeprazole (OPZ) (5-methyl-2-h[(4-methoxy-3,5-di-methyl-2-pyridinyl)methyl]sulfonylj-1H-benzimidazole), a substituted benzimidazole, exhibits potent and long-lasting inhibition of gastric acid secretion by selectively interacting with the gastric proton pump (K^+ /H^+ - ATPase) in the parietal cell secretory membrane[7]. The bioavailability of omeprazole following oral administration is usually very low, since it degrades very rapidly in the stomach and undergoes hepatic first-pass metabolism. Thus, various oral dosage forms of omeprazole such as enteric coated granule, enteric-coated tablet and inclusion complex with cyclodextrin have been developed to improve its bioavailability[7]. In this study an

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Table 1: Factorial design for preparation of OPZ matrix tablet.

Formulation Code	Independent Variables		Dependent Variables
	X1	X2	
F1	-1	-1	pH 1.2 media
F2	-1	0	(R1)
F3	-1	+1	pH 7.4 media
F4	0	-1	(R2)
F5	0	0	
F6	0	+1	
F7	+1	-1	
F8	+1	0	
F9	+1	+1	
X1	Blending ratio of HPMC K15M and Carbopol 934P		
X2	Polymer concentrations (%/tablet)		
Coded Values	Actual Values		
	X1	X2	
-1	3:7	15%	
0	5:5	20%	
+1	7:3	25%	

All batches contained 40 mg of OPZ, 1% Talc, 1% Magnesium stearate.

attempt has been made to develop matrix tablets containing OPZ that release the drug gradually in the GI tract to avoid gastric degradation and first pass metabolism and hence increase its bioavailability and reduce the dosing frequency.

MATERIALS AND METHODS

Materials

Omeprazole (OPZ) was kindly donated by Cipla, Bangaluru, India. Lactose, Carbopol 934P and Hydroxy Propyl Methyl Cellulose (HPMCK15M) were procured from SD Fine Chemicals, Mumbai, India. Magnesium stearate was purchased from Himedia Chem Lab, Mumbai, India. Talc was purchased from Lancia Laboratories Reagent Chemistry, India. All other remaining materials used were of analytical grade (SD Fine Chemicals, Mumbai, India).

Response surface methodology

By careful design of experiments, the objective was to optimize a response (output variable) which is influenced by several independent and dependent variables (input variables). A two factor, three-level design was employed for optimization of tablets *in vitro* release performance. The ratio of HPMC K15M -to-Carbopol 934P (X1) and the content of polymer blend (X2) were selected as independent variables. Ratio of HPMC K15M -to-Carbopol 934P was evaluated at 70:30, 50:50 and 30:70 of total polymer content and content of polymer blend was evaluated at 15, 20 and 25% of total tablet weight. The percentage drug release at pH 1.2 for 2 hrs and at pH 7.4 for 6hrs were selected as dependent variables. Design Expert 9 software (Stat-Ease Inc., USA) was used for the generation and evaluation of statistical experimental design. The experimental design with corresponding formulations is outlined in Table 1. A statistical model incorporating interactive and polynomial terms were used to evaluate the effects of independent variables upon the responses. One-way ANOVA was employed to estimate the significance of the model ($p < 0.05$). The response surface plots, and contour plots were analyzed to evaluate the effect of independent variables on the measured responses[8,9].

Preparation of OPZ matrix tablet

Matrix tablets containing OPZ were prepared by wet granulation method taking different proportions of HPMC K15M and Carbopol 934P as per formulation given in Table 2. The calculated amount of the drug and polymers were dry blended and then granulated with 9:1 isopropyl alcohol and water mixture. The wet granules were passed through sieve no. 30 and dried overnight at50^0C in tray drier. The final granules were blended with 2% magnesium stearate and 1% Talc and compressed using 11 mm round, concave punches and dies in a 10 Stations Mini Press II MT Tableting Machine (Karnavati Engineering, India)[10].

Standard physical test of tablets

The physical testing of tablets was performed 24 h after production to allow for stress relaxation. Matrix tablets were evaluated for hardness, friability, weight variation and drug content. Hardness of the tablets was tested using a Strong-Cobb hardness tester (Tab-machine, Mumbai, India). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai, India). Weight variation test was performed according to the official method[8].

Drug content uniformity

The content uniformity was assessed according to USP requirements for content uniformity[8]. The test is used to ensure that every tablet contains the intended amount of drug substance with a negligible variation among tablets within a batch. Ten tablets from each formulation were tested. Each tablet was weighed individually and crushed to a powder. An accurately weighed sample (100 mg) was placed in a 50 mL volumetric flask and the volume was made with phosphate buffer pH 6.8 upto the mark. The content of the flask was sonicated for 20 min at room temperature. Five milliliters aliquot was filtered through 0.45 µm filter, suitably diluted two times and analyzed spectrophotometrically at λ_{max} of 301 nm[8].

