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RESEARCH ARTICLE

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A Path for Horizing Your Innovative Work

DESIGN & DEVELOPMENT OF DILTIAZEM HCL FLOATING TABLET

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Abstract: The aim of this study was to develop floating matrix tablet of Diltiazem HCl. Diltiazem HCl, a benzothiazepine derivative with vasodilating action due to its antagonism of the actions of the calcium ion in membrane functions. The tablets were prepared by direct compression method using HPMC K4M, HPMC K15M and HPMC K100M polymer and $NaHCO_3$ as gas generating agent. Simplex Lattice design was used for optimization. The concentrations of HPMC K4M(X_1), HPMC K15M(X_2) and HPMC K100M(X_3) were selected as the independent variables. The amount of the drug released at 2 hr (Q_2), 6 hr (Q_6) and 10 hr (Q_{10}), floating lag time, diffusion coefficient (n) and rate constant (k) were selected as the dependent variables. Tablets were evaluated for *in vitro* dissolution, floating lag time, friability, hardness, drug content, and weight variation. Dissolution data were fitted to various models to ascertain kinetic of drug release. The drug release from the matrix tablet best fitted in korsemeyer's peppas model showing anamolous release i.e both diffusion and dissolution controlled release. Optimized formulation (D5) showed good similarity with theoretical profile of Diltiazem HCl. Different grades of HPMC had profound effect on both floating lag time and release rate, this is because of difference in viscosity of various grades of HPMC. Increase in amount and grade of HPMC from K4M to K100M decreased floating lag time as well as release rate and vice-versa.

Keywords: Diltiazem HCl, Floating Lag Time, dissolution, *in-vitro* release study

INTRODUCTION

Gastroretentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically gastroretentive systems swells following ingestion and is retained in the stomach for a number of hours, while it continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or are unstable in the medium of distal intestine[i].

A. Floating drug delivery

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach, (Fig1.5), for a prolonged period of time, without affecting the gastric emptying rate and the drug is released slowly at a desired rate from the system, results in an increase in the gastric residence time and a better control of fluctuations in the plasma drug concentrations and after complete release of the drug, the residual system is emptied from the stomach.[ii,iii]

a) Intragastric single layer floating tablets or Hydrodynamically Balanced System (HBS)[iv]

These formulations have bulk density lower than gastric fluids and thus float in the stomach that increases the gastric emptying rate for a prolonged period, (Fig.1). These are formulated by intimately mixing the gas (CO_2) generating agents and the drug within the matrix tablet. The drug is released slowly at a desired rate from the floating system and the residual system is emptied from the stomach after the complete release of the drug. This leads to an increase in the gastric residence time (GRT) and a better control over fluctuations in plasma drug concentration.

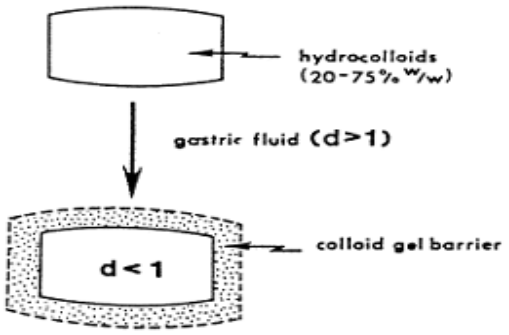

Figure 1 Intragastric single layer floating tablet

b) Rationale

1. Diltiazem hydrochloride is BCS class I drug hence to control solubility and extend release for longer duration.
2. It has narrow absorption window hence formulated as stomach specific drug delivery.
3. It has short biological half life, therefore administration frequency can be decreased.
4. More effective absorption in proximal region hence gastroretentive delivery more favourable.
5. Improved patient compliance & comfort.

MATERIALS AND METHODS

Drug Excipient Compatibility Study

Drug- excipients interactions play a vital role in the release of drug from formulation. Fourier transform infrared spectroscopy has been used to study the physical and chemical interactions between drug and the excipients used. Fourier transform infrared (FTIR) spectra of Diltiazem HCl, HPMC K4M, HPMC K15M, HPMC K100M, were recorded using KBr mixing method on FTIR instrument of the institute (FTIR-8400S, Shimadzu, Kyoto, Japan).

a) OPTIMIZATION OF VARIABLES USING STATISTICAL DESIGN

A {3, 3} Simplex Lattice design was employed in the present study. In these design we check the effect of different polymers in combination. In this design the concentration of different polymers HPMC K4M (X1), HPMC K15M (X2) and HPMC K100M (X3) were selected as independent variable & dependent variable were floating lag time, release at 2,6 and 10 hours, diffusion co-efficient(n), rate constant(k) and experimental trials were performed for all 10 possible combinations. The composition of statistical design batches (D1-D10) is shown in Table 4. The prepared formulations were evaluated for assay, friability and hardness and *in vitro* release study, floating lag time, total floating time and weight variation.

