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Formulation and Optimization of Sustained Release Matrix Tablet of Metformin HCl 500 mg Using Response Surface Methodology

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The aim of the current study was to design an oral sustained release matrix tablet of metformin HCl and to optimize the drug release profile using response surface methodology. Tablets were prepared by non-aqueous wet granulation method using HPMC K 15M as matrix forming polymer. A central composite design for 2 factors at 3 levels each was employed to systematically optimize drug release profile. HPMC K 15M (X_1) and PVP K 30 (X_2) were taken as the independent variables. The dependent variables selected were % of drug released in 1 hr ($rel_{1\ hr}$), % of drug released in 8 hrs ($rel_{8\ hrs}$) and time to 50% drug release ($t_{50\%}$). Contour plots were drawn, and optimum formulations were selected by feasibility and grid searches. The formulated tablets followed Higuchi drug release kinetics and diffusion was the dominant mechanism of drug release, resulting in regulated and complete release within 8 hrs. The polymer (HPMC K 15M) and binder (PVP K 30) had significant effect on the drug release from the tablets ($p<0.05$). Polynomial mathematical models, generated for various response variables using multiple linear regression analysis, were found to be statistically significant ($p<0.05$). Validation of optimization study, performed using 8 confirmatory runs, indicated very high degree of prognostic ability of response surface methodology, with mean percentage error ($\pm$S.D.) 0.0437$\pm$0.3285. Besides unraveling the effect of the 2 factors on the *in vitro* drug release, the study helped in finding the optimum formulation with sustained drug release.

Key words——response surface methodology; sustained release; matrix tablet; hydroxypropyl methyl cellulose (HPMC K 15M); polyvinyl pyrrolidone (PVP K 30)

INTRODUCTION

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form.[1–4]

Hydroxypropyl methyl cellulose (HPMC) is the widely used hydrophilic polymer to prolong drug release due to its rapid hydration, good compression and gelling characteristics along with its ease of use, availability and very low toxicity. It regulates the release of drug by controlling the swelling and cross-linking.[5,6]

In the development of 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.[7–13] 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 used 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.

Metformin HCl is an orally administered biguanide, which is widely used in the management of type-2 diabetes, a common disease that combines defects of both insulin secretion and insulin action.[14]

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It improves hepatic and peripheral tissue sensitivity to insulin without the problem of serious lactic acidosis commonly found with its analogue, phenformin. It has three different actions: it slows the absorption of sugar in our small intestine; it also stops our liver from converting stored sugar into blood sugar; and it helps our body use our natural insulin more efficiently. It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract and the absolute bioavailability of a single 500 mg dose is reported to be 50–60%.[15] An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea that especially occur during the initial weeks of treatment. Also the compound has relatively short plasma elimination half-life of 1.5 to 4.5 hrs.[16,17] Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. Sustained release formulations that would maintain plasma levels of drug for 8 to 12 hrs might be sufficient for once daily dosing for metformin. SR products are needed for metformin to prolong its duration of action and to improve patient compliance.[15,18]

Fiona et al.[19] of Colorcon Ltd., UK has described the method for preparation of metformin HCl 500 mg extended release tablet by direct compression method. But in commercial scale it creates problem of powder flow ability from hoper to compression machine followed by weight variation, content uniformity, hardness and friability due to poor inherent compressibility of metformin HCl.

SR microcapsules of metformin by ethylcellulose had been described by Balan et al.[17] where metformin gave *in vitro* release for up to 22 hrs. But preparation of microcapsules in commercial scale and optimization of drug release rate is troublesome. Defang et al.[16] had described the bilayer matrix tablet and osmotic pump tablet consisting metformin and glipizide both as SR form. The aim of this investigation was to develop a sustained release matrix tablet of metformin HCl using HPMC K 15M by non-aqueous wet granulation method and optimize the formulation using RSM.

MATERIALS AND METHODS

Materials Metformin HCl was received from Deys Medical, Kolkata, India as donate sample. Hydroxy propyl methyl cellulose (HPMC K 15M) was a gift sample received from M/S Colorcon Asia Pvt. Ltd., Mumbai, India. Microcrystalline cellulose (MCC) and PVP K 30 (polyvinyl pyrrolidone K 30) were purchased from S. D. Fine Chemicals Ltd., Mumbai, India. Magnesium stearate and talc were procured from Mohanlal Dayaram and Company, Hyderabad. All other chemicals/reagents used were of analytical grade, except for those used in HPLC analysis, which were of HPLC grade.