Observation of dissolution behavior of OPZ from matrix tablets

In vitro drug release studies from the prepared matrix tablets were conducted for a period of 7 h using USP 28 type II apparatus (paddle) at 37 $\pm 0.5^0$C and 50 rpm speed (dissolution apparatus (Electronics India, HP))[23]. The dissolution studies were conducted in triplicate for 7 h (initial 2 h using 750 mL 0.1 N HCl, and the remaining 5 h added 250 mL 0.5 N Disodium hydrogen phosphate (pH 8.66), then finally dissolution medium was adjusted to pH 7.4 by adding 6 mL 2N NaOH.under sink condition). At every 1 h interval samples of 5 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 by UV spectrophotometer. The amounts of

Table 2: Factorial design layout of OPZ matrix tablets.

S. No.	Formulation Code	Independent Variables		Dependent Variables		SCMC	Lactose	Talc	Magnesium Stearate
		X1	X2	R1	R2				
1.	F1	-1	-1	3.60	69.57	0	150	3	2
2.	F2	-1	0	67.42	42.99	50	100	3	2
3.	F3	-1	+1	38.67	88.08	0	150	3	2
4.	F4	0	-1	29.34	65.98	0	100	3	2
5.	F5	0	0	40.14	70.39	50	100	3	2
6.	F6	0	+1	36.51	90.42	0	100	3	2
7.	F7	+1	-1	31.49	98.85	50	100	3	2
8.	F8	+1	0	88.98	69.58	50	100	3	2
9.	F9	+1	+1	56.70	84.61	0	150	3	2

Table 3: Physical parameters of prepared matrix tablets.

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (kg/cm^2)	6.51 ± 0.11	6.49 ± 0.21	6.76 ± 0.51	6.60 ± 0.73	6.56 ± 0.91	7.15 ± 0.12	7.59 ± 0.22	6.00 ± 0.31	6.55 ± 0.10
Friability (%)	0.3± 0.10	0.5± 0.17	0.2± 0.61	0.2± 0.22	0.6± 0.19	0.2± 0.21	0.3± 0.61	0.5± 0.01	0.3± 0.21
Weight variation (mg)	379± 1.01	389± 2.25	399± 1.52	394± 2.21	393± 1.90	397± 1.81	389± 1.42	379± 0.09	396± 2.41
Drug content (%)	96.02± 2.09	95.98± 3.83	94.30± 2.01	89.90± 3.49	89.54± 2.82	95.86± 3.73	97.37± 2.91	92.56± 1.77	87.37± 3.11

drug present in the samples were calculated with the help of appropriate calibration curves. The drug release studies were conducted in triplicates and the mean values were plotted versus time. Drug release kinetics was investigated by fitting the dissolution data to PCP Disso V 2.0 software, Pune, India.

Mathematical modeling of release kinetics

The kinetics of drug release from the matrix tablets was determinedby fitting the appropriate drug release data to zero order[13], first order[14], Higuchi equation[15], Hixson-Crowell equation[16] and the Korsmeyer-Pepas model[17,18].

$Q = Q_0 + k_0 t$ (Zero Order)

$\ln Q = \ln Q_0 + k_1 t$ (First Order)

$Q = k_H t^{1/2}$ (Higuchi Model)

$Q_0^{1/3} - Q_R^{1/3} = k_s t$ (Hixson Crowell Model)

$Q/Q_T = k_{kp} t^n$ (KorsemeyerPeppas Model)

where Q is amount of drug release at time t, Q_0 is the initial amount of drug, Q_R is the amount of drug remaining at time t, and Q_T is the total amount of drug release. k_0, k_1, k_H, $k_s$and k_{kp} are the kinetic constants for zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models respectively, and n is the release exponent.

Statistical analysis

All results were expressed as mean values ± standard deviation (SD). The determined dissolution data was subjected to statistical analysis using a computer program, Graphpad INSTAT tm Copyright[a] 1990-1993 (Version 2.04, Ralf Stahlman, Purdue University, USA, 931897S) for a one-way analysis of variance (ANOVA) at $p<0.05$.

