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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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ABSTRACT

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 wet granulation method using HPMC K 100M as matrix forming polymer, PVP K 30 as binder. A central composite design for 2 factors at 3 levels each was employed to systematically optimize drug release profile. HPMC K 100 M (X1) and PVP K 30(X2) were taken as the in-dependent variables. The dependent variables selected were %of drug released in 1hr (Y1), % of drug released in 3 hrs (Y2) and %drug release in 10 hrs (Y3). Contour plots were drawn and optimum formulations were selected by feasibility and grid searches. All The polymer (HPMC K100M) and binder (PVP K 30) had significant effect on the drug release ($p < 0.05$). Polynomial mathematical models, generated for various response variables using multiple linear regression analysis, were found to be statistically significant ($p < 0.05$). 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.

INTRODUCTION:

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple Processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable,

increased convenience and patient compliance[1,2]. Many innovative methods have been developed for obtaining modified drug release. From the practical view point, hydrophilic matrix tablet is one of the least complicated approaches for developing modified release dosage form. Hydroxy propyl methyl cellulose (HPMC) is hydrophilic cellulose ether widely used as a pH-independent gelling agent in controlled release preparation, due to their release behavior of the drug[3]. Due to non-toxicity, easy handling and no requirement of specified technology for production of sustained release tablets, HPMC is often used as release retarding materials [4]. The transport phenomena involved in the drug release from hydrophilic matrices are complex because the microstructure and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly[5]. The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution. The dissolution can be diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. 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 [6-11]. 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, the only available biguanide, remains the first line drug therapy for patients with Type 2 diabetes mellitus (T2DM), acts by decreasing hepatic glucose output and peripheral insulin resistance[12]. The advantages of metformin are a very low risk of hypoglycaemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality[13]. It is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 –60 % with relatively short plasma half-life of 1.5 -4.5 h [14,15]. 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 [16].Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. A sustained-release (SR) formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once-daily dosing of metformin. SR products are needed for metformin to prolong its duration of action and to improve patient compliance. The overall objective of this study was to develop matrix sustained-release tablets of metformin using HPMC K 100M by wet granulation method and optimize the formulation using RSM.

MATERIALS AND METHODS

Materials

Metformin HCl was received from Aarti Drugs Pvt.Ltd. India Hydroxy propyl methyl cellulose (HPMC K 15M and K 100M) was a gift sample received from Colorcon Asia Pvt. Ltd., Mumbai, India.

Magnesium stearate, Microcrystalline cellulose (MCC) and PVP K 30 (polyvinyl pyrrolidone K 30) were purchased from S. D. Fine Chem. Labs, (Mumbai, India) and Aerosil 200 were procured from Sai Mirra Inno Pharma, Chennai. All other chemicals/reagents used were of analytical grade.

Preparation of Sustained Release Matrix Tablets: Sustained release Matrix tablet of drug were prepared by wet granulation technique. Table 1 enlists the composition of different trial formulations prepared using varying amounts of HPMCK 100M as release controlling polymer and PVP K 30 as binder along with fixed quantity of aerosil and magnesium stearate as lubricant and glidant . MCC was used as filler. High shear granulation (RMG) was chosen as method of granulation. Dry mix metformin HCl and MCC in RMG for 10 min at low speed 70RPM. Binder solution was prepared by adding Povidone K-30 in water to get a clear solution. The blend of drug and the excipients was wet granulated with binder solution at high speed 140 RPM for 1 min and the granules were dried in FBD at temperature 60^{O}C and airflow 40 with residual moisture content of 1-1.5 % w/w. The granules are then passed through a sieve 16 mesh to get uniform granules. Load sized granules in an octagonal blender with presifted HPMC, and aerosil mix for 5 min at 18 rpm. After completion of blending add sifted Magnesium stearate in an octagonal blender and lubricated for 5 min at 18 rpm. Granules thus obtained were compressed into 850 mg tablets to average hardness of 150-200 N on an sixteen station rotary tablet machine (CIP Machineries Pvt. Ltd., Ah-medabad, India) with 16 x 8 mm caplet tooling with rotational speed of 72 rpm. Prior to compression, granules were evaluated for their flow and compressibility characteristics

Experimental Design: A central composite design (CCD) was employed as per the standard protocol. The amounts of HPMC K 15M (X1) and PVP K 30 (X2) 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. % of drug released in 1 hr (Y1), %of drug released in 3 hrs (Y2) and % of drug released in 10 h ((Y3) were taken as the response variables.

