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Application of Response Surface Methodology in the Formulation of Sustained Release Matrix Tablets of Metformin Hydrochloride

A. GHOSH, A. BOSE, U. BHAUMIK, U. MANDAL,
K. VEERAN GOWDA and T.K. PAL*
Bioequivalence Study Centre, Department of Pharmaceutical Technology
Jadavpur University, Kolkata-700 032, India
E-mail: tkpal12@gmail.com; anim_1607@yahoo.co.in

The aim of the current research was to design an oral sustained release (SR) matrix tablet of metformin HCl (400 mg) and to optimize the drug release profile by using response surface methodology (RSM). Tablets were prepared by non-aqueous wet granulation method using hydroxy propyl methyl cellulose (HPMC K-15 M) and sodium carboxy methyl cellulose (Na CMC) as matrix forming polymers. Independent variables such as HPMC K-15 M (X_1), Na CMC (X_2) and polyvinyl pyrrolidone (PVP K-30) (X_3) were optimized by using a 3-factor, 3-level Box-Behnken statistical design. The dependent variables selected were cumulative percentage of drug release after 1 h (Y_1), 2 h (Y_2), 4 h (Y_3), 6 h (Y_4), 8 h (Y_5) and 10 h (Y_6). The values of Y_1, Y_2, Y_3, Y_4, Y_5 and Y_6 were restricted to not more than 30, 40, 60, 70, 90 and 110 %, respectively. It was found that both of the polymers and binder had significant effects on the drug release from the tablets ($p < 0.05$). The formulated tablets followed the Higuchi drug release kinetics and the diffusion was the dominant mechanism of drug release, resulting in regulated and complete release within 10 h. For estimation of coefficients in the approximating polynomial function, the least square regression method was applied. Afterward, the information about the model reliability was verified by using the analysis of variance (ANOVA). The result showed that the optimized formulation provided a dissolution pattern equivalent to the predicted values (residual values varies from -2.4271 to 2.1348), which indicated that the optimal formulation could be obtained by using response surface methodology.

Key Words: Metformin hydrochloride, Box-Behnken design, Response surface methodology.

INTRODUCTION

Introduction of matrix tablet as sustained release (SR) has open a new era for novel drug delivery system (NDDS) in the field of pharmaceutical technology. It bypasses 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) and sodium carboxy methyl cellulose (Na CMC) is widely used hydrophilic polymer to prolong drug release due to their rapid hydration, good compression and gelling characteristics along with their ease of use, availability and very low toxicity. They regulates the release of drug by controlling the swelling and cross-linking[3,5].

In the development of a sustained release tablet dosage form, many statistical experimental designs have been recognized as useful techniques to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum number of trials. For this purpose, a computer based optimization technique with a response surface methodology (RSM) utilizing a polynomial equation and artificial neural network (ANN) has been widely used[6-12]. Different types of screening designs such as fractional factorial and Plackett Burman screening designs have been used for preformulation evaluation[13,14].

Response surface methodology (RSM) is used when only a few significant factors are involved in optimization. Different types of RSM designs include 3-level factorial design, central composite design (CCD), Box-Behnken design and D-optimal design. A modified central composite experiment, Box-Behnken design[15-18] is an independent, rotatable or nearly rotatable quadratic design (contains no embedded factorial, fractional factorial design), in which the treatment combinations are at the midpoints of the edge of the process space and at the center. Among all the designs, Box-Behnken design requires fewer runs (15 runs) in a 3-factor, 3-level experimental design. A 3-factor, 3-level factorial design would require a total of 27 unique runs without any repetitions. Hence, the Box-Behnken design was applied to optimize the SR matrix tablet of metformin HCl. The technique requires minimum experimentation and time, thus proving to be far effective and cost effective than the conventional methods of formulating matrix tablet dosage forms.

Metformin HCl is an oral hypoglycemic agent, belongs to bigunides group[19]. It is mainly used to control the glycemic level of non-insulin dependent diabetes *i.e.*, type-II diabetes. Its conventional dose is within 250 mg to 1500 mg tablet, 2-3 times a day. 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 h[20,21]. 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 h 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[22,23].

Palmer *et al.*[24] 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 flowability 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.*[21], where metformin gave *in vitro* release for up to 22 h. But preparation of microcapsules in commercial scale and optimization of drug release rate is troublesome. Defang *et al.*[20] 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 and Na CMC by non-aqueous wet granulation method and optimize the formulation using RSM.

EXPERIMENTAL

Metformin hydrochloride (Stad med Pvt. Ltd., India), hydroxy propyl methyl cellulose K-15 M, sodium carboxy methyl cellulose (Colorcon Asia Pvt. Ltd.) polyvinyl pyrrolidone K-30 (SD Fine Chemical, India), magnesium stearate, talc (Mohanlal Dayaram and Company) were used for model formulation. For all experimental runs these chemicals were used from the same batch.