Similarity and dissimilarity factor analysis

The similarity (*f2*) and dissimilarity (*f1*) factors were used to evaluate pH-independent release patterns of OPZ from the optimized tablet (as a reference) in the release media pH 1.2 and pH 7.4. Similarity and dissimilarity factors are calculated by using the following equation[19]:

$$f2 = 50\log\left(\frac{1}{\sqrt{1+(1/p)\sum_{i=1}^{p}(Rt-Tt)^2}}\times 100\right)$$

$$f1 = \{[S_{t=1^n}|Rt-Tt|]\}\times 100$$

here, Rt and Tt are the cumulative percent of drug dissolved from matrices for the references and test samples at time t and n is the number of time points. The similarity factor values ranges between 0 and 100. The similarity between two profiles increases when f2 value approaches 100, whereas dissimilarity occurs with a decrease of the f2 value (less than 50)[20].

RESULTS AND DISCUSSION

Evaluation of physical parameters of tablets

The hardness of tablets of entire batches was found to be in the range of 6.49 ± 0.21 to 7.59 ± 0.22 kg/cm^2. The friability test of tablets of entire batches as presented in Table 3 depicted that the tablets of entire batches had passed the USP criteria of friability testing (<1%, w/w). The results revealed that tablets possess good mechanical strength. The average weight of 20 tablets along with standard deviation of entire formulations is presented in Table 4. The percentage of weight variation of individual tablets from the average weight was found to be within ±5% (w/w) which indicated that the entire batches have passed the USP weight variation test. The drug content of all the tablets in each batch was found to be in the range of 87.37± 3.11 to 97.37± 2.91% which was found within

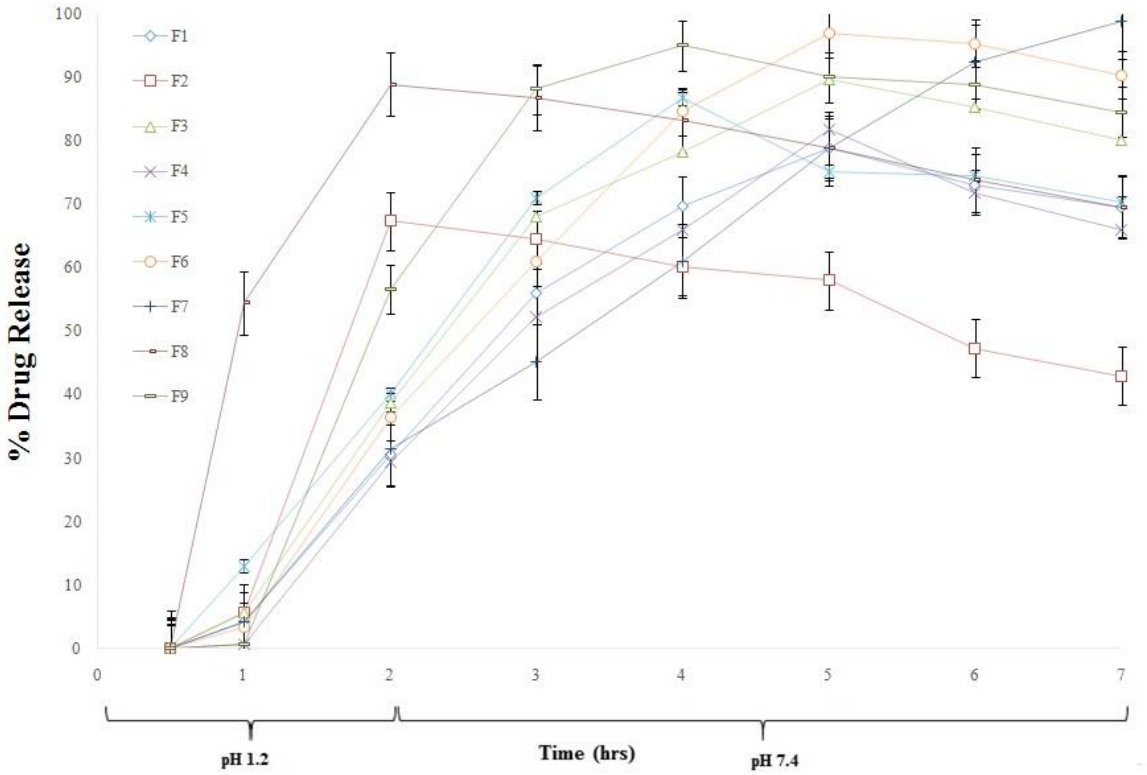

Figure 1: *In vitro* release profile of OPZ from matrix tablets at pH 1.2 followed by pH 7.4.

Table 4: Model dependent and independent parameters of prepared matrix tablets.