Characterization of granules: The pre-compression parameters of the granules were evaluated before compression of tablet. Precompression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were determined for their micromeritic properties

Evaluation of tablets: The prepared matrix tablets were characterized immediately after preparation for hardness, weight variation, thickness, friability and drug content [14,15]. The weight variation of the tablets was carried out with 20 tablets using an electronic balance (Shimadzu, Japan). Friability was determined using 10 tablets in a Roche friabilator (Pharma Lab, Ahmadabad,India) for 4 minutes at of 25 rpm. For each formulation, the hardness of 10 tablets was also evaluated using a Monsanto hardness tester (Campbell Electronics, India). The thickness of the each 10 tablets was measured with a Vernier Caliper

Drug Release Study: Drug release of each formulation, in triplicate, was determined using the USP Type 2 (Electrolab, TDT06P) where 900 ml of phosphate buffer pH 6.8 were used as dissolution media maintained at 37°C (±0.5°C) at 100 rpm. The release rates from the tablets were conducted in a dissolution medium of phosphate buffer of

pH 6.8 for 1, 3 and 10 hours hrs. 5 ml of aliquot were withdrawn at 1, 3 and 10hrs with replacement of fresh media. Solution samples were analyzed by UV method.

Data analysis and validation of optimization model for matrix tablet: Various response surface methodology (RSM) computations for the current optimization study were performed employing Design Expert software (Design Expert 9.0.1).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:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1^2 X_2 + \beta_7 X_1 X_2^2$$

Here,

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

X_1 and X_2 are the coded levels of the independent variable.

X_1, X_2, X_1^2 and X_2^2 represent the interaction and quadratic terms.

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. Three-dimensional (3D) response surface plots and 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 of the factors on the responses. Seven optimum checkpoints for drug were selected 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.

RESULTS AND DISCUSSION

Characterization of granules: Granules of all the batches were evaluated for different parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The results of study (Table 3**)** showed that granules were free flowing.

Evaluation of tablets: Compressed batches of tablets were evaluated for hardness, weight variation, thickness, friability and drug content. The results for which are shown in table 4. Average weight of tablet was 850mg, hardness was 150 to 200 N, Thickness was around 6mm and friability was below 1%.

Drug Release Study: The results of dissolution studies are demonstrated in table 5.indicates that formulations F1 contains lower concentration of HPMC K100M and PVP K released 82, 93 and 100.1% of drug, after 1, 3 and 10 h respectively and formulations F13 contains higher concentration of HPMC K100M and PVP K released 29.3, 62% and 94.2 % of drug after 1,3 and 10 h respectively. The dissolution profile of metformin tablets containing combinations of a hydrophilic polymer HPMC with PVP K in the different polymer/polymer ratio are shown in fig 1. Indicates that the release rate decreased as the concentration of HPMC K100M and PVP K is increased.

Mathematical Modeling: Mathematical relation-ships generated using MLRA for the studied response variables are expressed as equations.

Y1 (Dissolution 1 Hrs.) = 39.06 – 25.84X_1– 6.38X_2 + 3.32X_1X_2 + 10.63X_1^2 + 0.13X_2^2….(1).

Table 1: Composition of 500 mg Metformin HCl Sustained Release Matrix Tablet

Ingredients	Amount (mg)
Metformin HCl	500
HPMC K 100M	145 to 175
PVP K 30	17 to 34 mg
Magnesium stearate	8
Aerosil	4
MCC PH 101	QS to 850

* QS: quantity sufficient, HPMC K 100M: Hydroxypropyl methyl cellulose of K 100M viscosity grade, PVP K 30: Polyvinyl pyrrolidone of K 30 viscosity grade, MCC: Microcrystalline cellulose

Table 2: Factorial Design Layout

Run	Trial No.	Actual values of variables (mg)	
		Factor X_1 (HPMC)	Factor X_2 (PVP)
1	F1	145.85	26
2	F2	150	20
3	F3	150	32
4	F4	160	17.51
5	F5	160	26
6	F6	160	26
7	F7	160	26
8	F8	160	26
9	F9	160	26
10	F10	160	34.48
11	F11	170	20
12	F12	170	32
13	F13	174.14	26

Table 3: Pre-Compression Parameters

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Bulk density (g/ml)	0.470	0.468	0.440	0.465	0.468	0.480	0.450	0.405	0.448	0.468	0.468	0.490	0.468
Tapped density (g/ml)	0.588	0.571	0.530	0.554	0.600	0.589	0.563	0.482	0.530	0.564	0.557	0.576	0.544
Compressibility index (%)	20.000	18.000	17.000	16.000	22.000	18.500	20.000	16.000	15.500	17.000	16.000	15.000	14.000
Hausner's Ratio	1.250	1.220	1.205	1.190	1.282	1.227	1.250	1.190	1.183	1.205	1.190	1.176	1.163
Angle of Repose	32.34	28.52	24.05	20.07	33.34	28.52	26.11	22.96	21.55	22.28	25.18	24.05	24.8

