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FORMULATION AND EVALUATION OF FLOATING MATRIX TABLETS OF METFORMIN HCl FOR THE TREATMENT OF TYPE-2 DIABETES MELLITUS

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ABSTRACT: Floating matrix tablets of Metformin hydrochloride were developed and evaluated to increase bioavailability by increasing gastric residence time and sustained release of drug in the upper part of gastrointestinal tract thereby diminishing side effects and enhanced patient compliance. The tablets were formulated by using central composite design having two independent variables at three levels. Independent variables were total amount of hydrophilic gel forming polymers (Hydroxyl Propyl Methyl Cellulose K15M and Carbopol 934P) X_1 and polymer-polymer ratio X_2. The prepared formulations were evaluated for various physicochemical, buoyant and *in-vitro* drug release characteristics. All formulations possessed good floating properties with total floating time more than 12 hours. 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 float for longer duration and provided more sustained release of the drug. Release kinetics of optimized formulation followed Higuchi model with anomalous non -fickian diffusion. Hence Optimized floating matrix tablet could be a promising delivery system for Metformin hydrochloride with sustained release action and improved drug availability.

INTRODUCTION: Diabetes mellitus is a metabolic disease characterized by high blood glucose level resulting from defects in insulin secretion, insulin action or both [1]. It is a chronic disorder that affects the metabolism of carbohydrates, fats, proteins and electrolytes in the body, leading to severe complications which are classified into acute, sub-acute and chronic [2].

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Acute complications include diabetic ketoacidosis, hyperosmolar and hyperglycaemic non-ketotic syndrome [3] while sub-acute complications include thirst, polyuria, and lack of energy, visual blurriness and weight loss [4].

Chronic hyperglycemia causes glycation of body proteins which in turn leads to complications that may affect the eyes, kidneys, nerves and arteries [5].

On the basis of etiology and clinical presentation, diabetes mellitus is classified into two types. Type 1, known as insulin-dependent diabetes mellitus (IDDM) is caused by immunological destruction of pancreatic β cells resulting in insulin deficiency [6].

Type 2, also known as non-insulin-dependent diabetes mellitus (NIDDM) is characterized by both impaired insulin secretion and insulin resistance, which is often associated with obesity and hereditary disposition [7].

The drug chosen for the present investigation, Metformin hydrochloride, a biguanide, is an orally active antidiabetic agent. It is effectively used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). 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 [8]. It has a plasma elimination half-life of 3 hours. Its daily oral dose is 0.5 to 3 g/day in divided doses [9].

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 [10–12]. Central composite design (CCD) having 2- independent variables at 3-level is one of the RSM designs available for statistical optimization of the formulations [13].

The current study aimed at developing and optimizing a floating 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 Carbopol 934P (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).

MATERIALS 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 was procured commercially from Loba Chem Pvt. Ltd., Mumbai. Citric acid was procured from S.D. Fine Chem. Ltd., Mumbai. Sodium bicarbonate, talc and Magnesium stearate were procured from Loba Chemie, Mumbai. All other chemicals used were of analytical reagent grade.

Preparation of Floating tablets: Metformin hydrochloride, HPMC K 15M, Carbopol 934P, sodium bicarbonate, citric acid and talc were weighed accurately according to formula (**Table 1**). Then all of the 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.

TABLE 1: COMPOSITION OF FLOATING MATRIX TABLETS OF METFORMIN HCl

Formulations	Metformin HCl (mg)	HPMC K15M (mg)	Carbopol 934P (mg)	Sodium Bicarbonate (mg)	Citric Acid (mg)	Magnesium Stearate (mg)	Talc (mg)
F1	500	100	-	72	18	22	22
F2	500	200	-	84	21	26	26
F3	500	300	-	96	24	29	29
F4	500	80	20	72	18	22	22
F5	500	160	40	84	21	26	26
F6	500	240	60	96	24	29	29
F7	500	60	40	72	18	22	22
F8	500	120	80	84	21	26	26
F9	500	180	120	96	24	29	29

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 the drug. A 2-factor, 3-level design 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. Linear model:

$$Y = \beta_0 + \beta_1 A + \beta_2 B$$

Second order (2 factors interaction) model:

$$Y = \beta_0 + \beta_1 A + \beta_2 B + \beta_{12} AB$$

Quadratic model:

$$Y = \beta_0 + \beta_1 A + \beta_2 B + \beta_{12} AB + \beta_{11} A^2 + \beta_{22} B^2$$

Where Y is the measured response associated with each factor level combination; β_0 is an intercept; β_1 to β_{22} are regression coefficients computed from the observed experimental values of Y from experimental runs; and A, B and C are the coded levels of independent variables. The terms AB, A^2 and B^2 represent the interaction and quadratic terms, respectively [14].