Formulations	Model dependent parameters						Model independent parameters	
	Zero order	First Order	Higuchi Model	Hixson Crowell Model	Korsemeyer Model	Peppas n value	Similarity factor (*f2*)	Dissimilarity factor (*f1*)
F1	0.7851	0.0163	0.8343	0.2142	0.0193	0.5	25.39	34.77
F2	0.2505	0.2348	0.3831	0.0030	0.7400	0.7	11.36	78.76
F3	0.7993	0.0011	0.8937	0.2327	0.9036	0.7	35.04	20.98
F4	0.7927	0.0273	0.8770	0.1927	0.8316	0.5	22.88	39.88
F5	0.6659	0.0334	0.7905	0.1419	0.8323	0.8	26.00	33.63
F6	0.8631	0.1174	0.9310	0.2042	0.9245	0.7	51.42	8.90
F7	0.9835	0.1688	0.9884	0.3155	0.9551	0.7	100.00	0
F8	0.2522	0.2746	0.3911	0.0499	0.5643	1.1	25.40	34.75
F9	0.6558	0.0094	0.7797	0.2037	0.7865	0.5	41.04	15.52

the range of content uniformity provided by USP i.e., ≥ 25%. This has also indicated that tablets of each batch have passed the USP criteria for drug content (Table 3).

Effect of Polymer Type and Ratio on Release Profile

The in vitro release studies of all matrix tablets of entire formulations were performed in simulated gastric fluid (pH 1.2) to evaluate the release of OPZ in stomach for prolonged periods of time. The release profiles of tablets of entire formulations were shown in (Fig. 1). From the release profile, it was observed that the HPMC K15M-to-Carbopol 934P ratio influenced the drug release from the tablets. Varying the amount of polymer blends affected the drug release from the tablets. As the amount of polymer blend increased from 15% to 25%, the drug released was decreased due to increase in resistance for penetration of water into tablet matrix. As the hydrophilic HPMC K15M quickly undergoes hydration on the outermost surface of tablet, thus forming a gel barrier, which acts as a physical and diffusion barrier thus retarding the drug release by diffusion. This gel barrier also prevents wetting of the core and hinders the tablet to undergo disintegration[21]. It is also suggested that the gel barrier with higher viscosity of HPMC K15M resulted in a more sluggish release of OPZ due to formation of barrier to that is more tortuous and resistant diffusion[24]. From the drug release profile of formulations F2, F5, F8 it was observed that at 20% polymer blend concentration drug release was found to be increased in pH 1.2 (within 2 hrs.) and very less amount of drug was left for release at pH 7.4. Release profile of formulation F7 showed that almost entire drug was released within 7 hrs. while the burst drug release (67.42% for F2, 40.14% F5 and F8

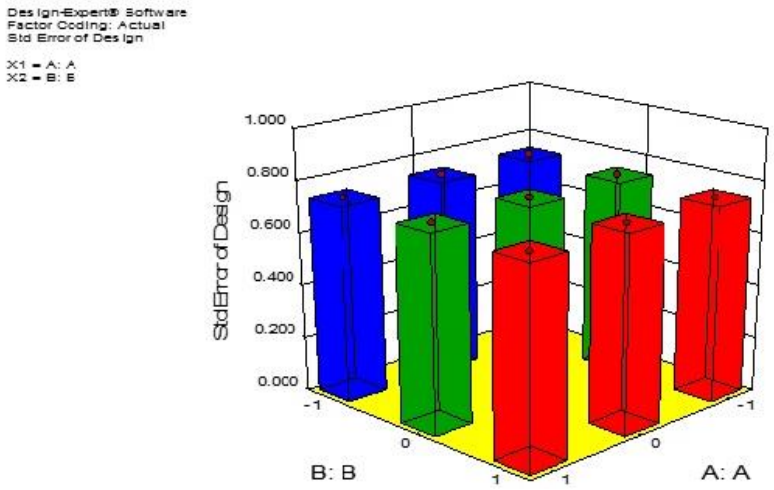

Figure 2: 3D Bar Graph of standard error of design.