Preparation of Sustained Release Matrix Tablets Table 1 enlists the composition of different trial formulations prepared using varying amounts of HPMC K 15M as release controlling polymer and PVP K 30 as binder along with fixed quantity of talcum and magnesium stearate as lubricant. MCC was used as filler. HPMC K 15M polymer at different ratio was blended with metformin HCl, MCC and PVP K 30 in a planetary mixer for 5 mins after passing all the materials through a mesh (1150 μm). Thereafter the powders were granulated with isopropyl alcohol, sieved using a mesh (100 μm) and dried at 50°C for about 2 hrs with residual moisture content of 2 to 3% w/w. The dried granules were sized by a mesh (250 μm) and mixed with magnesium stearate and talc for 2 mins. All granules were weighed finally to adjust the final weight of individual tablet considering its loss during operational handling. Granules thus obtained were compressed into 1150 mg tablets to average hardness of 6 to 8 kg/sq.cm on an eight station rotary tablet machine (CIP Machineries Pvt. Ltd., Ahmedabad, India) with 19.5x8.9 mm caplet tooling at a rotational speed of 72 rpm.

Experimental Design A central composite design (CCD) with $\alpha=1$ was employed as per the standard protocol.[8,11] The amounts of HPMC K 15M

Table 1. Composition of 500 mg Metformin HCl Sustained Release Matrix Tablet[a]

Ingredient	Amount (mg)
Metformin HCl	500 mg
HPMC K 15M	240 to 480 mg
PVP K 30	50 to 150 mg
Magnesium stearate	5 mg
Talcum powder	5 mg
MCC	qs to 1150 mg

a) qs: quantity sufficient, HPMC K 15M: Hydroxypropyl methyl cellulose of K 15M viscosity grade, PVP K 30: Polyvinyl pyrrolidone of K 30 viscosity grade, MCC: Microcrystalline cellulose.

Table 2. Factor Combinations as per the Chosen Experimental Design

Trial No.	Coded factor levels	
	X_1	X_2
I	−1	−1
II	−1	0
III	−1	1
IV	0	−1
V	0	0
VI	0	1
VII	1	−1
VIII	1	0
IX	1	1
X	0	0
XI	0	0
XII	0	0
XIII	0	0
Translation of coded levels in actual units		
Coded level	−1	0	1
X_1: HPMC K 15M (mg)	240	360	480
X_2: PVP K 30 (mg)	50	100	150

(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. All other formulation and processing variables were kept invariant throughout the study. Table 2 summarizes 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. % of drug released in 1 hr ($rel_{1\,hr}$) (Y_1), % of drug released in 8 hrs ($rel_{8\,hrs}$) (Y_2) and time to 50% drug release ($t_{50\%}$) (Y_3) were taken as the response variables.

Tablet Assay and Physical Evaluation 20 tablets were taken and crushed to powder with mortar and pestle. Exact amount of powder (average weight) was taken and diluted with methanol up to 200 ml of volumetric flask. After sonication for 15 mins, solution was filtered through 0.45 μm filter paper. The total amount of drugs within the tablets was analyzed after appropriate dilution of test solution by using the HPLC method as described below against the reference solution of metformin pure powder prepared in the same procedure.

Column: Hypersil BDS C18 (250x4.6 mm, 5 μm particle size)
Mobile phase: 10 m.mol phosphate buffer of pH 6.0: Acetonitrile=50: 50 (v/v)
Detector: UV detection with 232 nm
Loop size: 20 μl

Tablets were also evaluated for hardness (n=10), friability (n=10), weight variation (n=20), and thickness (n=10).

Drug Release Study Drug release from 6 tablets of each formulation, in triplicate, was determined using the USP I (basket) apparatus (Electrolab, TDT 06P, USP XXIII) where 900 ml of 0.1 N HCl and phosphate buffer of pH 6.8 were used as dissolution media maintained at 37℃ (±0.5℃) at 100 rpm. The release rates from the tablets were conducted in a dissolution medium of 0.1 N HCl for 2 hrs and thereafter in phosphate buffer of pH 6.8 for 6 hrs. 5 ml of aliquot were withdrawn at 1, 2, 4 and 8 hrs with replacement of fresh media. Solution samples were analyzed by high performance liquid chromatography (HPLC) method mentioned in earlier section. Drug release profiles were drawn using MS-Excel software and the values of $t_{50\%}$ were obtained by interpolation from Excel graph.

Drug Release Kinetics In order to propose a possible release mechanism, drug release from HPMC matrix tablets was fitted to the following equations:

Higuchi's[21] equation: $Q=K_H t^{1/2}$ (1)

Where, Q is the amount of drug release at time t, and K_H is the Higuchi rate constant.

Koresmeyer et al.'s[20] equation: $M_t/M_\infty=kt^n$ (2)

Where, M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, M_t/M_∞ is the fractional drug release percentage at time t, k is a constant related to the properties of the drug delivery system, and n is the release exponent indicative of the drug release mechanism.

Optimum Release Profile Optimum release profile for once-daily SR formulation was calculated by the following equation[22] using available pharmacokinetic data:[23]

$$D_t=\text{Dose}(1+0.693\times t/t_{1/2}) \quad (3)$$

Where, D_t=total dose of drug; Dose=dose of the immediate release part; t=time (hr) during which the sustained release is desired (8 hrs); $t_{1/2}$=half-life of the drug (3 hrs).

