Research Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

FORMULATION AND EVALUATION OF SINTERED HIGH DENSITY MATRIX TABLETS OF METFORMIN HCL FOR THE TREATMENT OF TYPE-2 DIABETES MELLITUS

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ABSTRACT

The current paper was an attempt to design Sintered high density matrix tablets of Metformin hydrochloride to evaluate for increase bioavailability by increasing gastric residence time and prolongs drug absorption in the upper gastrointestinal tract and permits once daily dosing in patient with Type 2 Diabetes Mellitus with enhance patient compliance. Metformin hydrochloride containing high density matrix tablets were formulated by using central composite design having 2 independent variables at 3 levels. Independent variables were total amount of hydrophilic gel forming polymers (Hydroxyl Propyl Methyl Cellulose K15M, Carbopol 934P and Guar gum) X_1 and polymer-polymer ratio X_2. The prepared formulations were evaluated for various physicochemical properties and *in vitro* drug release characteristics. Statistical optimization carried out for various responses like 'n' of peppas equation, 'K' of zero order and 'n' of higuchi equation and $T_{80\%}$. Optimized formulation was found to provide more sustained release of drug. Release kinetics of optimized formulation followed Higuchi model with anomalous non -fickian diffusion. Hence optimized sintered high density matrix tablet could be a promising delivery system for Metformin hydrochloride with sustained release action and improved drug availability.

KEYWORDS

Sintered high density Matrix Tablet, Central composite design, Statistical optimization.

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INTRODUCTION

Diabetes mellitus, simply referred to as diabetes, is a group of metabolic diseases in which a person has high level of blood sugar. The possible causative reason maybe that the body does not produce enough insulin, or cells do not respond to the insulin that is produced by the pancreatic cells[1].

Metformin hydrochloride, a biguanide, is an orally active antidiabetic agent. It is effectively used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). Unlike sulfonylurea, Metformin usually does not produce hypoglycemia in diabetic and non-diabetic individuals. So, it is more appropriately referred to as antihyperglycemic agent and found to be well-tolerated and safe on chronic use. On oral administration, it is absorbed through upper part of GI tract and absolute bioavailability of metformin is approximately 50- 60%. Metformin negligibly binds to plasma proteins.[2] It is excreted unchanged in the urine and does not undergo hepatic metabolism. It has a plasma elimination half-life of 3 hours. Its daily oral dose is 0.5 to 3 g/day in divided doses.[3]

Response surface methodology (RSM) is one of the popular methods in the development and optimization of drug delivery systems. Based on the principles of design of experiments (DOE), the methodology involves the use of various types of experimental designs, generation of polynomial mathematical relationships and mapping of the response over the experimental domain to select the optimum formulation[4–6]. Central composite design (CCD) having 2- independent variables at 3-level is one of the RSM designs available for statistical optimization of the formulations. It requires fewer experimental runs and less time and thus provides a far more effective and cost-effective technique than the conventional processes of formulating and optimization of dosage forms.[7] The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of drug release. [9]

The current study aimed at developing and optimizing a sintered high density drug delivery system form of Metformin HCl using Central composite design. The Independent variables for the present study were: Total amount of polymer (X_1) and % of guar gum (X_2). The dependent variables studied were 'n' of Higuchi equation (Y_1), 'n' of peppas equation (Y_2), 'K' of zero order equation (Y_3) and $T_{80\%}$(Y_4). A sintered high density matrix tablet was planned for Metformin HCl as such a system when administered would remain in the gastric fluids for a prolonged period of time and the drug would be available in the dissolved form at the main site of its absorption i.e., proximal small intestines.

MATERIAL AND METHODS

Materials

Metformin HCl from Alembic Pvt. Ltd. Baroda, Gujarat and HPMC K15M Cipla pharmaceuticals Ltd., Mumbai were received as gift samples. Carbopol 934P, Gaur gums were procured commercially from National Scientific Products, Mumbai. Tio_2, talc and Magnesium stearate were procured from Loba Chemie, Mumbai. All other chemicals used were of analytical reagent grade.