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).

Floating or Buoyancy Test: The buoyancy of the tablets was studied in USP type II dissolution apparatus at 37 ± 0.5˚C in 900ml of simulated gastric fluid at pH 1.2.The time of duration of floatation was observed visually.

***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 spectrophotometrically 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 excipients were dried at 40ºC for 2 h, and their FT-IR transmission spectra were obtained using a NICOLET iS10 spectrophotometer (Thermo scientific, MA).

Optimization data analysis and model-validation: ANOVA 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. The optimized checkpoint formulation was prepared and evaluated for various response properties.

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 and the acceptance value provided by USPNF-2007. Weight Variation test complied the official requirement as per IP-2007 and USPNF-2007. Hardness was between 3.8 and 4.4 kg/cm^2, thickness between 6.15 and 8.32 mm and friability ranged from 0.18% and 0.39%. Diameter was between 13.51 and 13.54 mm, thickness was between 6.15 and 8.32 mm and floating lag time was between 10 and 18 sec.

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 1**). The kinetic models included zero order, Higuchi, Korsmeyer's-Peppas model (**Table 2**). 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 desired drug release rate [13].

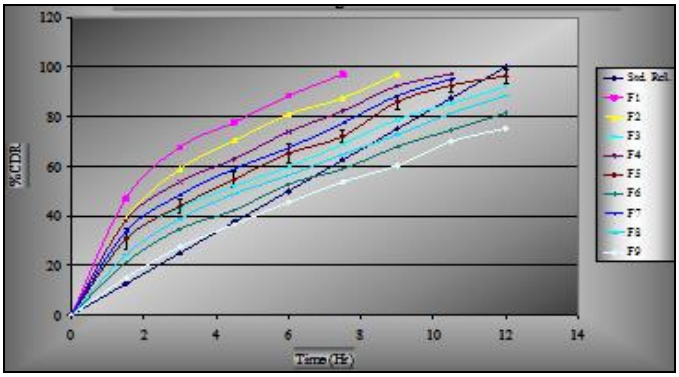


FIGURE 1: *IN-VITRO* DRUG RELEASE STUDY OF VARIOUS FORMULATION OF METFORMIN HCl FLOATING MATRIX TABLET

TABLE 2: ANALYSIS OF RELEASE MECHANISM OF VARIOUS FORMULATIONS OF METFORMIN HCl

Formulation Code	A: Total amount of polymer (mg)	B: % of Carbopol 934P	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	36.532	0.398	15.206	4.818
F2	200	0	32.646	0.455	12.145	6.078
F3	300	0	25.735	0.487	8.704	9.288
F4	100	20	30.263	0.444	11.433	7.094
F5-T1	200	20	26.366	0.550	9.273	8.359
F5-T2	200	20	25.264	0.573	8.932	8.656
F5-T3	200	20	27.468	0.483	9.615	8.069
F6	300	20	21.101	0.593	7.028	11.687
F7	100	40	28.593	0.487	10.290	8.251
F8	200	40	24.139	0.595	8.202	9.673
F9	300	40	19.805	0.716	6.805	13.048

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 2. Eleven batches showed 'n' of Higuchi eq. (Y_1) for all batches was found to be in the range of 19.805–36.532. The ranges of other responses, Y_2 'n' of Peppas eq.), were 0.398- 0.595, Y_3 ('K' of zero order eq.), were 6.805–15.206 and Y_4 ($T_{80\%}$), were 4.818–13.048 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 3** 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 reduced quadratic, second order, reduced quadratic and reduced quadratic 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 polymer (A) and % of Carbopol 934P (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)

The interaction effect of total amount of polymer (A) was seen with % of Carbopol 934P (B) for response ‘n’ of Peppas Equation (Y_2), 'K' of Zero order Equation (Y_3) and $T_{80\%}$ (Y_4). Total amount of polymer (A) also showed a higher quadratic effect as compared to % of Carbopol 934P (B) on response $T_{80\%}$ (Y_4).

% of Carbopol 934P (B) showed a higher quadratic effect as compared to the total amount of polymer (A) on response ‘n’ of Higuchi Equation (Y_1) and 'K' of Zero order Equation (Y_3).