Experimental design: Box-Behnken statistical screening design was used to optimize and evaluate main effects, interaction effects and quadratic effects of the formulation ingredients on the *in vitro* dissolution performance of metformin HCl 400 mg SR matrix tablet. A 3-factor, 3-level design used is suitable for exploring quadratic response surfaces and constructing second order polynomial models. This cubic design is given by a set of points at the midpoints of each edge of a multi-dimensional cube and a center point replicate (Fig. 1). The non-linear computer generated quadratic model obtained by using Design Expert 7.1.1 Trial version (Stat-Ease Inc. Minneapolis, Minnesota) is given as

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_4x_1x_2 + b_5x_1x_3 + b_6x_2x_3 + b_7x_1^2 + b_8x_2^2 + b_9x_3^2 \quad (1)$$

where Y is the measured response associated with each factor level combination; b_0 is an intercept; b_1 to b_9 are the regression coefficient and X_1, X_2 and X_3 are the independent variables.

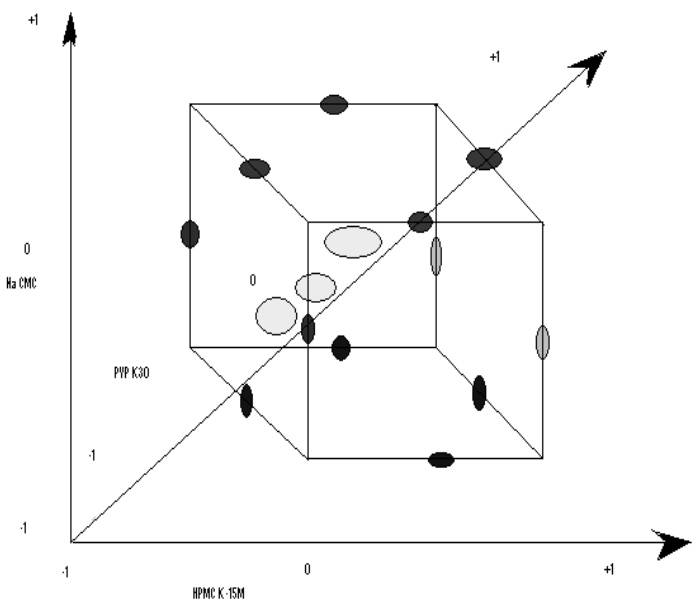

Fig. 1. Graphical representation of experimental points of Box-Behnken experimental design

The dependent and independent variables selected are shown in Table-1. High, medium and low levels were selected from the preliminary experimentation. The levels of HPMC K-15 M, Na-CMC and PVP K-30 used to prepare each of the formulations and their release profiles are given in Table-2.

TABLE-1
VARIABLES IN THE BOX-BEHNKEN DESIGN

Variables	Level used		
Independent variables	Low (-1)	Medium (0)	High (+1)
X_1 HPMC K-15 M	125	150	175
X_2 Na CMC	40	60	80
X_3 PVP K-30	50	60	70
Dependent variables			
Y_1 = drug release after 1 h	Not more than 30 %		
Y_2 = drug release after 2 h	Not more than 40 %		
Y_3 = drug release after 4 h	Not more than 60 %		
Y_4 = drug release after 6 h	Not more than 70 %		
Y_5 = drug release after 8 h	Not more than 90 %		
Y_6 = drug release after 10 h	Not more than 110 %		

TABLE-2
THE DEPENDENT VARIABLES AND RESPONSES (MEAN±SD) OF MODEL FORMULATIONS OF METFORMIN HCL SUSTAINED RELEASE TABLETS UTILIZING BOX-BEHNKEN EXPERIMENTAL DESIGN

Batch no.	X1	X2	X3	Release (%) 1 h (Y_1)	Release (%) 2 h (Y_2)	Release (%) 4 h (Y_3)	Release (%) 6 h (Y_4)	Release (%) 8 h (Y_5)	Release (%) 10 h (Y_6)
F1	0	0	0	27.28±1.25	38.07±3.02	55.45±2.21	68.11±2.15	83.25±1.97	90.21±2.67
F2	1	0	-1	20.76±4.37	32.52±2.23	43.57±1.35	51.09±2.55	64.44±4.78	75.03±1.26
F3	0	1	1	12.06±1.57	17.59±2.57	28.59±3.66	33.25±3.09	40.28±1.27	46.57±2.53
F4	-1	1	0	31.55±2.65	42.52±3.53	63.01±3.54	72.52±2.27	86.72±2.15	98.23±3.21
F5	1	-1	0	17.57±3.71	23.59±1.17	34.56±2.74	43.25±3.68	52.36±1.24	59.37±3.47
F6	0	-1	-1	33.21±3.45	44.55±2.44	61.55±3.11	73.49±2.42	87.65±2.35	95.26±3.79
F7	0	-1	1	23.11±3.05	34.22±2.15	48.98±1.67	61.09±1.88	73.99±2.22	85.31±3.01
F8	0	0	0	26.98±2.25	39.11±2.01	55.01±3.19	69.72±3.27	82.49±3.97	91.19±3.07
F9	0	0	0	27.58±2.57	37.41±1.41	54.77±3.37	68.53±2.56	84.76±3.65	92.22±3.02
F10	-1	-1	0	40.58±2.05	51.21±1.79	69.05±4.01	80.71±3.89	94.45±2.15	110.29±3.15
F11	1	0	1	11.24±2.75	17.53±2.17	27.34±4.03	34.58±1.17	41.47±3.19	49.75±1.37
F12	-1	0	-1	37.52±1.58	48.05±2.67	65.22±2.52	76.58±1.51	90.46±4.46	104.52±3.33
F13	0	1	-1	23.37±3.54	35.25±2.25	48.55±1.77	60.54±2.22	72.33±3.37	83.36±3.36
F14	-1	0	1	35.22±4.67	45.57±2.22	62.97±1.89	74.02±2.49	88.53±3.43	103.44±2.55
F15	1	1	0	10.03±1.25	16.25±1.77	24.28±5.09	30.45±2.87	37.59±5.21	44.31±4.29