Preparation of sintered high density matrix tablet

Metformin hydrochloride, HPMC K 15M, Carbopol 934p, Gaur gum, TiO_2 and talc were weighed accurately according to formula (Table-2). Then all above materials were passed through sieve # 44 for uniformity. The drug was mixed with all above excipients geometrically for 10 min to achieve homogeneous blend. Then the Magnesium stearate was mixed with above homogeneous blend. Tablet ware prepared by direct compression technique using 8 station rotary tablet press and formulated dosage forms were sintered with by exposing for 1 hour with acetone.

Experimental design

Central composite statistical screening design was used to optimize and evaluate main effects, interaction effects and quadratic effects of the formulation ingredients on the in vitro release of formulations. A 2-factor, 3-level design(Table No.1) used is suitable for exploring quadratic response surfaces and constructing second order polynomial models with Design Expert (Version 8.0.6., Stat-Ease Inc., Minneapolis, MN).

This design is characterized by set of points lying at 4-edges and 4-midpoint of each edge of a square and 1-center point replicates (n=3). For central composite designs having two factors (where, α=1), Suitable models include linear, second order and quadratic models.

The best fitting mathematical model was selected based on the comparisons of several statistical

parameters including the coefficient of variation (CV), the multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2), and the predicted residual sum of square (PRESS), analyzed by Design-Expert® software.[8]

Tablet assay and physical evaluation

The tablets were assayed for drug content, and the samples were analyzed spectrophotometrically (Shimadzu 1700, Shimadzu Corp.) at 233 nm. Tablets were also evaluated for the hardness (n =10) (Monsanto hardness tester), friability (n = 20) (Roche Friabilator, 100 rotations in 4 minutes), weight variation (n = 20) and thickness and diameter (n = 10) (Vernier caliper, Hanna instruments).

***In vitro* drug release studies**

Dissolution studies were performed using the USP dissolution testing apparatus II, (paddle type) (Electrolab dissolution tester, Electrolab, India) at 37 °C ± 0.5 °C and 50 rpm using 900 ml simulated gastric fluid (pH-1.2) as the dissolution media. A 5 ml aliquot of sample was withdrawn at regular time intervals, filtered and assayed spectrophoto metrically at 233 nm. The cumulative % drug release was calculated for the formulations.

Fourier Transform Infrared Spectroscopy (FTIR)

Drug polymer compatibility studies were carried out using FTIR. Drug and excipents were dried at 40 ºC for 2 h, and their FT-IR transmission spectra were obtained. The study was carried out on pure drug and its physical mixture with the selected polymers and excipients under study.

Optimization data analysis and model-validation

ANOVA provision available in the software was used to establish the statistical validation of the polynomial equations generated by Design Expert®. A total of 11 runs were generated by Central Composite Design. All the responses observed were simultaneously fitted to first order, second order and quadratic-models and were evaluated in terms of statistically significant coefficients and R^2 values. Three dimensional response surface plots were provided by the Design Expert® software, where by intensive grid search performed over the whole experimental region, one optimum checkpoint formulation was selected to validate the chosen experimental domain and polynomial equations.

Stability studies of the optimized formulations:

The stability studies were carried out on the most satisfactory formulations as per ICH guidelines Q1C. The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at 30 ± 2 °C/60 ± 5 % RH and 40 ± 2 °C/75 ± 5 % RH for 3 months.

RESULTS AND DISCUSSION

% Drug content and physical evaluation

% Drug content of the formulations was assayed spectrophotometrically at 233 nm. The drug content of the developed formulations was within the acceptance value provided by USPNF-2007. Weight Variation test complied the official requirement as per IP-2007 and USPNF-2007. Hardness was between 3.5 and 4.3 kg/cm^2, thickness between 6.50 and 8.37 mm, friability ranged from 0.20% and 0.39%. and diameter was between 13.02 and 13.07 mm.