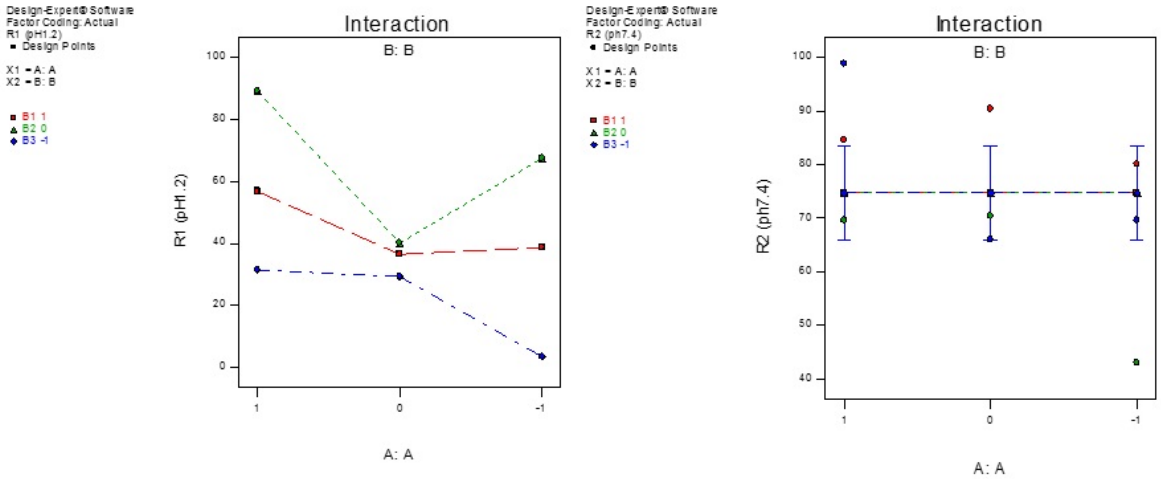

Figure 3: Interaction of independent variables on dependent variables i.e. (i) drug release at pH 1.2, (ii) drug release at pH 7.4.

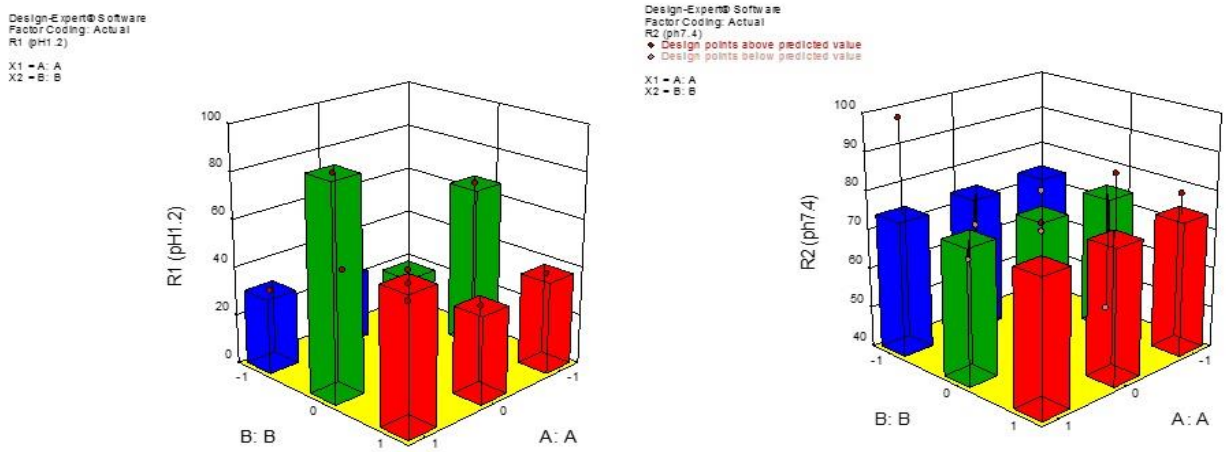

Figure 4: 3D Bar Graph depicting the influence of independent variables over dependent variables i.e. (i) drug release at pH 1.2, (ii) drug release at pH 7.4.

80.98%) was observed within 2 h from these formulations. Higher ratio of HPMC K15M in F7 leads to a time- dependent increase in diffusion coefficient due to continuous polymer swelling[22]. *In vitro* dissolution studies showed that as the concentration of HPMC K15M K4M was increased, drug release rate was decreased (Fig. 1). As the concentration of Carbopol 934P 934P was increased drug release rate was decreased (Fig. 1), this might be due to higher affinity of Carbopol 934P to water produce layer over tablet, which prevent dissolution of drug. Dissolution profiles of formulations F1 to F3 were not good because high amount of drug release (30.6 to 67.42%) at 2 h. The drug release profile of F7 showed a

Table 5: Statistical analysis of dissolution data.

Source of Variance	S.S.	d.f.	MSS	F
CSS	8875.7011	9	986.1890	Fcal 30.62
RSS	3293.3855	7	470.4836	Fcal 14.61
ESS	2028.6361	63	32.2005	

best fit to the desired control drug release profile among all the formulations[12]. The results of drug release profile of the F7 showed the release of 31.49% of drug during initial 2hrs. while within the first 4 h 61.1% of drug was released and the remaining drug was released during last 4 hrs. The tablets of F6 also showed controlled release pattern but significantly less amount of drug was released from them, so batch F6 was not considered for further study.