The optimum formulation was selected based on the above equation so that it could attain complete

and controlled drug release. Upon ''trading off'' various response variables, the following maximizing criteria were adopted: $rel_{1\ hr}$=28 to 30%; $rel_{8\ hr}$=95 to 100% and $t_{50\%}$=2.1 to 2.2 hrs.

Optimization Data Analysis and Validation of Optimization Model Various RSM computations for the current optimization study were performed employing Design Expert software (Design Expert trial version 7.0.3 State-Ease Inc, Minneapolis, MN). Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented as the following equation:

$$y=\beta_0+\beta_1x_1+\beta_2x_2+\beta_3x_1x_2+\beta_4x_1^2+\beta_5x_2^2+\beta_6x_1x_2^2+\beta_7x_1^2x_2 \quad (4)$$

Where, β_0 is the intercept representing the arithmetic average of all quantitative outcomes of 13 runs; β_1 to β_7 are the coefficients computed from the observed experimental response values of Y; and X_1 and X_2 are the coded levels of the independent variable(s). The terms X_1X_2 and X_i^2 (i=1 to 2) represent the interaction and quadratic terms, respectively. Statistical validity of the polynomials was established on the basis of ANOVA provision in the Design Expert Software. Subsequently, the feasibility and grid searches were performed to locate the composition of optimum formulations.[13,24]

Two-dimensional (2-D) contour plots were constructed based on the model polynomial functions using Design Expert Software. These plots are very useful to see interaction effects on the factors on the responses.

Eight optimum checkpoints were selected based on the criteria from optimum formulation described earlier by intensive grid search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The formulations corresponding to these checkpoints were prepared and evaluated for various response properties. Subsequently, the resultant experimental data of response properties were quantitatively compared with that of their predicted values. Also, linear regression plots between observed and predicted values of the response properties were drawn using MS-Excel, forcing the line through origin

RESULTS AND DISCUSSION

Drug Content and Physical Evaluation The assayed content of drug in various formulations varied between 97.65% and 99.53% (mean 98.66%). Tablets weights varied between 1140.5 and 1160.3 mg (mean 1152.57 mg), thickness between 7.45 and 7.56 mm (mean 7.52 mm), hardness between 5.8 and 7.3 kg.cm^2 (mean 6.2 kg cm^2), and friability ranged between 0.15% and 0.42% (mean 0.31%). Thus, all the physical parameters of the matrices were practically within control.

***In vitro* Drug Release Studies** Dissolution samples were analyzed by HPLC method described in ''MATERIALS AND METHODS'' section. Metformin was eluted at 2.920 mins from the analytical column used for the analysis of dissolution sample. Table 3 lists various dissolution parameters computed for all the matrix formulations. To know the mechanism of drug release from the trial formulations, the data were treated according to Higuchi's[21] (cumulative percentage of drug released versus square root of time) and Koresmeyer et al.'s[20] (log cumulative percentage of drug released versus log time) equations. In our experiments the *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's[21] equation as the plots showed high linearity (R^2: 0.992 to 0.999, with K_H 30.51 to 38.52) as shown in Table 3. In the current study, the values of release rate exponent (n), calculated as per the equa-

Table 3. Drug Release Parameters of Various Trial Formulations Prepared as per the Experimental Design[a]

Trial No.	Factor amount (mg)		$rel_{1\ hr}$ (%)	$rel_{8\ hr}$ (%)	$t_{50\%}$ (hr.)	n	K_H	R^2
	X_1	X_2						
I	240	50	35.21	100.15	1.62	0.4993	35.43	0.994
II	240	100	34.17	100.21	1.90	0.5117	35.78	0.998
III	240	150	33.21	99.12	1.95	0.5145	35.20	0.998
IV	360	50	32.35	99.16	1.98	0.5263	35.72	0.999
V	360	100	30.47	99.19	2.11	0.5513	36.45	0.998
VI	360	150	27.65	85.32	2.25	0.5259	30.51	0.992
VII	480	50	29.56	99.11	2.61	0.5824	37.92	0.992
VIII	480	100	25.25	80.19	2.45	0.5387	29.18	0.988
IX	480	150	23.15	73.11	3.92	0.5314	26.20	0.996
X	360	100	28.18	99.14	2.13	0.5874	37.58	0.998
XI	360	100	30.41	98.47	2.10	0.5528	36.39	0.999
XII	360	100	28.75	99.31	2.15	0.5813	37.42	0.998
XIII	360	100	27.98	100.15	2.17	0.5998	38.52	0.999

a) X_1: HPMC K 15M, X_2: PVP K 30, $rel_{1\ hr}$: Release in 1 hr, $rel_{8\ hr}$: Release in 8 hrs, $t_{50\%}$: Time to 50% drug release, n: Release exponent obtained from Koresmeyer et al. equation ($M_t/M_\infty=kt^n$), K_H: Higuchi rate constant ($Q=k_Ht^{1/2}$), R^2: Regression coefficient of Higuchi equation.