Mechanism of drug release studies

To study the release mechanism, various dissolution models were applied to the *In vitro* release profiles of the 11 different formulations (F1-F9 and triplication of F5) (Figure No.1). The kinetic models included zero order, Higuchi, Korsmeyer-Peppas model (Table No.3).

The combinations of polymer swelling, drug dissolution and matrix erosion determine the drug release from swellable matrices, either on a macroscopic or on a molecular level. As dissolution progresses, the gradual swelling of the outer layer creates proportionately new areas for drug diffusion. Since the matrix is hydrophilic, the permeation of dissolution medium takes place in the matrix and initiates dissolution of drug from the inner layers. The dissolution rate is counter-balanced by gel formation of the matrix, which takes place simultaneously. The balance between the swelling and gelling characteristics of the matrix system is critical in maintaining the desire drug release rate [21].

Fitting of data to the model

A two-factor, three-level central composite statistical experimental design as the response surface method

requires 11 experiments. The independent variables and the responses for all 11 experimental runs are given in Table- 3. Eleven batches showed 'n' of Higuchi eq. (Y_1) for all batches was 19.186–32.314. The ranges of other responses, (Y_2 'n' of peppas eq.) were 0.440-0.626, Y_3 ('K' of zero order eq.) were 6.547–12.452 and Y_4 ($T_{80\%}$), were 6.225–16.441 h respectively. All the responses observed for 11 formulations prepared were simultaneously fitted to first order, second order and quadratic models using Design Expert® and the comparative values of R^2 and S.D are given in Table- 4, along with the regression equation generated for each response. Responses Y_1, Y_2. Y_3 and Y_4 were suggested by Design Expert to follow quadratic, second order, quadratic and second order but by manual selection of terms A,B, AB, A^2 and B^2, they were found to follow quadratic, linear, quadratic and second order model, respectively. Only statistically significant ($p < 0.05$) coefficients are included in the equations. A positive value represents an effect that favors the optimization, while a negative value indicates an inverse relationship between the factor and the response. It is evident that the total amount of polymers (A) and % of guar gum (B) have negative effects on the responses 'n' of Higuchi Equation (Y_1) and 'K' of Zero order Equation (Y_3) as well as they have positive effects on the responses 'n' of Peppas Equation (Y_2) and $T_{80\%}$ (Y_4)

Coefficients with higher order terms or more than one factor term in the regression equation represent quadratic relationships or interaction terms, respectively. It also shows that the relationship between responses and factors is not always linear. Used at different levels in a formulation or when more than one factors are changed simultaneously, a factor can produce different degree of response. The interaction effect of total amount of polymer (A) was seen with % of Guar gum (B) for response 'n' of Higuchi Equation (Y_1) and $T_{80\%}$ (Y_4). Total amount of polymer (A) also showed positive quadratic effect on response $T_{80\%}$ (Y_4). % of Guar gum (B) showed positive quadratic effect on response 'n' of Higuchi Equation (Y_1) and 'K' of Zero order Equation (Y_3). % of Guar gum (B) also showed negative quadratic effect on response 'n' of Peppas Equation (Y_2).

Standardized main effects and reliability of the models

Standardized Main Effects (SME) (presented in Table -5) was calculated by dividing the main effects with the standard error of the main effects.[10] Only statistically significant ($p < 0.05$) values are given. The larger SME values of A and B suggested the almost equal importance of total amount of polymer and % of Guar gum on drug release. R^2-value signifies the percentage of variability in responses that are fitted to the models. In the present study, the high R^2-value of >99% represents the reliability of the design. Additionally, the p-values of lack of fit were greater than 0.05.

Contour plots and response surface analysis

Two-dimensional contour plots and three-dimensional response surface plots are presented in Figures. 2 - 5, which are very useful to study the interaction effects of the factors on the responses. These types of plots show the effects of two factors on the response at a time.