X1 = X_1 HPMC K-15 M; X2 = X_2 Na CMC; X3 = X_3 PVP K-30

Preparation of metformin HCl matrix tablet: Metformin HCl, HPMC K-15 M, Na-CMC and PVP K-30 were weighed and mixed well. 3 mL of isopropyl alcohol (IPA) was taken and poured into the bulk of the mixture and mixed well for 10 min to prepare a wet mass. The wet mass was then granulated by passing through 16 mesh sieve. The granules were dried in an oven for 0.5 h at 40 ºC and then passed through a 22-mesh sieve. Then the dried granules were blended with 1 % magnesium stearate and 1 % talc. Magnesium stearate and talc were used as glident and lubricant, respectively. Tablets containing 400 mg of metformin HCl were compressed using 19.5 × 8.9 mm caplet tooling at a rotational speed 40 rpm. The total tablet weight was fixed by lactose, used as diluent to 750 mg. The average hardness of the tablet was 6-7 kg/cm^2. The trials were performed in a randomized order. All of the ingredients used in this study came from the same lots and the same procedures and equipments were used throughout the production and testing of the tablet.

Determination of metformin HCl release from matrix tablet: Release of metformin HCl from the tablets was determined using USP standard dissolution apparatus type-I (with basket); Electrolab (USP XXIII)-TDT-06P. The dissolution medium was 900 mL of distilled water at a temperature of 37 ± 2 ºC and at a rotational speed 100 rpm. From each batch of formulations,

6 tablets were tested. Samples were withdrawn automatically at the following time intervals: 1, 2, 4, 6, 8 and 10 h using a fraction collector. After necessary dilution, the samples were analyzed using an ultraviolet/visible spectrophotometer at 232 nm.

Drug release kinetics: In order to propose a possible release mechanism, drug release from HPMC and Na CMC matrix tablets was fitted to the following equations:

Higuchi's[25] 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.*[26] 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[27] using available pharmacokinetic data[20].

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

where, D_t = total dose of drug; Dose = dose of the immediate release part; t = time (h) during which the sustained release is desired (10 h); $t_{1/2}$ = half-life of the drug (3 h).

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: $rel_{1\,h}$ = 28 to 30 %, $rel_{2\,h}$ = 38 to 40 %, $rel_{4\,h}$ = 58 to 60 %, $rel_{6\,h}$ = 68 to 70 %, $rel_{8\,h}$ = 80 to 85 % and $rel_{10\,h}$ = 95 to 100%.

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 747.3 and 754.9 mg (mean 751.4 mg), thickness between 6.45 and 6.56 mm (mean 6.52 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 UV spectrophotometer method described in experimental section. 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[25] (cumulative percentage of drug released versus square root of time) and Korsmeyer *et al.*[26] (log cumulative

percentage of drug released *versus* log time) equations. In present experiments the *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's[25] equation as the plots showed high linearity (R^2: 0.9946 ± 0.0036, with K_H 26.063 ± 5.974) as shown in Table-3. In the current study, the values of release rate exponent (n), calculated as per the equation proposed by Koresmeyer *et al.*[26], was 0.5264 ± 0.063 (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[28,29]. In present 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.

TABLE-3
DRUG RELEASE PARAMETER OF VARIOUS TRIAL FORMULATIONS PREPARED AS PER EXPERIMENTAL DESIGN*

Trial no.	n	K_H	R^2
F1	0.5315	30.126	0.9971
F2	0.5314	23.931	0.9852
F3	0.5855	15.801	0.9952
F4	0.4928	30.620	0.9961
F5	0.5349	19.528	0.9952
F6	0.4624	29.100	0.9981
F7	0.5596	28.385	0.9959
F8	0.5314	30.014	0.9988
F9	0.5372	30.831	0.9944
F10	0.4258	31.375	0.9903
F11	0.6361	17.427	0.9948
F12	0.4383	30.350	0.9975
F13	0.5398	27.147	0.9962
F14	0.4599	30.796	0.9897
F15	0.6302	15.474	0.9942
Average	0.526453	26.06033	0.99458
SD (±)	0.062893	5.974189	0.003614

*n = Release exponent obtained from Koresmeyer *et al.*[26] Equation ($M_t/M_\infty = kt^n$), K_H: Higuchi rate constant ($Q = K_H t^{1/2}$); R^2 = Regression coefficient of Higuchi[25] equation.