TABLE 3: 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	1.3534	< 0.0001	0.938	0.922	0.884	27.418	-
Second order	1.3961	0.4951	0.942	0.917	0.851	35.138	-
Quadratic	0.823	0.0307	0.986	0.971	0.938	14.629	Suggested
Y_2: 'n' of Peppas Equation							
Linear	0.0353	0.0002	0.878	0.847	0.738	0.021	-
Second order	0.0267	0.0338	0.938	0.912	0.914	0.007	Suggested
Quadratic	0.0306	0.8487	0.942	0.885	0.869	0.011	-
Y_3: 'K' of Zero order Equation							
Linear	0.8134	< 0.0001	0.91	0.888	0.782	12.855	-
Second order	0.6565	0.0552	0.949	0.927	0.797	12.016	-
Quadratic	0.3012	0.0088	0.992	0.985	0.954	2.728	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	-
$Y_1 = 41.22 - 0.047912 *A - 0.36806 *B + 0.00454 * B^2$							
$Y_2 = 0.363789 + 0.000426*A + 0.000301*B + 0.000018 * AB$							
$Y_3 = 18.32442 - 0.03153 * A - 0.26201* B + 0.00038 * AB + 0.002423 * B^2$							
$Y_4 = 5.44320 + 0.01692*A + 0.14130*B + 0.0001* A^2 - 0.001285 * B^2$							

Standardized main effects and reliability of the models: Standardized Main Effects (SME) (**Table 4**) was calculated by dividing the main effects with their standard error [15]. 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 Carbopol 934P 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, which further strengthened the reliability of the models.

TABLE 4: 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	64.89033	64.86049	75.19155	89.64518
A-Total amount of Polymer	-13.0515	7.13578	-21.341	30.88182
B-% of Carbopol 934P	-10.1588	7.006422	-15.9512	24.04011
AB	-	2.625373	5.482049	-
A^2	-	-	-	8.69331
B^2	3.334986	-	5.814637	-4.46481
R^2	0.976	0.938	0.9923	0.9963
p-value of lack of fit	0.7538	0.995	0.7637	0.9792

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.

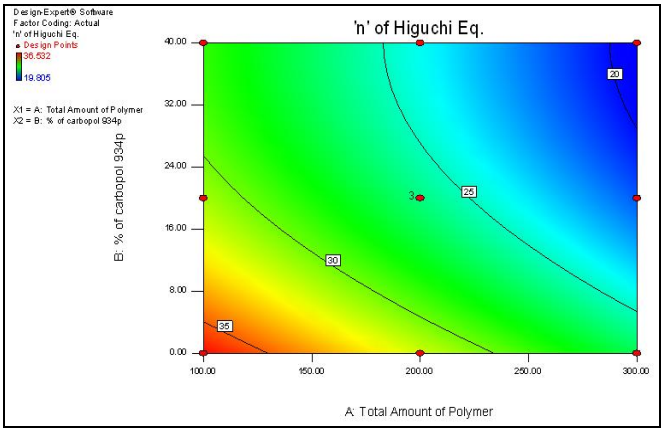
In all the presented figures, it was concluded that as;

(1) The total amount of polymer (A) and/or % Carbopol 934P in polymer mixture (B) increase/s, the value of 'n' of Higuchi (Y_1) is decreased;

(2) The total amount of polymer (A) and/or % Carbopol 934P in polymer mixture (B) increase/s, the value of 'n' of Peppas (Y_2)is increased;

(3) The total amount of polymer (A) and/or % Carbopol 934P in polymer mixture (B) increase/s, the value of 'K' of Zero order(Y_3) is decreased;

(4) The total amount of polymer (A) and/or % Carbopol 934P in polymer mixture (B) increase/s, the value of $T_{80\%}$ (Y_4) is increased.



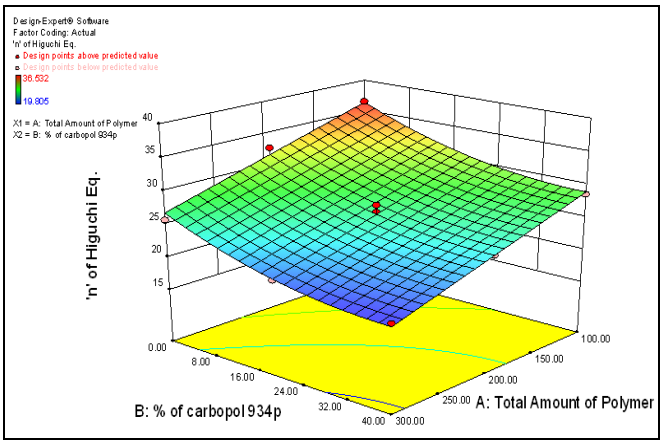
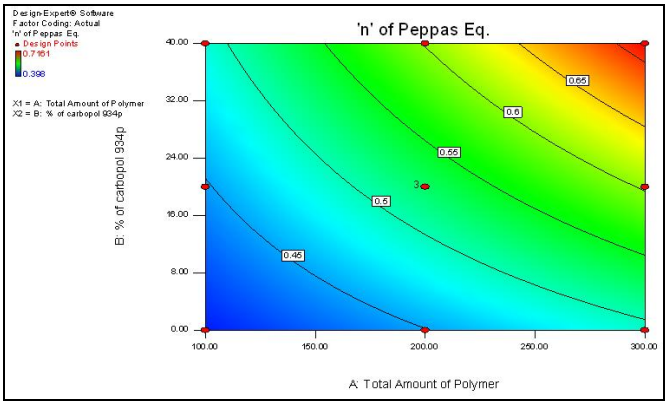