Evaluation of drug release parameters

The in vitro drug release data from different formulations were evaluated kinetically using various mathematical models such as: zero order, first order, Higuchi, and Korsmeyer–Peppas. The results of the curve fitting into these above-mentioned mathematical models are given in Table 4. Model with the highest correlation coefficient (r^2) was judged to be a more appropriate model for the dissolution data. The release profiles from all the formulations were best fitted to Higuchi model due to the highest linearity, followed by zero order. Zero order release kinetics referred to the process of constant drug release from matrix tablets with low-soluble drugs. Results suggested that the drug release is controlled by the diffusion of drug through the pores and not through the swollen polymer. From Korsemeyer-Peppas model, it was found that the mode of release from all formulations was anomalous (non-Fickian, a combination of the diffusion and erosion mechanism) diffusion. The formulations F3 to F7 showed good linearity (r^2= 0.8316-0.9551) with slope (n) values ranging from 0.5 to 0.8, indicating that diffusion is the dominant mechanism of drug release with these formulations. This indicates a first order release controlled by non- Fickian diffusion. Calculated F value was found to be 30.62 and 14.61 for column and rows respectively while 2.30 is needed for significance at 5% level. Therefore, it can be concluded that the formulations were found to be significantly different ($p<0.5$) at different time intervals (Table 5). Release profiles of different formulations were compared by calculating two statistically derived mathematical indices, difference factor (f_1) and similarity factor (f_2) using F7 as the reference. The pull points at 60-minute intervals, beginning from the first 60 minutes up to point above 80% released were included in the calculation. As shown in table 4, all formulations showed difference factor (f_1) greater than 15 and having similarity factor (f_2) less than 50 which indicated dissimilarity between formulations. At polymer blend ratio 50:50 and at higher polymer blend concentration 25%, drug release had no significant change compared to F7 (f_1: 8.90 and f_2: 51.42).

Response surface methodology of prepared formulations

Statistical analysis was done by Design expert software version 8.0.7.1 (Stat-Ease, Inc., Minneapolis, USA) and the second order polynomial equations were derived. A RSM was constructed to study the effect of the blending ratio of HPMC K15M K15M and Carbopol 934P 934P (X1) and the Polymer blend concentration (X2) on the drug release from controlled release matrix tablets. The percentage drug release at pH 1.2 for 2hr (R1) and pH 7.4 for remaining 5 hr (R2) were selected as dependent variables. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses. The interaction terms (X1, X2) showed how the response changes when 2 factors are changed simultaneously. The full Equation (equation containing only statistically significant terms) is then used for drawing plots to visualize the impact of changing variables at a glance. The optimum point may be identified from the plot[11].

The formulations of factorial batches (F1 to F9) were shown in Table 2. 3D surface plot clearly depicted the effects of independent variables i.e. varying the pH of media pH 1.2 (R1) and pH 7.4 (R2). The response Surface linear model generated for X1 and X2 was found to be significant with an *F*-value of 2.50 and 6.80 (P<0.0500) respectively. Factorial equation for R1 (Eq 1.1) and R2 (Eq 1.2) was found to be:

$R1 = 43.65 + 15.41\,x1 - 8.32x2 + 8.06\,x1x2 - 2.67x1^2 - 17.05x2^2$ ….. Eq 1.1

$R2 = 67.17 + 12.70x1 - 11.55x2 + residual$ ……. Eq 1.2

The co-efficient of X1 and X2 was found to be positive and negative respectively indicated that predicted values could be obtained when polymer blend concentration decreased (15%) with increase in polymer blend (HPMC K15M: Carbopol 934P; 70:30). The P value for variable X1 and X2 was 0.0352 and 0.0199 respectively(P<0.0500) indicated that both the independent variables show significant effect on dependent variable i.e. R1 and R2.

The results of experimentally observed responses and those predicted by mathematical models along with the percentage prediction errors were compared. The prediction error in the response parameters ranged between 0.47 and 0.79% to the value of absolute error of 0.90 ± 0.70% (Fig. 2). The low values of error indicate the high prognostic ability of factorial equation and counter plot methodology. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 7.56 indicates an adequate signal. Thus, this model can be used to navigate the design space.