Experiments of Box-Behnken experimental design: Response data for all 15 experimental runs of Box-Behnken experimental design (F1-F15) performed in accordance with Table-2 are presented in Fig. 2. Regarding different combinations of factors and factor levels, a considerable difference between drug release profiles was obtained. The responses of Box-Behnken experimental design ranged from an exceedingly low drug release profile, in run F15 (around 45 % of released metformin HCl after 10 h), to very fast drug release profiles, in runs F10, F12 and F14 (around 35 % of released metformin HCl in just 1 h).

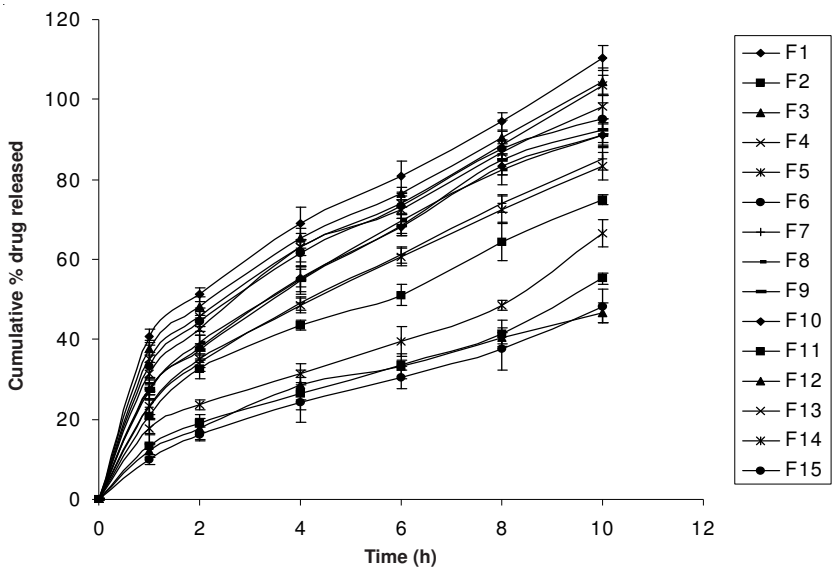

Fig. 2. Release profiles of metformin HCl in accordance with Box-Behnken design runs F1-F15

Formation of quadratic polynomial equation and analysis of variance (ANOVA): For estimation of coefficients in approximating the polynomial function (eqn. 1) applying uncoded values of factor levels, the least square regression method was performed using the Design Expert 7.1.1 Trial version (Stat-Ease Inc. Minneapolis, Minnesota) software. The corresponding equations obtained (eqns. 2-7) for all six responses Y_1, Y_2, Y_3, Y_4, Y_5 and Y_6 are given below.

$$Y_1 = 27.28-10.39x_1-4.68x_2-3.89x_3+0.37x_1x_2-1.27x_1x_3-0.30x_2x_3+0.72x_1^2 - 3.06x_2^2 - 1.28x_3^2 \quad (2)$$

$$Y_2 = 38.20-11.99x_1-5.24x_2-5.49x_3+0.34x_1x_2-2.74x_1x_3-1.83x_2x_3-0.70x_1^2 - 4.10x_2^2 - 1.19x_3^2 \quad (3)$$

$$Y_3 = 55.08-16.83x_1-5.80x_2-6.49x_3-0.24x_1x_2-3.72x_1x_3-1.85x_2x_3-2.77x_1^2 - 5.40x_2^2 - 2.75x_3^2 \quad (4)$$

$$Y_4 = 68.79-18.05x_1-7.26x_2-7.48x_3-0.23x_1x_2-3.75x_1x_3-3.72x_2x_3-5.63x_1^2 - 7.34x_2^2 - 4.35x_3^2 \quad (5)$$

$$Y_5 = 83.50-21.01x_1-8.47x_2-8.83x_3-0.81x_1x_2-5.26x_1x_3-4.60x_2x_3-7.00x_1^2 - 9.66x_2^2 - 5.27x_3^2 \quad (6)$$

$$Y_6 = 91.21-21.43x_1-10.11x_2-8.45x_3-1.53x_1x_2-4.68x_1x_3-6.71x_2x_3-1.72x_1^2 - 8.65x_2^2 - 4.93x_3^2 \quad (7)$$

For estimation of significance of the model, the analysis of variance (ANOVA) was applied. 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 six responses, the individual quadratic contribution of the model was not significant.