In all the presented figures, it was concluded that as (1) the Total amount of polymer (A) and/or % of Guar gum in polymer mixture (B) increase/s, the value of 'n' of Higuchi is decreased; (2) The Total amount of polymer (A) and/or % of Guar gum in polymer mixture (B) increase/s, the value of 'n'of Peppas is increased; (3) The Total amount of polymer (A) and/or % of Guar gum in polymer mixture (B) increase/s, the value of 'K' of Zero order is decreased; (4) The Total amount of polymer (A) and/or % of Guar gum in polymer mixture (B) increase/s, the value of $T_{80\%}$ is increased.

urther strengthened the reliability of the models

Optimization

The optimum formulation was selected based on the criteria of attaining the maximum 'n' of peppas equation for tablet formulations and applying constraints on 'n' of Higuchi Eq. (Y_1) (target to 23.83), 'K' of Zero Order Eq. (Y_3) (target to 8.333) and $T_{80\%}$ (Y_4) (target to 9.6 h). Upon 'trading off' various response variables and comprehensive evaluation of feasibility search and exhaustive grid search, the formulation composition with polymer levels of Total amount of polymer (A), 231.94 mg, %

of Guar gum in polymer mixture (B), 16.16 %, was found to fulfill the maximum requisite of an optimum formulation because of better correlation of the theoretically obtained values of Y_1 (24.5349), Y_2 (0.561394), Y_3 (8.333) and Y_4 (9.83615) with the standardized target values with the desirability of 0.96019. The optimized formulation was found to release about 89.276% drug in sustained release manner for 12 h. Study of the in vitro release profiles in simulated gastric fluid (pH 1.2) of the formulations showed release of 23.832% during 1 h followed by a gradual release phase for about 12 h. The release pattern of the optimized formulation was best fitted to both the zero order (K: 8.4768) and Korsmeyer-Peppas kinetics (n = 0.569). These values suggested the release to be primarily by non-Fickian diffusion.

Validation of RSM results

For the optimized checkpoint formulation, the results of the physical evaluation and tablet assay were found to be within limits (Table No.6). Table No.7 shows the composition of optimum checkpoint formulations, their predicted and experimental values of all the response variables, and the percentage error.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the drug, excipients and the optimized formulation were recorded in range of 4000 – 400 cm cm^{-1}. In the optimized formulation, the presence of all the characteristic peaks of the LP indicates lack of any strong interaction between the drug and the excipients.

Stability studies

Stability studies of the optimized formulation under accelerated storage conditions as per ICH guidelines did not reveal any degradation of the drug and changes in the in vitro release profiles of the optimized formulation after storage for 3 months were statistically insignificant as compared to the refrigeration control sample (ANOVA, $p > 0.05$).

Table No.1: Factors in Central Composite Design

Name of the Factor	Coded values	Level		
		-1	0	1
Total amount of polymer (in mg)	**A**	100	200	300
% Guargum (w/w of the total content of polymer)	**B**	0	20	40

Table No.2: Composition of Sintered High density matrix tablets of Metformin HCl

Formulations	Metformin HCl (mg)	HPMC K15M (mg)	Carbopol 934P (mg)	Gaur gum (mg)	TiO_2 (mg)	Magnesium stearate (mg)	Talc (mg)
F1	500	60	40	0	90	22	22
F2	500	120	80	0	105	26	26
F3	500	180	120	0	120	29	29
F4	500	40	40	20	90	22	22
F5	500	80	80	40	105	26	26
F6	500	120	120	60	120	29	29
F7	500	20	40	40	90	22	22
F8	500	40	80	80	105	26	26
F9	500	60	120	120	120	29	29

Table No.3: Analysis of release mechanism of various Formulations of Metformin HCl