Table 4: Post-Compression Parameters

Batches	Weight variation	Hardness (N)	Thickness (mm)	Friability (%)
F1	850-852	150-180	6.01-6.05	0.15
F2	849-851	164-192	5.99-6.03	0.18
F3	848-852	182-198	6.02-6.04	0.14
F4	850-852	185-200	5.99-601	0.20
F5	850-853	150-180	604-6.07	0.16
F6	848-856	164-192	6.03-6.05	0.14
F7	850-854	182-198	6.04-6.07	0.15
F8	849-851	185-200	6.01-6.03	0.21
F9	847-851	150-180	5.99-6.02	0.10
F10	850-854	164-192	5.58-6.04	0.20
F1 1	849-851	182-198	6.02-6.04	0.20
F12	847-854	185-200	5.99-6.02	0.15
F13	850-852	160-180	5.58-6.04	0.20

Table 5: *In Vitro* Drug Release Data of Factorial Design Batches

Batches	Factor 1	Factor 2	Response Y_1	Response Y_2	Response Y_3
Batch No.	HPMC	PVP K 30	1 Hrs	3 Hrs	10 Hrs
F1	145.85	26	82	93	100.1
F2	150	20	78	88	99.9
F3	150	32	70.2	90	100
F4	160	17.51	45.8	85	99.96
F5	160	26	40.1	74	94.2
F6	160	26	39.3	72	93.8
F7	160	26	39.2	69	90.2
F8	160	26	38.8	67.2	95.6
F9	160	26	37.9	67	93.5
F10	160	34.48	32	64	91.6
F11	170	20	29.3	62	94.2
F12	170	32	24.2	60	93.5
F13	174.14	26	19.4	55	90.2

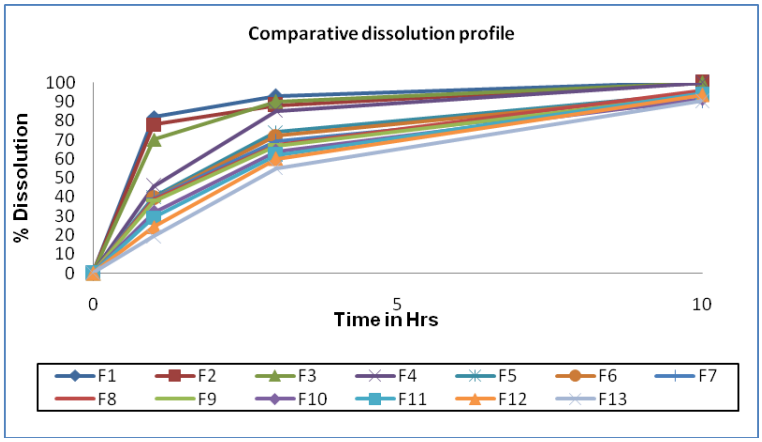

Fig.1: *In Vitro* Drug Release comparison of Factorial Design Batches

Table 6: Analysis of Variance (ANOVA) for All Three Responses

	Release in 1 Hr		**Release in 3 Hrs**		**Release in 10 Hrs**	
Source	**F Value**	**p-value**	**F Value**	**p-value**	**F Value**	**p-value**
Model	99.35	0.0001	10.93	0.0033	10.69	0.0036
X_1	407.66	0.0001	22.84	0.0020	25.67	0.0015
X_2	24.89	0.0016	3.24	0.1148	3.02	0.1256
X_1X_2	3.38	0.1088	1.714E-003	0.9681	0.41	0.5424
X_1^2	59.96	0.0001	15.89	0.0053	6.00	0.0442
X_2^2	8.464E-003	0.9293	16.40	0.0049	20.83	0.0026

*X1: HPMC K 100M, X2: PVP K 30

Table 7. Selected of Goal for Optimum Formulation.

A:HPMC	**Range**	**150-170**
B:Povidone	Range	20-32
Dissolution 1 Hrs	is in range	20-40
Dissolution 03 Hrs	is in range	45-65
Dissolution 10 Hrs	minimize	NLT 85

Table 8. Suggested Batches by the Software as Optimized Batch.