TABLE-4
ANALYSIS OF VARIANCE (p-VALUE < 0.05) FOR ALL RESPONSES Y_1, Y_2, Y_3, Y_4, Y_5 AND Y_6

Source	Response											
	Y_1		Y_2		Y_3		Y_4		Y_5		Y_6	
	F-value	P-value	F-value	P-value	F-value	P-value	F-value	P-value	F-value	P-value	F-value	P-value
X_1	179.53	**0.0002**	115.88	**0.0001**	97.94	**0.0002**	89.66	**0.0002**	76.16	**0.0003**	108.31	**0.0001**
X_2	36.45	**0.0018**	22.18	**0.0053**	11.64	**0.0190**	13.59	**0.0142**	12.37	**0.0170**	24.13	**0.0044**
X_3	25.12	**0.0041**	24.28	**0.0044**	14.54	**0.0125**	14.41	**0.0127**	13.44	**0.0145**	16.86	**0.0093**
X_1X_2	0.12	0.748	0.046	0.8388	0.0097	0.9252	0.0068	0.9374	0.057	0.8209	0.28	0.6206
X_1X_3	1.35	0.2984	3.02	0.1426	2.39	0.1829	1.82	0.2355	2.39	0.1830	2.58	0.1689
X_2X_3	0.076	0.7938	1.35	0.2971	0.59	0.4722	1.79	0.2390	1.82	0.2348	5.31	0.0694
X_1^2	0.39	0.5580	0.18	0.6873	1.22	0.3190	3.78	0.1096	3.90	0.1051	0.32	0.5947
X_2^2	7.20	**0.0436**	6.27	0.0542	4.66	0.0834	6.41	0.0524	7.44	**0.0414**	8.15	**0.0356**
X_3^2	1.25	0.3136	0.53	0.5005	1.21	0.3214	2.25	0.1937	2.21	0.1969	2.65	0.1646

Significant effect of factors on individual responses are shown in bold p-value < 0.05.

Calculating the regression coefficients (R^2), it was found that 97.99 % of the variability of experimental data could be explained using the model polynomial function Y_1. For responses Y_2, Y_3, Y_4, Y_5 and Y_6 the regression coefficients R^2 were 98.84, 97.60, 97.33, 96.72 and 98.25 %, respectively. Therefore it can be concluded that model functions Y_1, Y_2, Y_3, Y_4, Y_5 and Y_6 well interpreted the variability of data after 1, 2, 4, 6, 8 and 10 h of drug release.

Three dimensional response surface plots: Three-dimensional (3D) surface plots for the measured responses were formed, based on the model polynomial functions to assess the change of the response variables (Y_1 to Y_6). Also the relationship between the dependent and independent variables can further be understood by these plots. Since the model has more than two factors, one factor was held constant for each diagram, therefore, a

total of 18 response surface plots were generated. Considering the greatest difference in model polynomial functions response, the surface plots for responses Y_1 and Y_6 are only presented (Figs. 3-5).

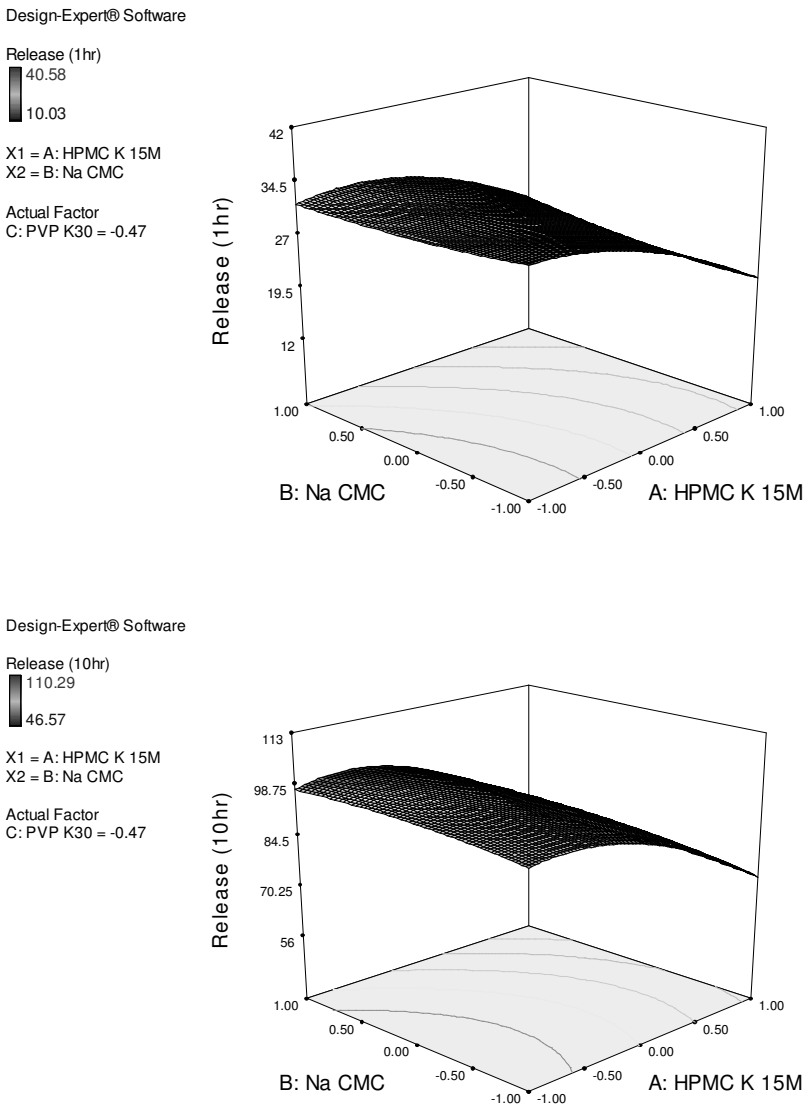

Fig. 3. Response surface plots (3D) showing the effect of the amount of HPMC K-15 M (X_1) and the amount of Na CMC (X_2) on the response Y_1 (% of metformin HCl released in 1 h) and the response Y_6 (% of metformin HCl released in 10 h) respectively