tion proposed by Koresmeyer et al.,[20] ranged between 0.4993 and 0.5874 (Table 3). For matrix tablets, an n value of near 0.5 indicates diffusion control, and an n value of near 1.0 indicates erosion or relaxation control. Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism.[25,26] In our experiments the results of n clearly indicated that the diffusion is the dominant mechanism of drug release from these formulations. Diffusion is related to transport of drug from the dosage matrix into the *in vitro* study fluid depending on the concentration of the hydrophilic polymer. As gradient varies, the drug is released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases.

Total amount of metformin released from all the formulations up to 8 hrs ranged between 73.11% and 100.21% indicating incomplete drug release at higher concentration of HPMC K 15M as well as PVP K 30. Rate of drug release (until 8 hrs) tended to decrease with increase in the content of either HPMC or PVP K 30. This is in agreement with literature findings[27,28] that the viscosity of the gel layer around the tablet increases with increase in the hydrogel concentration, thus limiting the release of active ingredient. The gel formed during the penetration of dissolution media into the matrix structure, consists of closely packed swollen particles. With further increase in polymer amount, thicker gel forms inhibiting dissolution media penetration more strongly, resulting in significant reduction in the values of $rel_{8\ hr}$ indicating slower drug release.

The values of $t_{50\%}$ enhanced markedly from 1.62 hrs, observed at low levels of both the variables, to as high as 3.92 hrs, observed at high levels of both the variables. This finding indicated considerable release retarding potential of the polymer and binder.

Figure 1 exhibits the mean (±S.D.) cumulative metformin release (%) versus time profiles obtained for various trial formulations, prepared as per CCD. The formulations with lower levels of polymer and binder exhibited initial burst in drug release. This result could be attributed to the dissolution of drug present initially at the surface of the matrices and rapid penetration of dissolution media to the matrix structure. However, the formulations showed little burst effect at higher polymer levels, ratifying better substance of drug release. Overall, all the formulations showed quite regulated drug release from 4 hrs onwards.

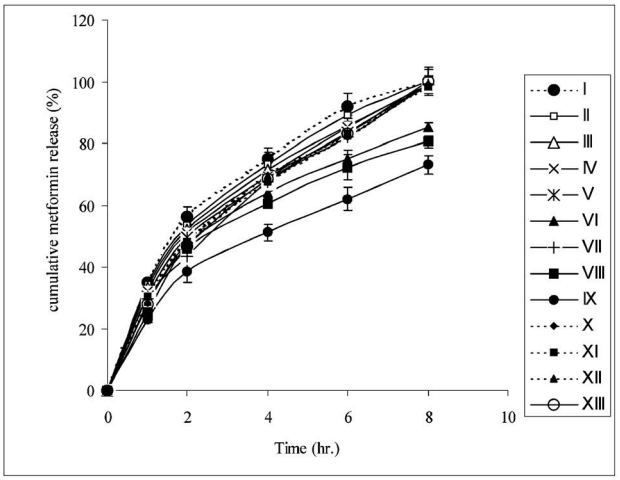

Fig. 1. Cumulative Metformin Release (%) versus Time Profiles for Metformin HCl Matrix Formulations Prepared as per the Experimental Design
Each value represents the mean ±S.D., n=18

Table 4. Analysis of Variance (ANOVA) for All Three Responses[a]

	$rel_{1\ hr}$ (Y_1)		$rel_{8\ hr}$ (Y_2)		$t_{50\%}$ (Y_3)	
Source	F	p-value	F	p-value	F	p-value
Model	16.90	**0.003**	9.96	**0.011**	26.90	**0.001**
X_1	34.00	**0.002**	15.20	**0.012**	7.86	**0.038**
X_2	9.44	**0.028**	7.24	**0.043**	19.00	**0.023**
X_1X_2	4.16	0.097	11.80	0.019	12.50	**0.017**
X_{12}	0.42	0.545	4.00	0.102	6.96	0.064
X_{22}	1.20	0.324	1.14	0.334	3.68	0.113
$X_{12}X_2$	0.07	0.802	0.01	0.961	5.24	0.071
X_1X_{22}	0.32	0.594	1.06	0.350	15.00	**0.012**

a) Significant effect (p value<0.5) of factors on individual responses are shown in bold, $rel_{1\ hr}$: Release in 1 hr, $rel_{8\ hr}$: Release in 8 hrs, $t_{50\%}$: Time to 50% drug release, X_1: HPMC K 15M, X_2: PVP K 30.