FIGURE 2: 3D SURFACE PLOT AND CONTOUR PLOT OF PREDICTED VALUES OF 'N' OF HIGUCHI EQUATION FOR VARIOUS FORMULATIONS OF METFORMIN HCl



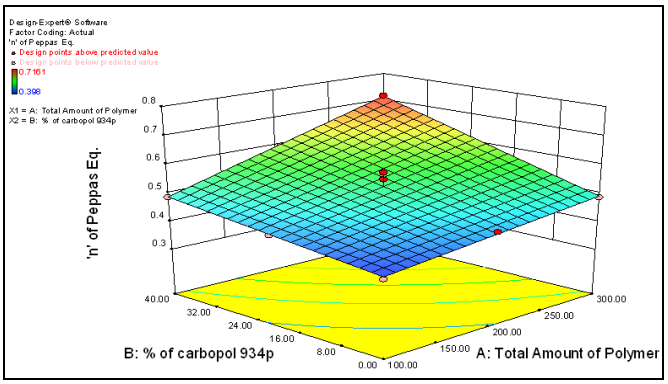
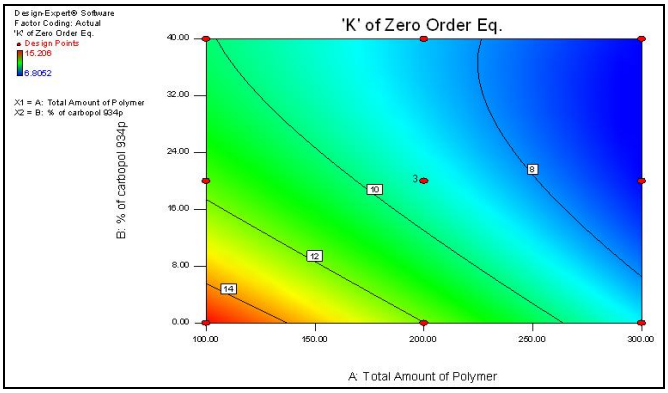


FIGURE 3: 3D SURFACE PLOT AND CONTOUR PLOT OF PREDICTED VALUES OF 'N' OF PEPPAS EQUATION FOR VARIOUS FORMULATIONS OF METFORMIN HCl



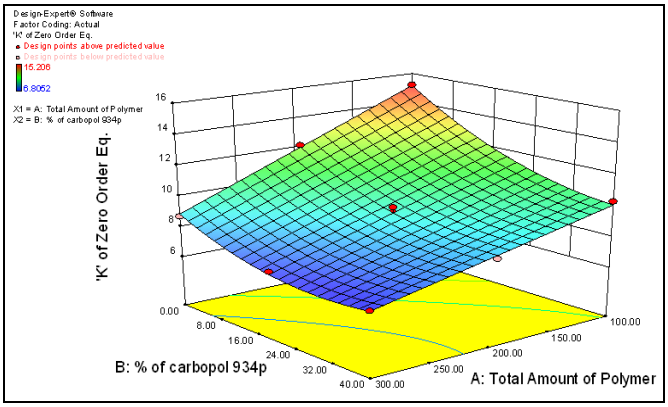


FIGURE 4: 3D SURFACE PLOT AND CONTOUR PLOT OF PREDICTED VALUES OF 'K' OF ZERO ORDER EQUATION FOR VARIOUS FORMULATIONS OF METFORMIN HCl