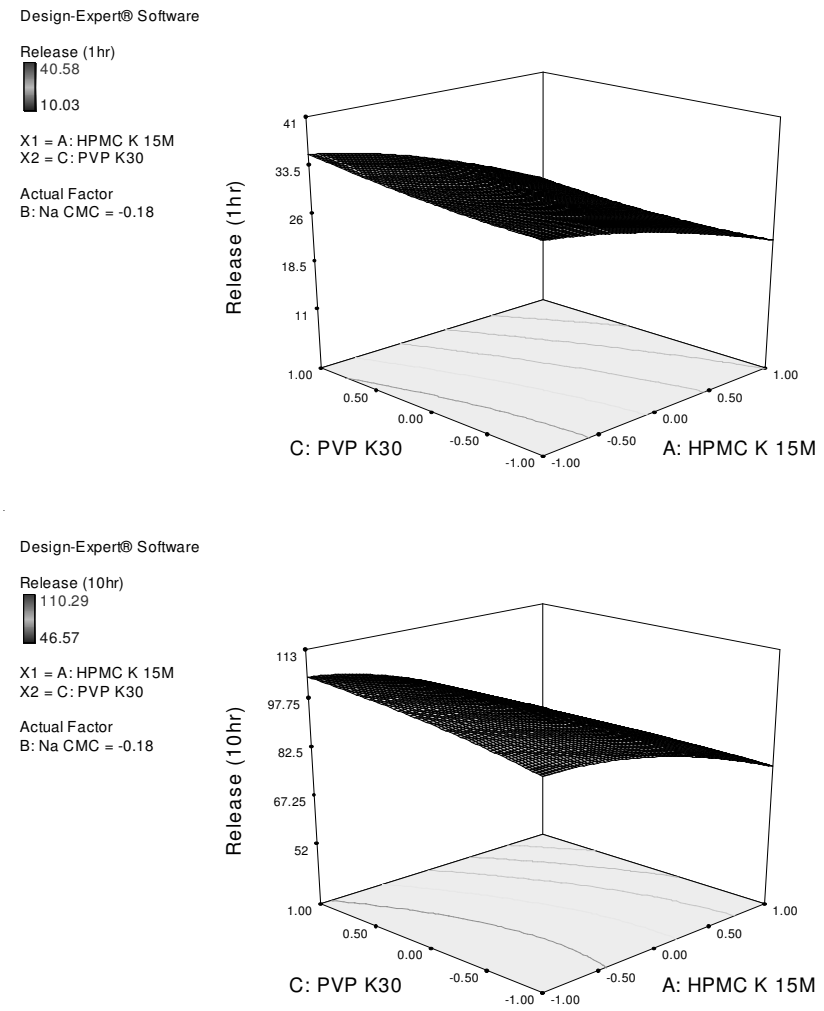

Fig. 4. Response surface plots (3D) showing the effect of the amount of HPMC K-15 M (X_1) and the amount of PVP-30 (X_3) on the response Y_1 (% of metformin HCl released in 1 h) and the response Y_6 (% of metformin HCl released in 10 h), respectively

In Fig. 3, response surface plots (3D) showing the effects of the amount of HPMC K-15 M (X_1) and the amount of Na CMC (X_2) on the response Y_1 (% of metformin HCl released in 1 h) and the response Y_6 (% of metformin HCl released in 10 h), respectively are presented. The amount of PVP K-30 (X_3) was kept constant (the level of X3 is -0.47). This figures shows that at a lower level of HPMC K 15 M, the % drug released at 1 h (Y_1) decreases with an increase in the level of Na CMC (41.18 to 31.13%).