(Fig. 3) showed the interaction between X1 and X2. From the plot, the spread of points on the left side of the graph (where X1 is high) is larger than the spread between the points at the right side of the graph where X1 is low. In other words, the effect of X2 is less significant where X1 is low. Therefore, at a very low X1 value, the effect of polymer blend concentration can be significantly reduced, thus reducing the drug release at pH 1.2 (R1). Also, there

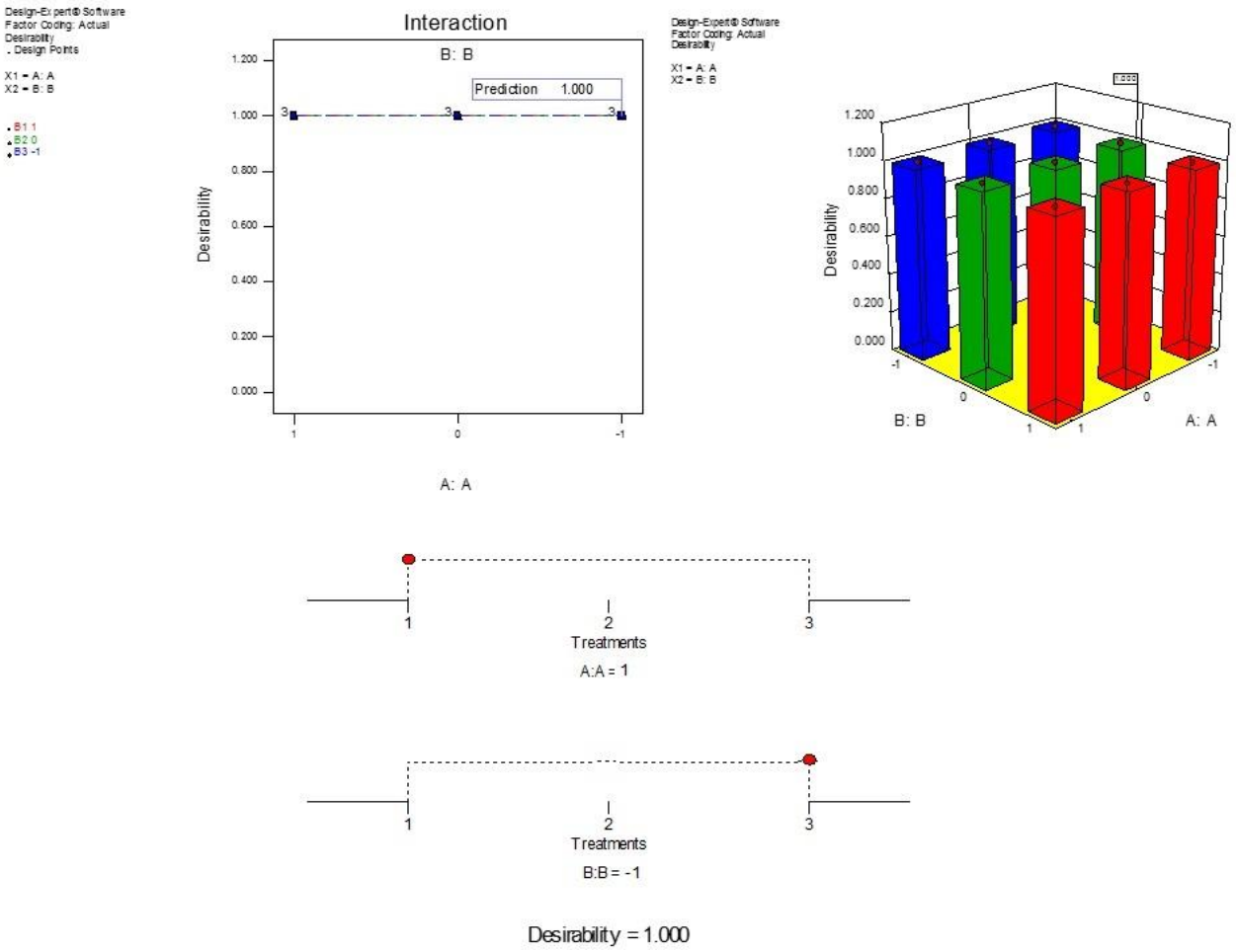

Figure 5: Numerical optimization ramps report and 3D Bar Graph indicating Desirability Factor of Optimized Matrix tablet (F7).