RSM Optimization Results

Mathematical Modeling Mathematical relationships generated using MLRA for the studied response variables are expressed as Eqs. 5 to 7.

$$y_1 = 29.2 - 4.46x_1 - 2.35x_2 - 1.10x_1x_2 + 0.422x_1^2 + 0.712x_2^2 + 0.532x_1x_2^2 + 0.248x_1^2x_2 \quad (5)$$

$$y_2 = 97.9 - 10.00x_1 - 6.92x_2 - 6.24x_1x_2 - 4.38x_1^2 - 2.34x_2^2 + 3.25x_1x_2^2 + 0.163x_1^2x_2 \quad (6)$$

$$y_3 = 2.08 + 0.275x_1 + 0.135x_2 + 0.245x_1x_2 + 0.220x_1^2 + 0.160x_2^2 + 0.465x_1x_2^2 + 0.275x_1^2x_2 \quad (7)$$

For estimation of significance of the model, the analysis of variance (ANOVA) was determined as

per the provision of Design Expert Software (Table 4). Using 5% significance level, a model is considered significant if the p value (significance probability value) is less than 0.05. From the p values presented in Table 4, it can be concluded that for all four responses, the cross-product contribution (X_1X_2) and quadratic contributions (X_1^2, X_2^2, $X_1^2X_2$ and $X_1X_2^2$) of the model was not significant. But the linear contribution (X_1 and X_2) for all three responses is significant (<0.05).

The polynomial equations comprise the coefficients for intercept, first-order main effects, interaction terms, and higher order effects. The sign and magnitude of the main effects signify the relative influence of each factor on the response. The values obtained for main effects of each factor from Eqs. 5 to 7 reveal that HPMC K 15M, individually, has rather more pronounced effect on all response values. At a given set factor levels, however, these higher-order polynomials yield results as the net effect of all the coefficient terms contained in the polynomial.

Response Surface Analysis Figures 2, 3 and 4 are the two-dimensional contour plots for the studied response properties viz $rel_{1\ hr}$, $rel_{8\ hr}$ and $t_{50\%}$.

Figure 2 exhibits that $rel_{1\ hr}$ vary in a nonlinear fashion, but in a descending pattern with an increase

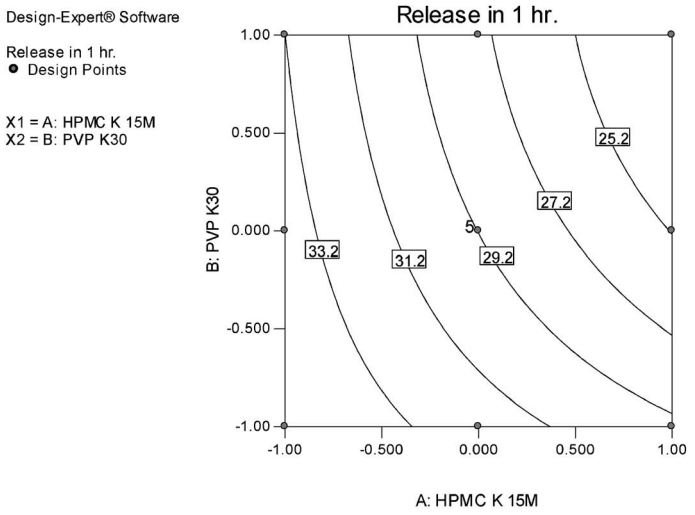

Fig. 2. Contour Plot Showing the Relationship between Various Levels of Polymer (HPMC K 15M) and Binder (PVP K 30) on Drug Release in 1 hr

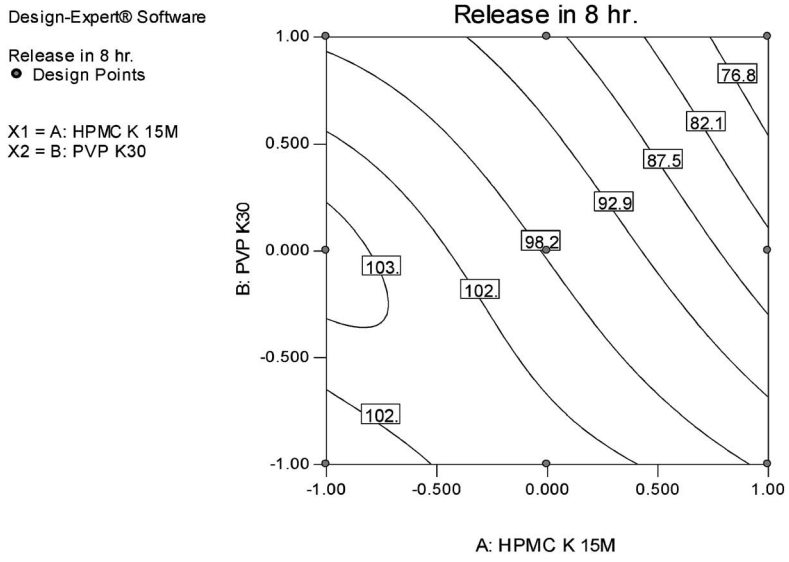

Fig. 3. Contour Plot Showing the Relationship between Various Levels of Polymer (HPMC K 15M) and Binder (PVP K 30) on Drug Release in 8 hrs