Formulation Code	A: Total amount of polymer (mg)	B: % of Gaur gum	Y_1: 'n' of higuchi eq.	Y_2: 'n' of peppas eq.	Y_3: 'K' of zero order	Y_4: $T_{80\%}$ (h)
F1	100	0	32.314	0.440	12.452	6.225
F2	200	0	29.237	0.488	10.967	6.864
F3	300	0	26.044	0.526	8.802	8.962
F4	100	20	28.642	0.497	9.653	7.553
F5-T1	200	40	24.411	0.586	8.284	10.131
F5-T2	200	40	25.611	0.526	8.720	9.223
F5-T3	200	40	25.132	0.556	8.496	9.467
F6	300	60	21.427	0.605	7.295	12.744
F7	100	40	27.346	0.511	9.227	8.195
F8	200	80	23.222	0.563	7.806	11.589
F9	300	120	19.186	0.626	6.547	16.441

Table No.4: Summary of results of regression analysis for responses Y_1, Y_2, Y_3 and Y_4

Model Summary Statistics							
Source	**Std. Dev.**	**p-value**	**R^2**	**Adjusted R^2**	**Predicted R^2**	**PRESS**	**Model Suggestion**
Y_1: 'n' of Higuchi Equation							
Linear	0.8235	< 0.0001	0.960	0.950	0.919	11.114	-
Second order	0.8047	0.2786	0.967	0.953	0.885	15.739	-
Quadratic	0.3830	0.0105	0.995	0.989	0.990	1.381	Suggested
Y_2: 'n' of Peppas Equation							
Linear	0.0230	0.0004	0.860	0.825	0.765	0.007	Suggested
Second order	0.0240	0.5631	0.867	0.810	0.648	0.011	-
Quadratic	0.0193	0.1468	0.938	0.877	0.867	0.004	-
Y_3: 'K' of Zero order Equation							
Linear	0.5502	< 0.0001	0.912	0.890	0.821	4.901	-
Second order	0.5588	0.4140	0.920	0.886	0.727	7.491	-
Quadratic	0.2749	0.0124	0.986	0.972	0.885	3.150	Suggested
Y_4: $T_{80\%}$							
Linear	1.0696	0.0001	0.894	0.867	0.703	25.606	-
Second order	0.4731	0.0006	0.982	0.974	0.957	3.738	Suggested
Quadratic	0.3146	0.0561	0.994	0.989	0.985	1.284	-
Y_1 = **$35.468333 - 0.03135*A - 0.219448*B - 0.000236*AB + 0.0029506*B^2$**							
Y_2 = **$0.3815333 + 0.0005157*A + 0.0048615*B - 0.0000701*B^2$**							
Y_3 = **$13.63630 - 0.01448*A - 0.15306*B + 0.0020264*B^2$**							
Y_4 = **$6.716431 + 0.009423*A + 0.019605*B + 0.000689*AB + 0.000057*A^2$**							

Table No5: Standardized main effects of the factors on the responses

Factor	Standardized main effects (SME)			
	Y_1: 'n' of Higuchi Equation	**Y_2: 'n' of Peppas Equation**	**Y_3: 'K' of Zero order Equation**	**Y_4: $T_{80\%}$**
Intercept	160.1317	71.92727	63.30738	62.0803
A-Total amount of Polymer	-25.2626	7.26338	-11.8207	19.3932
B-% of Guar gum	-20.8228	5.791549	-11.7565	16.9943
AB	-2.70309	-	-	8.0914
A^2	-	-	-	2.7410
B^2	5.57487	-2.67619	4.463106	-
R^2	0.99	0.931	0.9771	0.9919
p-value of lack of fit	1.0000	0.9925	0.3353	0.8677

Table No.6: Evaluation of various physicochemical parameters of optimized check point formulations of Metformin HCl