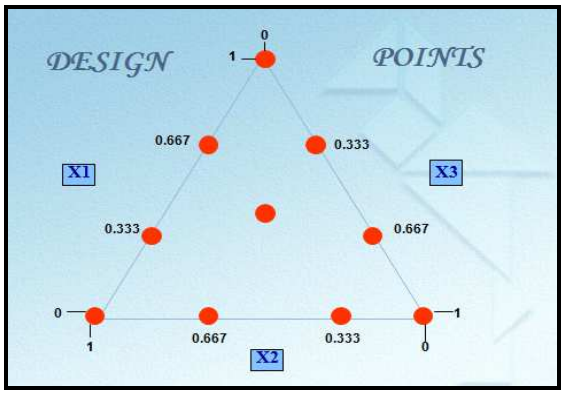

Figure 2 Design of {3, 3} Simplex Lattice design

b) KINETIC MODEL FOR RELEASE DATA

The drug released data of all batches were fitted with desired kinetic model such as Zero order kinetic, First order kinetic, Higuchi model and Korsemeyer peppas model to ascertain the drug release. The Zero order and First order drug release explain the drug release depend on drug concentration or not. The Korsemeyer peppas model described the method of drug release and Higuchi model described the diffusional drug release.

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate describes the systems where the drug release rate is independent of its concentration (Hadjiioannou *et al*., 1993). The first order describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation.

$$Wo - Wt = Kt$$

Where W is the initial amount of drug in the pharmaceutical dosage form, W is the amount of drug in pharmaceutical dosage form at time t and K is a proportionality constant. The following relation can, in a simple way, express this model:

$$Q_1 = Q_o + K_o t$$

Where Q is the amount of drug dissolved in time t, Q is the initial amount of drug in the solution (most times, Q_{50}) and K is the zero order release constant.

First order kinetics

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969). This model has been also used to describe absorption and/or elimination of some drugs (Gibaldi and Perrier, 1982), although it is difficult to conceptualize this mechanism in a theoretical basis. The following relation can also express this model:

$$Q_t = Q_o e^{-K1t}$$

Where *Qt* is the amount of drug released in time *t*, Q_0 is the initial amount of drug in the solution and *K* is the first order release constant.

Higuchi model

Higuchi (1961, 1963) developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid matrixes. In a general way it is possible to resume the Higuchi model to the following expression (generally known as the simplified Higuchi model):

$$f_t = K_H t^{1/2}$$

Where K_H = Higuchi dissolution constant.

Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent.

Hixson–Crowell model

Hixson and Crowell (1931) recognizing that the particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner:

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

Where *W* is the initial amount of drug in the pharmaceutical dosage form, *W* is the remaining amount of drug in the pharmaceutical dosage form at time *t* and *K* is a constant incorporating the surface–volume relation. This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally in such a manner that the initial geometrical form keeps constant all the time.

Korsmeyer–Peppas model

Korsmeyer et al. (1983) developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (*t*):

$$f = at^n$$

where *a* is a constant incorporating structural and geometric characteristics of the drug dosage form, *n* is the release exponent, indicative of the drug release mechanism, and the function of *t* is *M* /*M* (fractional release of drug).

c) STATISTICAL ANALYSIS

The statistical analysis of the design batches were performed by multiple regression analysis and analysis of variance (ANOVA) using Microsoft Excel® 2007. To demonstrate graphically the influence of each factor on response, the response

surface plots was generated using Design expert ® software.

Response Surface Methods are designs and models for working with continuous treatments when finding the optima or describing the response is the goal (Oehlert 2000). The first goal for Response Surface Method is to find the optimum response. When there is more than one response then it is important to find the compromise optimum that does not optimize only one response (Oehlert 2000). When there are constraints on the design data, then the experimental design has to meet requirements of the constraints. The second goal is to understand how the response changes in a given direction by adjusting the design variables. In general, the response surface can be visualized graphically. The graph is helpful to see the shape of a response surface, hills, valleys, and ridge lines.[v]

RESULTS AND DISCUSSION

a) Drug Excipient Compatibility Study

Drug- excipients interactions play a vital role in the release of drug from formulation. Fourier transform infrared spectroscopy has been used to study the physical and chemical interactions between drug and the excipients used. Diltiazem HCl exhibits peak due to carbonyl (1681.98, 1743.71) and amine (2387.95) group. It was observed that there were no changes in these main peaks in the FTIR spectra of a mixture of drug and polymers (Figure 5.1-5.5). Hence, it was concluded that there is no physical or chemical interactions of Diltiazem HCl with HPMC K4M, HPMC K15M and HPMC K100M.