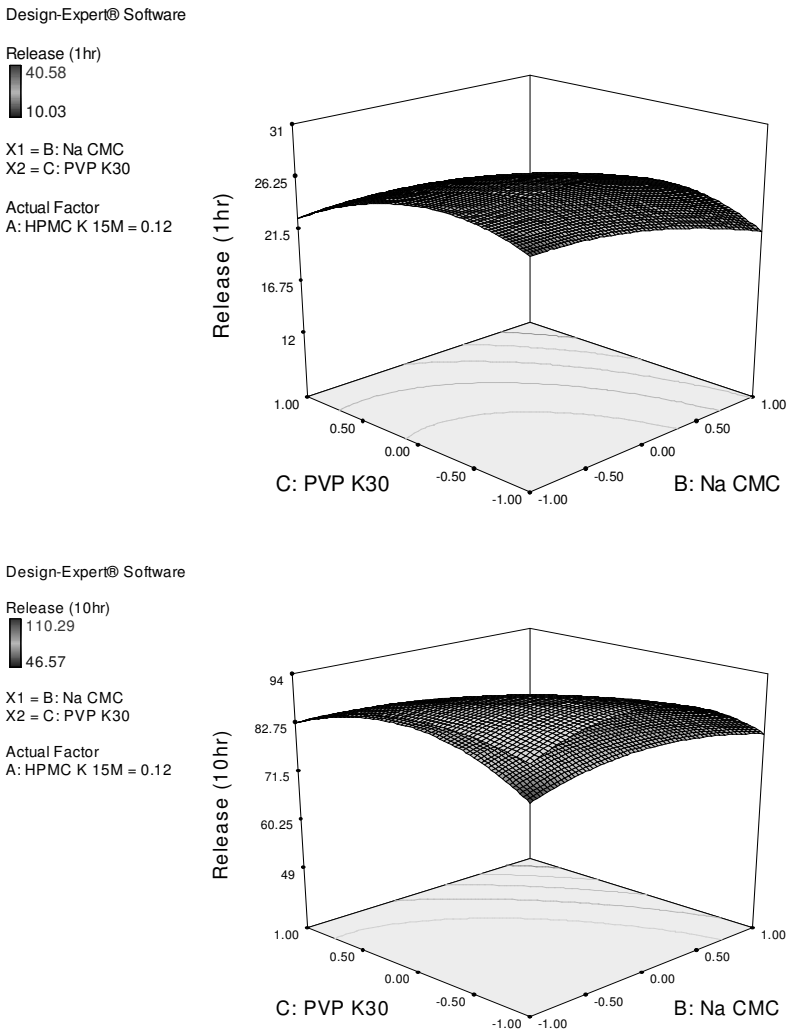

Fig. 5. Response surface plots (3D) showing the effect of the amount of Na CMC (X_2) and the amount of PVP -30 (X_3) on the response Y_1 (% of metformin HCl released in 1 h) and the response Y_6 (% of metformin HCl released in 10 h), respectively

However at the lowest concentration of Na CMC, the % drug released at 1 h (Y_1) decreases with an increase in the level of HPMC (41.18 to 20.98 %). The effect of different levels of X_1, X_2 on % drug release at 10 h (Y_6) do not follow a similar pattern. At the lowest level of X_1, the % drug released at 10 h (Y_6) increases to some extent and then decreases with an increase of the level of X_2. So it is observed that Na CMC is very much effective for controlling the release pattern of a SR tablet.

In Fig. 4, response surface plots (3D) shows the effects of the amount of HPMC K-15 M (X_1) and the amount of PVP K-30 (X_3) on the response Y_1 and Y_6, respectively. The amount of Na CMC (X_2) was kept in constant (the level of X_2 is -0.18). It shows that the % drug released after 1 h (Y_1) decreases at the lowest level of HPMC and with an increase in the level of PVP (40.40 to 35.31 %) and *vice versa*. From the graph it is clear that at the lowest level of HPMC, if PVP level is increased, the drug release at 10 h (Y_6) varies from 109.78 to 104.58 %. Metformin HCl is very much water soluble drug. So for controlling the drug release from SR tablet, PVPK 30 which acts as a binder has a major role. As constraints for Y_1 and Y_6 are not more than 30 and 110 %, respectively, the amount of PVP K30 is to be optimized.

In Fig. 5, response surface plots (3D) showing the effects of the amount of Na CMC (X_2) and the amount of PVP K-30 (X_3) on the response Y_1 and Y_6, respectively are presented. The amount of HPMC K-15 M (X_1) was kept in constant (the level of X_1 is 0.12). At lowest levels of Na CMC, when PVP level is increased, Y_1 varies from 30.09 to 22.67 % and at the lowest levels of PVP, when Na CMC level is increased, Y_1 varies from 30.09 to 21.56 %.

From the above observations, it was clear that all the 3 independent variables included in the experimental design showed a significant effect on the release pattern of the formulations.

Optimization: After generating the model polynomial equations to relate the dependent and independent variables, the combination was optimized for all six responses. The final optimal experimental parameters were calculated using the optimization technique in this Design Expert software, which allows to compromise among various responses and searches for a combination of factor levels that jointly optimize a set of responses by satisfying the requirements for each response in the set. In this study, the optimization was performed with constraints for all six responses, presented in Table-1. The optimum amount of three independent variables is given below.

Independent factors	Optimal amount (mg)
HPMC K-15M	153
Na CMC	56.4
PVP K-30	55.9

To confirm the validity of the calculated optimal parameters and predicted responses, the drug release profile at optimal combination of physico-chemical parameters was carried out. The observed and predicted response and residual values for the drug release test have been performed at optimal

values of the analytical parameters investigated in this study. The residual value varies from -2.4271 to 2.1348. It can be concluded that optimized formulation ensured the release profile, which was very close to the predicted values. Fig. 6 shows the comparison of observed dissolution profile and predicted dissolution profile of the optimal formulation obtained from the response surface methodology.