Physicochemical Parameters	**Results**
Bulk density(g/cm^3)	1.156
Tapped density(g/cm^3)	1.397
Hausner Ratio	1.2084
Compressibility index	17.251
Angle of repose (θ)	25.73 ± 1.34
Hardness* (Kg/cm^2) Mean ± S.D.	3.7 ± 0.1
% Friability	0.33
% Weight Variation** (±S.D.)	± 2.4
% Drug Content* Mean ± S.D.	100.73 ± 2.16
Diameter*(in mm) Mean ± S.D.	13.57 ± 0.04
Thickness* (in mm) Mean ± S.D.	7.42 ± 0.03

Table No.7: Predicted and average experimental values of response variables and % Prediction error of various optimized check point formulations of Metformin HCl

Response variable	Experimental value	Predicted value	% Prediction error
Y_1: **'n' of Higuchi Eq.**	25.01	24.534	-1.93
Y_2: **'n' of peppas equation**	0.569	0.561	-1.35
Y_3: **'K' of Zero Order Eq.**	8.4768	8.333	-1.72
Y_4: **$T_{80\%}$**	9.778	9.83	0.59

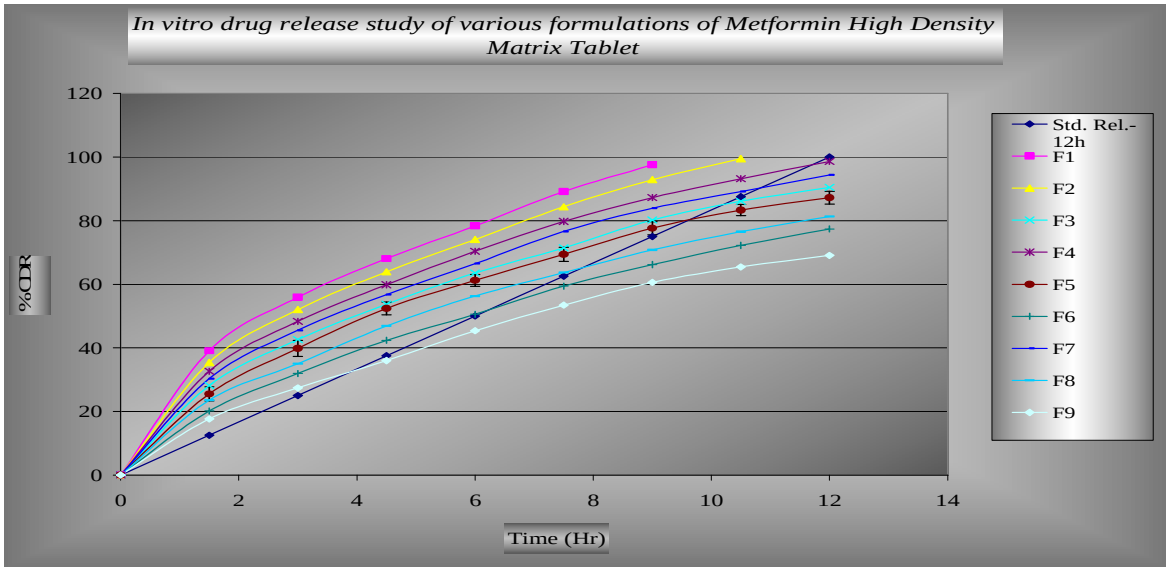

Figure No.1: *In vitro* drug release study of various formulation of Metformin HCL High Density Matrix Tablet