Number	**HPMC**	**Povidone**	**Dissolution 1 Hrs**	**Dissolution 03 Hrs**	**Dissolution 10 Hrs**	**Desirability**	
G1	170.000	27.622	26.971	60.395	91.038	0.600	Selected
G2	169.998	27.694	27.045	60.410	91.038	0.600	

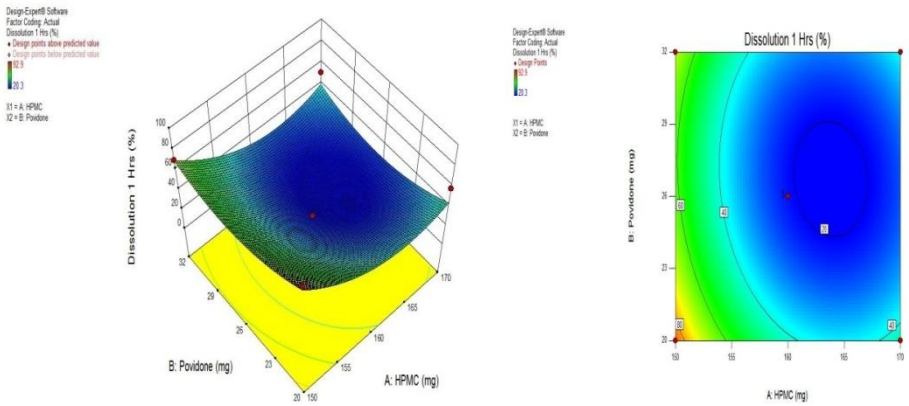

Fig 2: Two dimensional contour plot (a); three dimensional (3D) response surface plots for Y_1 (% drug release in 1 Hr (b)

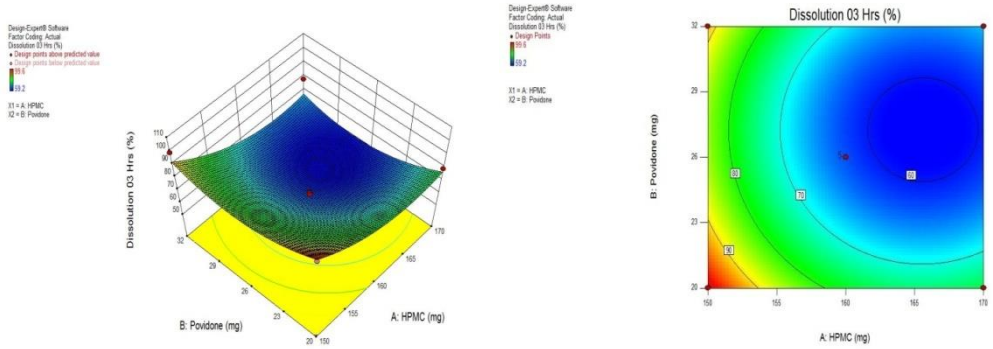

Fig 3. Two dimensional contour plot (a); three dimensional (3D) response surface plots for Y_2 (% drug release in 3 Hrs (b)

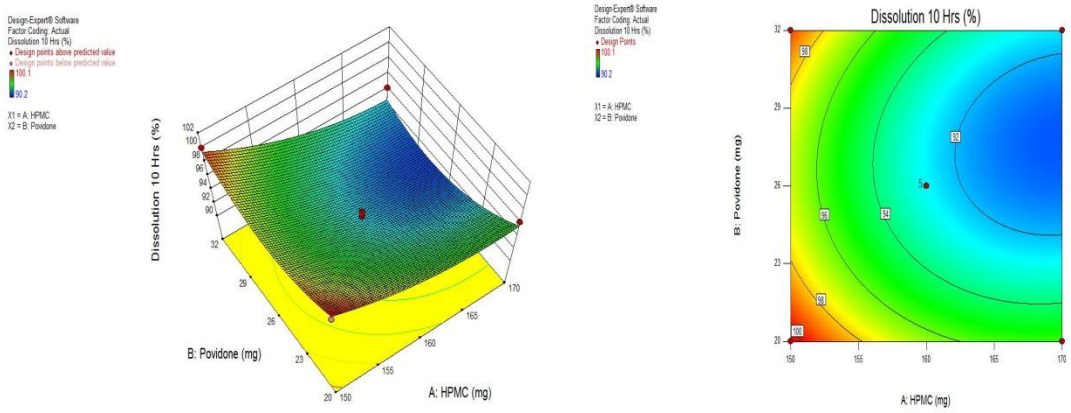

Fig 4: Two dimensional contour plot (a); three dimensional (3D) response surface plots for Y_3 (% drug release in 10 Hrs (b)