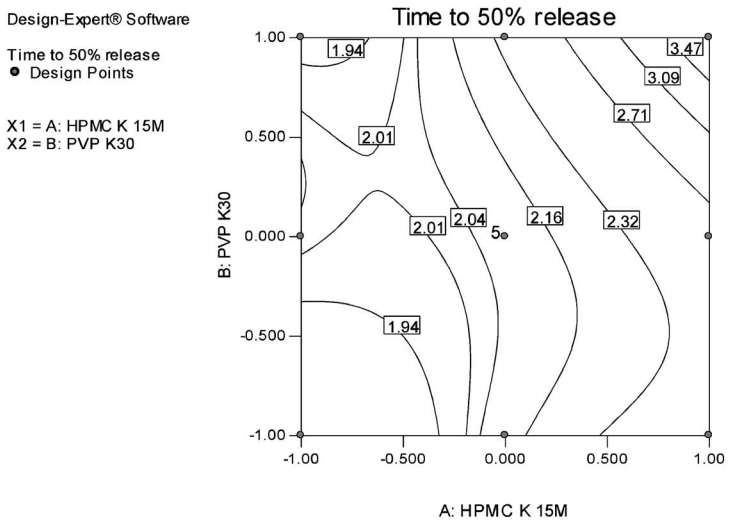

Fig. 4. Contour Plot Showing the Relationship between Various Levels of Polymer (HPMC K 15M) and Binder (PVP K 30) on Time to Release 50% Drug Release

Table 5. Composition of the Checkpoint Formulations, the Predicted and Experimental Values of Response Variables, and Percentage Prediction Error[a)]

Composition: HPMC K 15M : PVP K 30	Response variable	Experimented value	Predicted value	Percentage error
	$rel_{1\ hr}$	29.05	29.10	−0.172
336 : 130	$rel_{8\ hr}$	95.73	95.30	0.449
	$t_{50\%}$	2.13	2.12	0.469
	$rel_{1\ hr}$	28.75	28.60	0.522
405.72 : 83.15	$rel_{8\ hr}$	96.27	96.50	−0.239
	$t_{50\%}$	2.17	2.17	0
	$rel_{1\ hr}$	29.81	29.80	0.034
399 : 68.75	$rel_{8\ hr}$	99.11	99.30	−0.192
	$t_{50\%}$	2.15	2.16	−0.465
	$rel_{1\ hr}$	28.83	28.90	−0.243
366 : 102.50	$rel_{8\ hr}$	97.19	97.10	0.093
	$t_{50\%}$	2.10	2.10	0
	$rel_{1\ hr}$	28.85	28.80	0.173
348 : 123.10	$rel_{8\ hr}$	95.79	95.40	0.407
	$t_{50\%}$	2.12	2.13	−0.472
	$rel_{1\ hr}$	29.27	29.20	0.239
392.16 : 80.35	$rel_{8\ hr}$	97.98	98.10	−0.123
	$t_{50\%}$	2.13	2.13	0
	$rel_{1\ hr}$	28.79	28.70	0.313
354 : 117.50	$rel_{8\ hr}$	95.95	95.80	0.156
	$t_{50\%}$	2.13	2.13	0
	$rel_{1\ hr}$	30.20	30.10	0.331
390 : 70	$rel_{8\ hr}$	99.01	99.70	−0.697
	$t_{50\%}$	2.15	2.14	0.465

a) $rel_{1\ hr}$: Release in 1 hr, $rel_{8\ hr}$: Release in 8 hrs, $t_{50\%}$: Time to 50% drug release, Percentage error (mean ± S.D.) 0.0437 ± 0.3285.

in the amount of polymer and binder. It also shows that HPMC K 15M has a comparatively greater influence on the response variable than PVP K 30.

In contrast to the results of drug release in 1 hr, contour plot for drug release in 8 hrs (Fig. 3) reveal that $rel_{8\ hr}$ varies in somewhat linear fashion with in-

crease of polymer and binder contents. However, the effect of HPMC K 15M seems to be more pronounced as compared with that of PVP K 30.

Figure 4 exhibits that time to 50% drug release ($t_{50\%}$) vary in a nonlinear manner, but in a ascending pattern with an increase in the amount of each variables. But at the higher amount of HPMC K 15M and PVP K 30 the contour lines turned to be linear.

Validation of RSM Results For all of the 8 checkpoint formulations, the results of the physical evaluation and tablet assay were found to be within limits. Table 5 lists the compositions of the checkpoints, their predicted and experimental values of all the response variables, and the percentage error in prognosis.