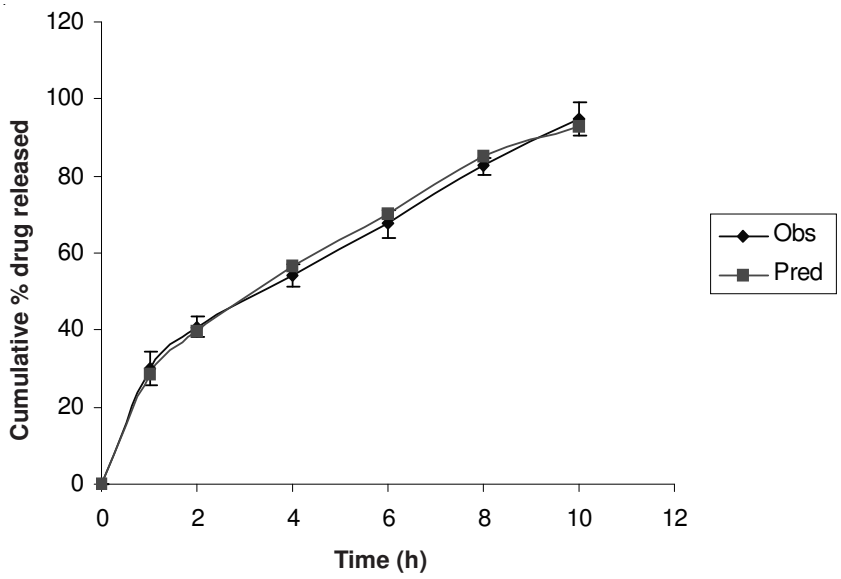

Fig. 6. Comparison of observed dissolution profile and predicted dissolution profile of the optimal formulation obtained from the response surface methodology

Validation of RSM results: For all of the checkpoint formulation, the results of the all-dependent responses were found to be within limits. Table-5 lists the levels of the independent variables, their predicted and observed values of all the responses and percentage error in prognosis. Fig. 7 shows linear correlation plots between the observed and predicted response variables. Upon comparison of the responses with that of the predicted responses, the percentage error varied between -3.88228 % and +6.317931 %. The linear correlation plots drawn between the predicted and observed responses demonstrated high values of R^2 (ranging from 0.9409 and 0.9965). Thus, the low magnitudes of error as well as the significant values of R^2 in the current study indicate a high prognostic ability of RSM.

TABLE-5
LEVELS OF CHECKPOINT FORMULATIONS, THE PREDICTED AND OBSERVED VALUES OF DEPENDENT VARIABLES (Y_1, Y_6) AND PERCENTAGE ERROR

Ratio of levels of indepenent variables	% Release in 1 h (Y_1)			% Release in 10 h (Y_6)		
	Observed	Predicted	Error (%)	Observed	Predicted	Error (%)
0.08:0.07:-0.59	28.9504	28.0693	3.139017	90.9574	92.5531	-1.724090
0.12:-0.18:-0.47	30.1574	28.3653	6.317931	94.8953	92.7605	2.301411
0.10:-0.14:-0.41	29.6517	28.2382	5.005631	94.8712	92.737	2.301347
0.08:0.06:-0.47	29.0458	28.0736	3.463040	91.0987	92.5572	-1.575780
0.09:-0.09:-0.41	29.4518	28.1662	4.564336	94.0257	92.6828	1.448920
0.08:-0.03:-0.42	29.0475	28.0830	3.434462	93.0475	92.6187	0.462973
0.07:0.04:-0.51	28.7504	28.0427	2.523651	91.4708	92.5600	-1.176750
0.07:0.07:-0.57	28.6985	28.0492	2.314861	90.7452	92.5495	-1.949550

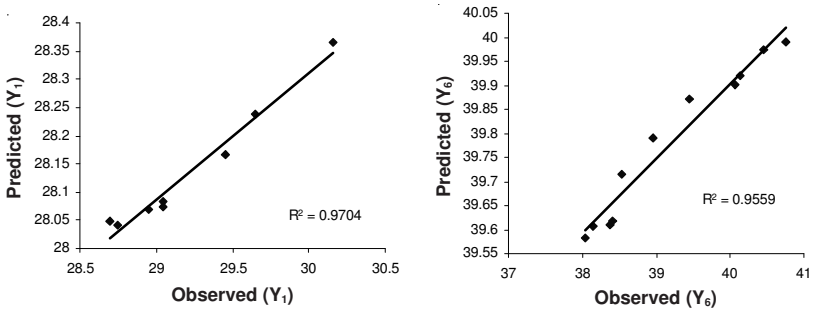

Fig. 7. Linear correlation plots between observed and predicted values for Y_1 (A) and Y_6 (B)

Conclusion

It was concluded that the response surface methodology (RSM) and multiple response optimization utilizing a polynomial equation can be successfully used to design a sustained release formulation for predetermined release profile in a very short time period and with a small number of experimental runs. A sustained release metformin HCl formulation with satisfactory release characteristics was successfully prepared with HPMC K-15 M, Na CMC and PVP K30.

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