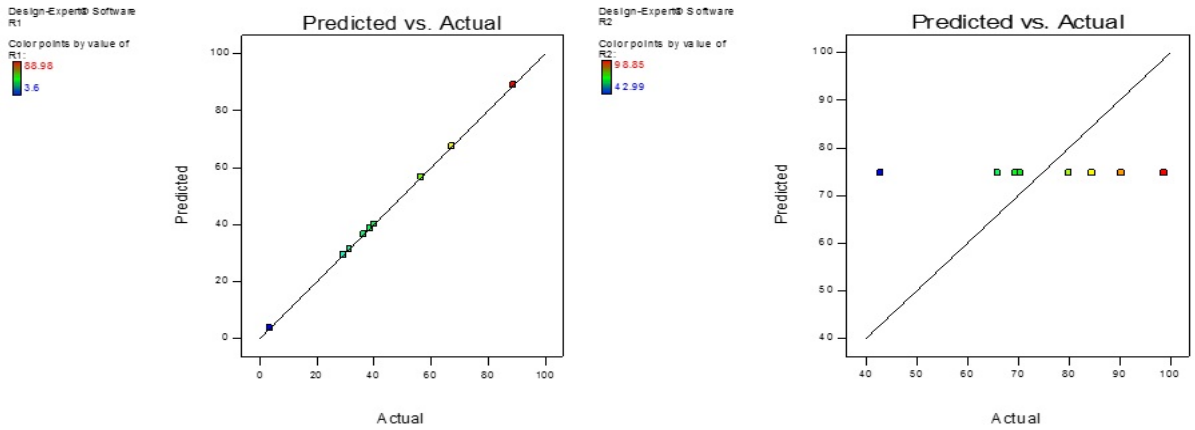

Figure 6: Predicted versus actual values of dependent variables i.e. (i) drug release at pH 1.2, (ii) drug release at pH 7.4.

exists generic increase in drug release as polymer blend concentration significantly increases. While for R2 effect of X2 is not affected by X1, and hence the drug release is not affected.

The 3D plots (Fig.4) indicated that drug release in response R1 decreases with increase in polymer blend ratio and decrease in polymer blend concentration. Higher X1 and lower X2 reduced the % drug release for response R1. Simultaneous effect of interactive factors X1 and X2 was observed in 3D plot for response R2. F7 with highest desirability factor of 1.00 with high polymer blend ratio (HPMC K15M :Carbopol 934P; 70:30) and low polymer blend concentration (15%) with low % drug release in pH 1.2 and highest % drug release in pH 7.4 was selected as

optimized formulation. Ramps reports clearly supported optimized formulation. Ramps report and actual versus predicted values supported the optimized results (Fig. 5, 6). After generating the polynominal equation for the dependent and independent variables, the combination was optimized forresponses. Upon comprehensive evaluation of feasibility search and subsequently grid searches, the formulation composition with 15% of polymer blend and 70:30 of HPMC K15M -to-Carbopol 934P ratio fulfilled the maximum desired requisites. The prepared tablet formulation of F7 showed R1as 31.49% and R2 as 98.85%.

CONCLUSION

The present investigation shows that OPZ sustained release matrix tablets were designed and successfully achieved the aims of preventing gastric degradation which can be indicated by *in vitro* dissolution studies at pH 1.2 for 2hr and hence increases its bioavailability and reduce the dosing frequency. It was observed that the combination of HPMCK15M-Carbopol 934P and its concentration can be used effectively to modify the release rates in hydrophilic matrix tablets prepared by dry granulation technique. Moreover, concentration of extra granular polymer HPMC K15M had significant influence on the drug release pattern. The physiochemical characterizations of all prepared formulations were found to be satisfactory. From dissolution study, dissimilarity (*f1*) and similarity factor (*f2*) value, formulation F7 was selected as best laboratory scale grade batch (data has been supported with RSM). Furthermore, the *in-vivo* and pharmacokinetic study have to be carried out.

Current and Future Developments

The emerging trends in the combinatorial chemistry and drug design have led to the development of drug candidates with greater lipophilicity, high molecular weight and poor water solubility. Majority of the failures in new drug development have been attributed to poor water solubility of the drug. Issues associated with poor solubility can lead to low bioavailability resulting in suboptimal drug delivery. Several marketed drugs were reformulated to improve efficacy, safety and patient compliance. In order to gain marketing exclusivity and patent protection for such products, revitalization of poorly soluble drugs using insoluble drug delivery technologies have been successfully adopted by many pharmaceutical companies. Oral delivery of water insoluble drugs has become cynosure for pharmaceutical industries where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. OPZ matrix tablets are versatile, effective and low cost dosage forms. Prepared matrix formulations were supposed to minimize side effects (local and systemic) and drug accumulation with chronic dosing. Matrix tablets have an advantage to improve bioavailability of some drugs. Because of strong patient demand, several products have been commercialized.

CONFLICT OF INTEREST

None of the authors of this manuscript have any financial interest that has influenced the results or interpretation of this manuscript.

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