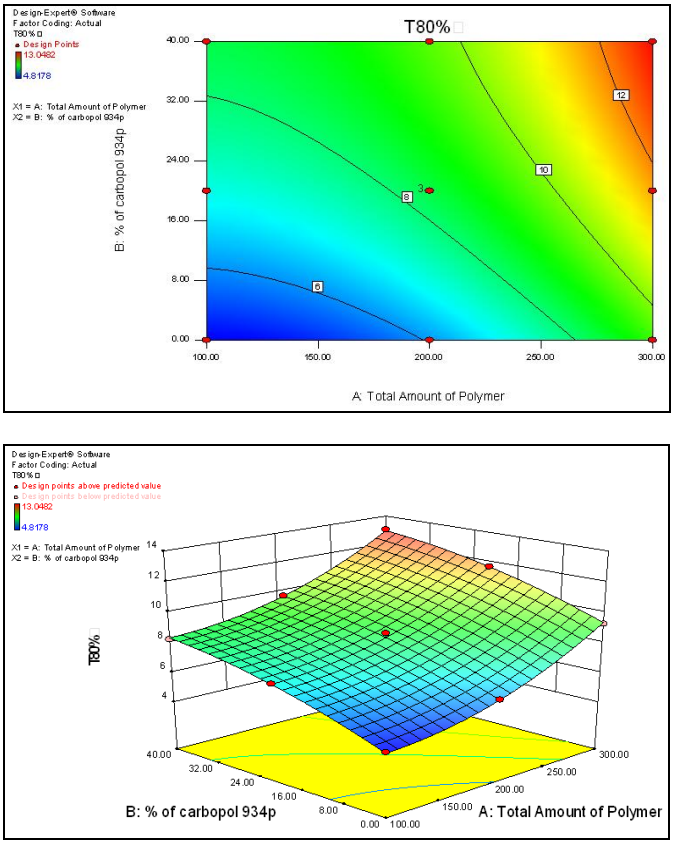


FIGURE 5: 3D SURFACE PLOT AND CONTOUR PLOT OF PREDICTED VALUES OF $T_{80\%}$ EQUATION FOR VARIOUS FORMULATIONS OF METFORMIN HCl

Optimization: The optimized 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. (Y1) (target to 23.83), 'K' of Zero Order Eq. (Y3) (target to 8.333) and T80% (Y4) (target to 9.60h). 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), 206.83 mg, % Carbopol 934P in polymer mixture (B), 35.10 %, was found to fulfill the maximum requisite of an optimum formulation because of better correlation of the theoretically obtained values of Y1 (23.9846), Y2 (0.590152), Y3 (8.329) and Y4 (9.600) with the standardized target values with the desirability of 0.996. The optimized formulation was found to release about 99.12% 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 22.76% 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: 8.3919) and Korsmeyer's-Peppas kinetics (n = 0.5989). 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 5**). **Table 6** shows the composition of optimum checkpoint formulations, their predicted and experimental values of all the response variables and the percentage error.

TABLE 5: EVALUATION OF VARIOUS PHYSICOCHEMICAL PARAMETERS OF OPTIMIZED CHECK POINT FORMULATIONS OF METFORMIN HCl

Physicochemical Parameters	Results
Bulk density(g/cm^3)	1.136
Tapped density(g/cm^3)	1.326
Hausner's Ratio	1.1672
Compressibility index	14.328
Angle of repose (θ)	26.46 ± 1.63
Hardness* (Kg/cm^2) Mean ± S.D.	4.2 ± 0.5
% Friability	0.27
% Weight Variation** (±S.D.)	± 2.6
% Drug Content* Mean ± S.D.	100.16 ± 2.34
Diameter*(in mm) Mean ± S.D.	13.54 ± 0.02
Thickness* (in mm) Mean ± S.D.	7.39 ± 0.05
Floating Time** (in Hours) Mean ± S.D.	11.36 ± 0.51
Floating Lag Time** (in Seconds) Mean ± S.D.	17 ± 15

TABLE 6: 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.	24.352	23.984	-1.53
Y_2: 'n' of peppas equation	0.598	0.590	-1.48
Y_3: 'K' of Zero Order Eq.	8.3919	8.330	-0.74
Y_4: $T_{80\%}$	9.753	9.6	-1.59

Fourier Transform Infrared Spectroscopy (FTIR): FTIR spectra of the drug, excipients and the optimized formulation were recorded in range of 4000 - 400 cm^{-1}. In the optimized formulation, the presence of all the characteristic peaks of the Metformin HCl indicates lack of any strong interaction between the drug and the excipients. If the interaction is week, as mentioned that any strong interaction, what could be the reasons for week interaction or highlight minor peaks.

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, $p > 0.05$).

CONCLUSION: Floating matrix tablets of Metformin HCl with HPMC K15M and Carbopol 934P 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.

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