Figure 5 (A, C and E) shows linear correlation

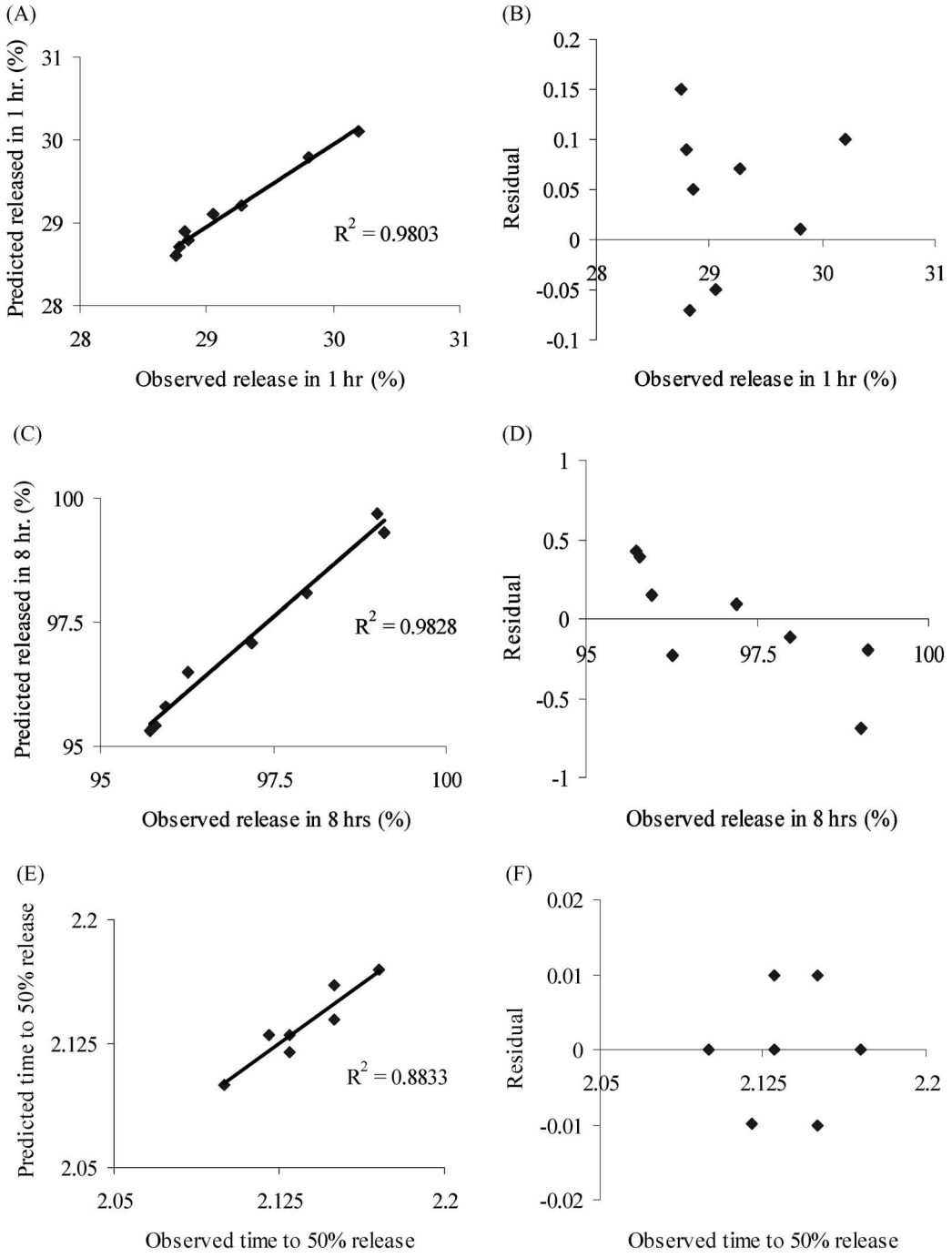

Fig. 5. Linear Correlation Plots (A, C, E) between Observed and Predicted Values and the Corresponding Residual Plots (B, D, F) for Various Variables

plots between the observed and predicted response variables, and the residual plots [Fig. 5 (B, D and F)] showing the scatter of the residuals versus observed values.

Upon comparison of the observed responses with that of the anticipated responses, the prediction error varied between −0.697% and 0.522% (mean ±S.D. as 0.0437 ±0.3285). The linear correlation plots drawn between the predicted and observed responses demonstrated high values of r^2 (ranging between 0.9803 and 0.9900 excluding 0.8833 for $t_{50\%}$), indicating excellent goodness of fit ($p<0.05$). Relatively less magnitudes of r^2 observed with $t_{50\%}$ (0.8833) could be attributed to the limitation of software (Design Expert trial version 7.0.3 State-Ease Inc., Minneapolis, MN) to predict $t_{50\%}$ up to two decimal points only as well as indirect estimation of observed $t_{50\%}$ values through interpolation techniques.