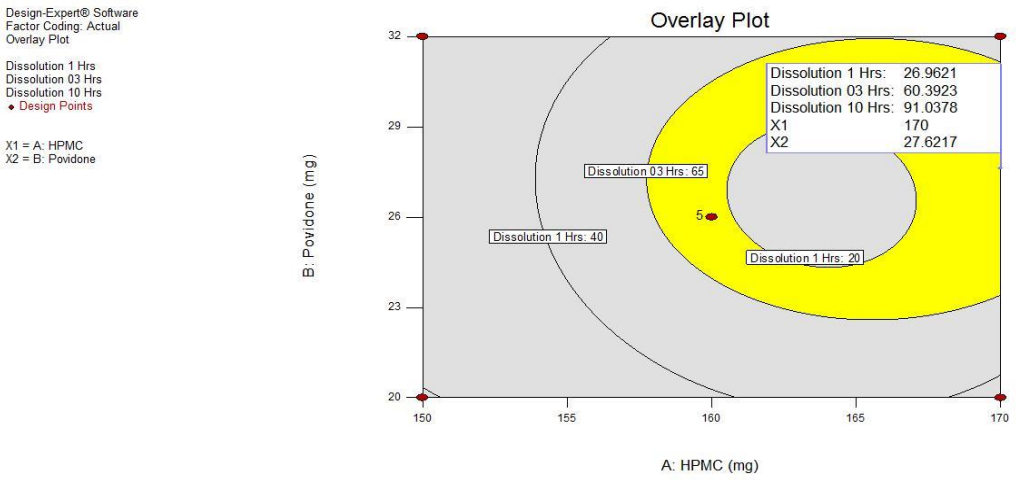

Fig 5: Overlay Plot from Software for Maximum Desirability.

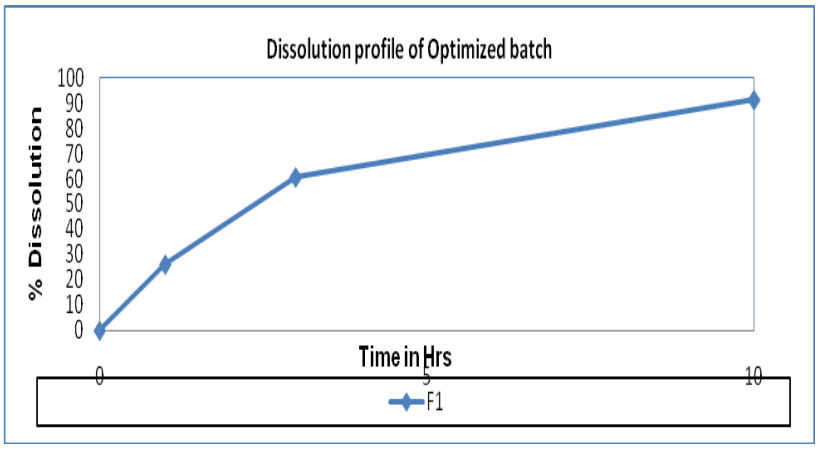

Fig 5(a): Dissolution Profile of G1

Y_2 (Dissolution 3 Hrs.) = 62.16 – $12.24X_1$– $4.61X_2$ –$0.15X_1X_2$ + $10.95X_1^2$ + $11.13X_2^2$…. (2) Y_3 (Dissolution 10 Hrs.) = 92.66 – $2.94X_1$– $1.01X_2$ – $0.52X_1X_2$ + $1.52X_1^2$ + $2.84X_2^2$…. (3). for estimation of significance of the model, the analysis of variance (ANOVA) was determined as per the provision of Design Expert Software (Table 6). 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 , it can be concluded that for all responses, the cross-product contribution(X1X2)and quadratic contributions (X_2^2, X_2) of the model was not significant but the linear contribution(X1, X_1^2) for all responses is significant ($p < 0.05$).

Selection of Optimized Batch: Batches shown in table 8 were formulated and % drug release was checked. G1 % Drug release was close to the value by software. Hence it was considered as the optimized batch for further evaluation. The best batch was selected after application of optimization technique. The desired release profile was matched with respect to predicted release by software.

CONCLUSION

Sustain release matrix tablets were prepared by wet granulation method using hydrophilic polymers like HPMC and PVP K 30 as binder. After application of central composite design (CCD) optimization technique, it was found that the concentration of HPMC K 100M and PVP K 30 had significant effect on dependent variables like % drug release in 1, 3 and 10 hours. The optimized batch was taken as G1 as it showed desirable drug release profile. Result from experiment data demonstrated the successful development of sustained release matrix tablet using HPMC K 100 M and PVP K 30. Both the polymer and binder plays major role for the sustained release of drug. *In-vitro* study showed sustained release of drug, which reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional tablets.

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