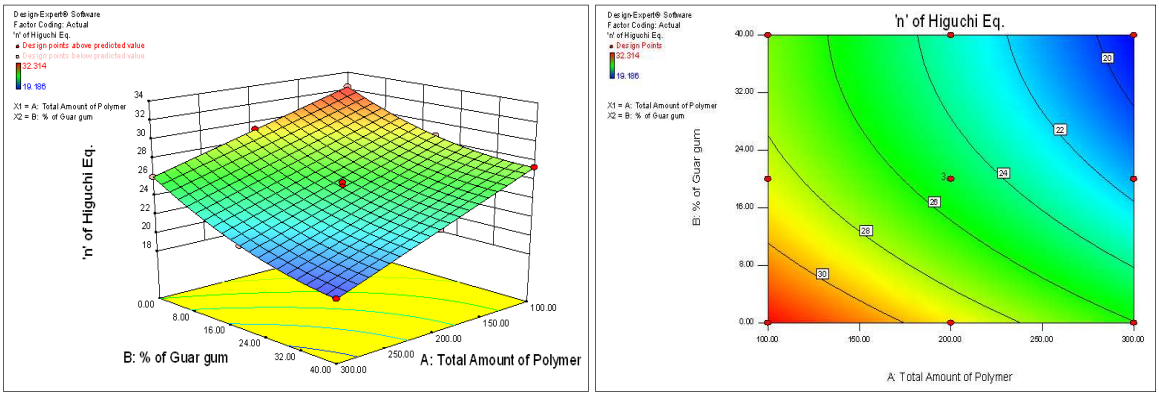

Figure No.2: 3D Surface plot and Contour plot of Predicted values of 'n' of Higuchi Equation for various formulations of Metformin HCl

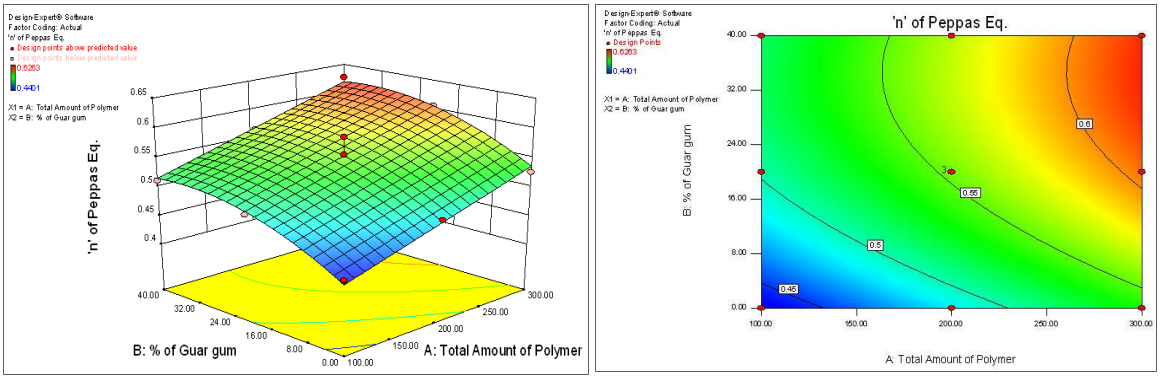

Figure No.3: 3D Surface plot and Contour plot of Predicted values of 'n' of Peppas Equation for various formulations of Metformin HCl