CONCLUSION

Controlled drug release following Higuchi kinetics attained in the current study indicates that the hydrophilic matrix tablet of metformin, prepared using HPMC K 15M and PVP K 30, can successfully be employed as once-a-day oral controlled release drug delivery system. Both the polymer and binder plays major role for the sustained release of metformin. However, appropriate balancing between various levels of the polymer and binder may contribute better results. High degree of prognosis obtained using RSM corroborates that a 2-factor CCD is quite efficient in optimizing drug delivery systems that exhibit non-linearity in response(s).

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REFERENCES

1) Vidyadhara S., Rao P. R., Prasad J. A., *Indian J. Pharm. Sci.*, **66**, 188–192 (2004).
2) Reddy K. R., Mutalik S., Reddy S., *AAPS Pharm. Sci. Tech.*, **4**, 1–9 (2003).
3) Mohammed A. D., James L. F., Michael H. R., John E. H., Rajabi-Siahboomi A. R., *Pharm. Dev. Tech.*, **4**, 313–324 (1999).
4) Lee B. J., Ryu S. G., Cui J. H., *Drug Dev. Ind. Pharm.*, **25**, 493–501 (1999).
5) Chien Y. W., "Novel Drug Delivery Systems," 2nd ed., Marcel Dekker, New York, 1992.
6) Ravi Kumar M. N. V., Kumar N., *Drug Dev. Ind. Pharm.*, **27**, 1–30 (2001).
7) Dave B. S., Amin A. F., Patel M. M., *AAPS Pharm. Sci. Tech.*, **5**, 34 (2004).
8) Singh B., Kumar R., Ahuja N., *Crit. Rev. Ther. Drug Carrier Syst.*, **22**, 27–105 (2005).
9) Singh B., Ahuja N., *Int. J. Pharm.*, **195**, 247–248 (1999).
10) Singh B., Dahiya M., Saharan V., Ahuja N., *Crit. Rev. Ther. Drug Carrier Syst.*, **22**, 215–293 (2005).
11) Singh B., Mehta G., Kumar R., Bhatia A., Ahuja N., Katare O. P., *Curr. Drug Deliv.*, **2**, 143–153 (2005).
12) Aberturas M. R., Molpeceres J., Guzman M., Garcia F., *J. Microencapsul.*, **19**, 61–72 (2002).
13) Singh B., Ahuja N., "Response Surface Optimization of Drug Delivery System, Progress in Controlled and Novel Drug Delivery Systems," eds. by Jain N. K., New Delhi, 2004.
14) Stith B. J., Goalstone M. L., Espinoza R., Mossel C., Roberts D., Wiernsperger N. *Endocrinology*, **137**, 2990–2999 (1996).
15) Dunn C. J., Peters D. H., *Drugs*, **49**, 721–749 (1995).
16) Defang O., Shufang N., Wei L., *Drug Dev. Ind. Pharm.*, **31**, 677–685 (2005).
17) Balan G., Timmins P., Greene D. S., Marathe P. H., *J. Pharm. Sci.*, **8**, 1176–1185 (2001).
18) Montvale N. J., "Physicians' Desk Reference," 53rd ed., Medical Economics Co., 1999.
19) Fiona P., Marina L., Ali R. S., "Investigation of a Directly Compressible Metformin HCl 500 mg Extended Release Formulation based on Hypromellose," Poster Reprint, Controlled Release Society Annual Meeting, 2005.
20) Koresmeyer R. W., Gurny R., Doelker E. M., Buri P., Peppas N. A., *Int. J. Pharm.*, **15**, 25 (1983).
21) Higuchi W. I., *J. Pharm. Sci.*, **51**, 802–804 (1962).

22) Rawlins E. A. ''Bentley's Text Book of Pharmaceutics,'' Cassell and Collier Macmillan, London, 1977.
23) Defang O., Shufang N., Wei L., *Drug Dev. Ind. Pharm.*, **31**, 677–685 (2005).
24) Singh B., Ahuja N., *Drug Dev. Ind. Pharm.*, **28**, 431–442 (2002).
25) Fassihi R. A., Ritschel W. A., *J. Pharm. Sci.*, **82**, 750–754 (1993).
26) Peppas N. A., *Pharm. Acta Helv.*, **60**, 110 (1985).
27) Ford J. L., Rubinstein M. H., Hogan J. E., *Int. J. Pharm.*, **24**, 327–338 (1985).
28) Vazques M. J., Perez-Marcos B., Gomez-Amoza J. L., Martinez-Pacheco R., Souto C., Concheiro A., *Drug Dev. Ind. Pharm.*, **18**, 1355–1375 (1992).