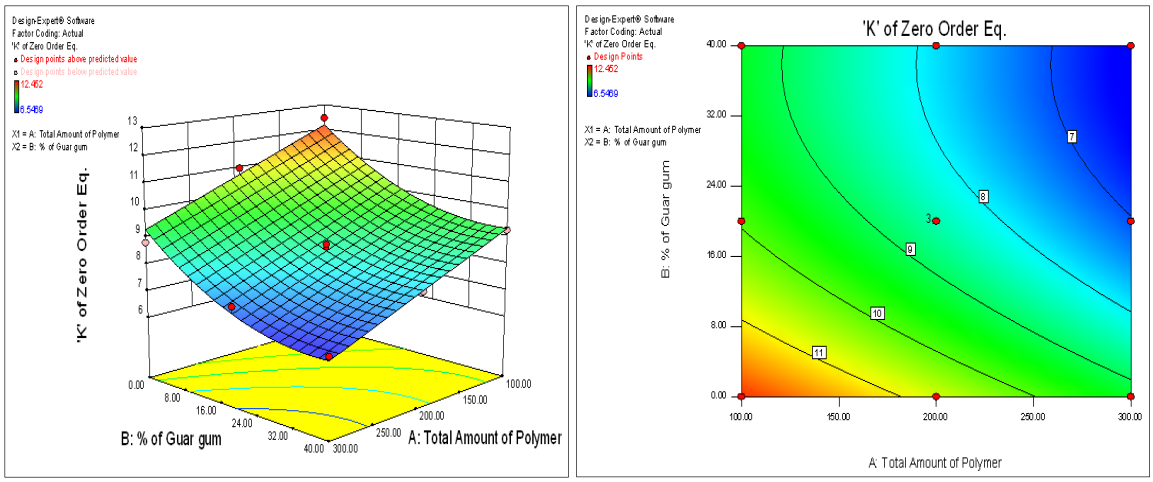

Figure No.4: 3D Surface plot and Contour plot of Predicted values of 'K' of Zero order Equation for various formulations of Metformin HCl

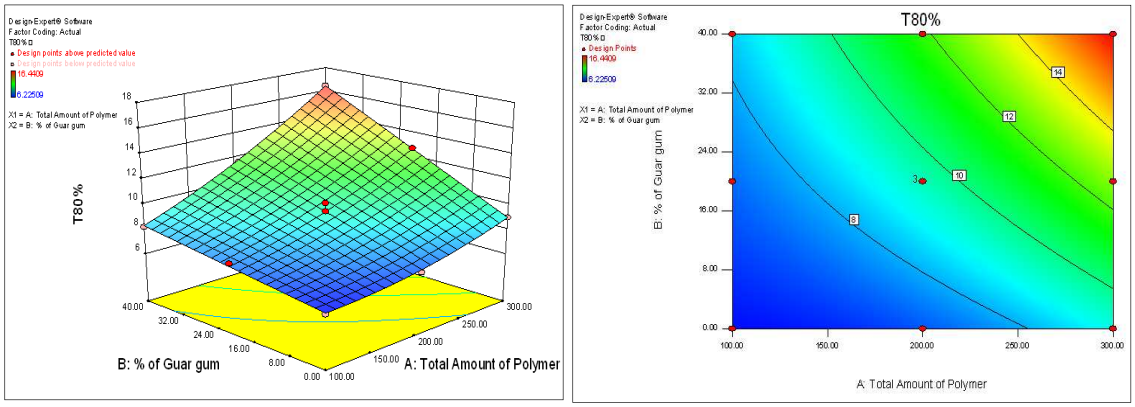

Figure No.5: 3D Surface plot and Contour plot of Predicted values of $T_{80\%}$ Equation Equation for various formulations of Metformin HCL

CONCLUSION

Sintered high density matrix tablets of Metformin HCl with HPMC K15M, Carbopol 934P and Guar gum were prepared and optimized using central composite statistical design. The quantitative effect of these factors at different levels on the release rate could be predicted by using polynomial equations. Linearity observed between the actual and predicted values of the response variables suggested the prognostic ability of the RSM design. The quadratic response surface methodology studied for the release rate helped in understanding the interaction effects between the combination and ratio of the two polymers. FTIR studies combined with the stability study of the optimized formulation proved the integrity of the developed floating matrix tablets. Thus, high degree of prediction obtained using RSM is quite efficient in optimizing drug delivery systems that exhibit non-linearity in responses. *In vitro* drug release studies were closely met to standard zero order release and exhibited the controlled release profile within desired time duration.

ACKNOWLEDGEMENT

The authors are sincerely thanks to the Narasaraopet Institute of Pharmaceutical Sciences, Department of Pharmaceutical Sciences, Jodhpur National University, Narnadi, Jhanwar Road, Jodhpur (Rajasthan), India for providing the facilities to complete this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Ishab Kumar. *et al.*, Formulation and evaluation of sintered high density matrix tablets of metformin hcl for the treatment of type-2 diabetes mellitus, *International Journal of Research in Pharmaceutical and Nano Sciences*, 2(5), 2013, 602-611.