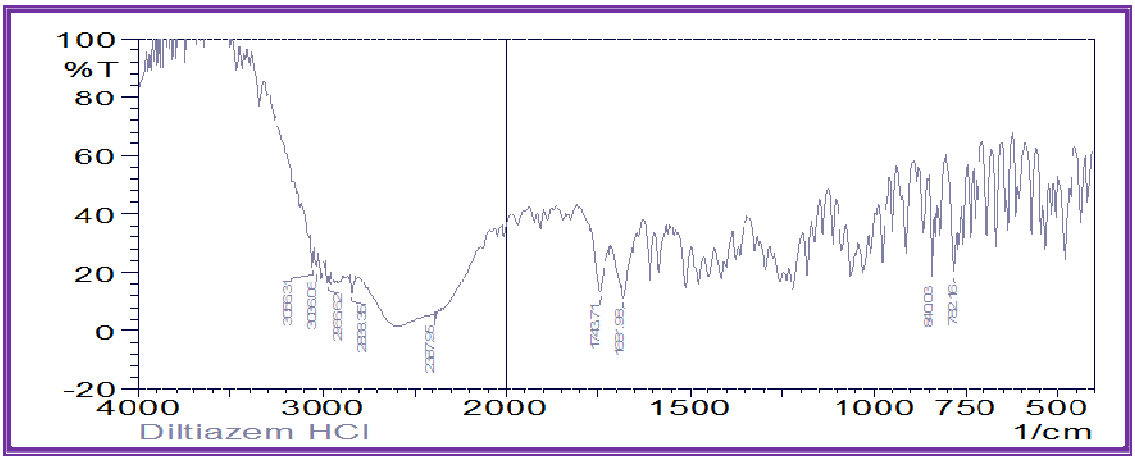

Figure 3 FTIR spectrum of Diltiazem HCl

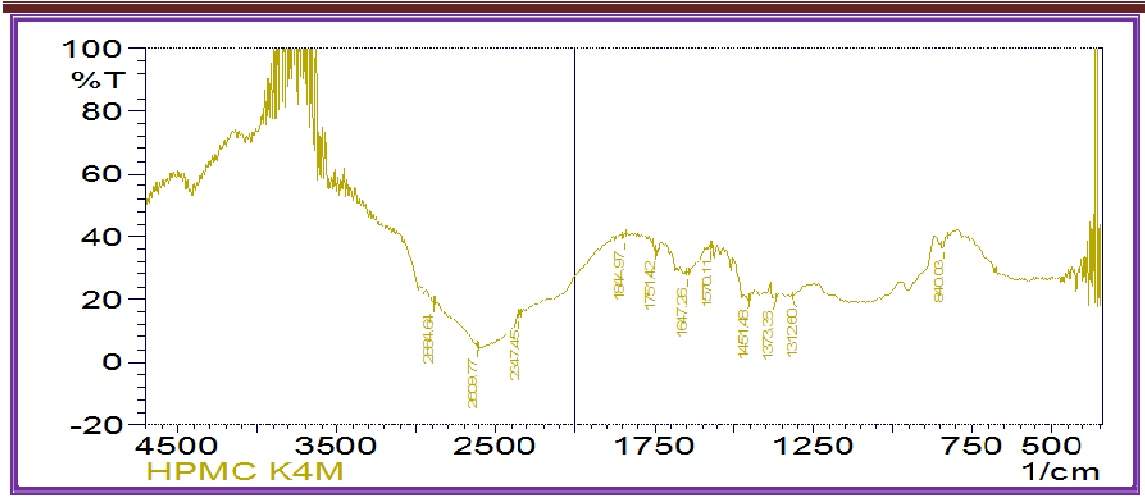

Figure 4 FTIR spectrum of HPMC K4M

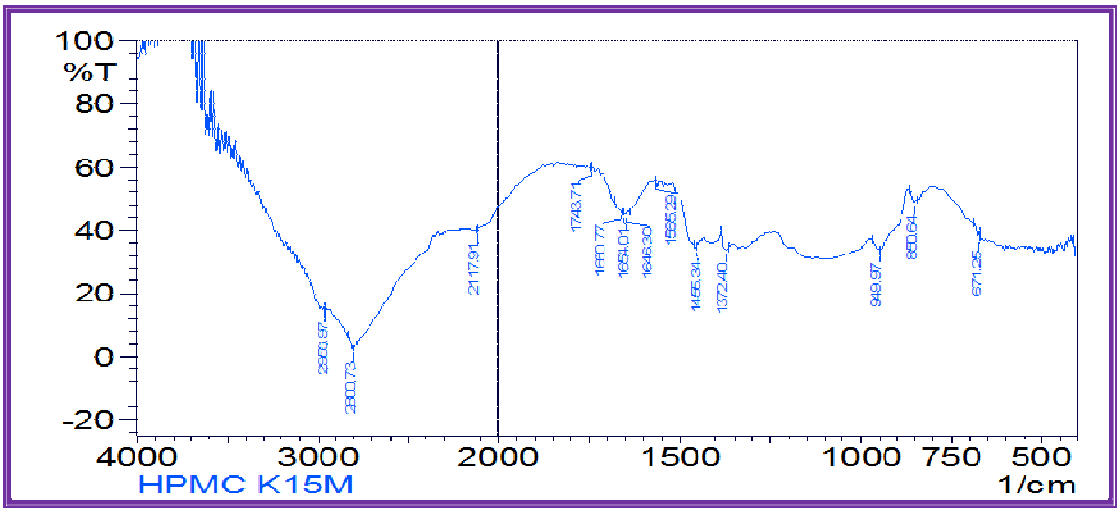

Figure 5 FTIR spectrum of HPMC K15M

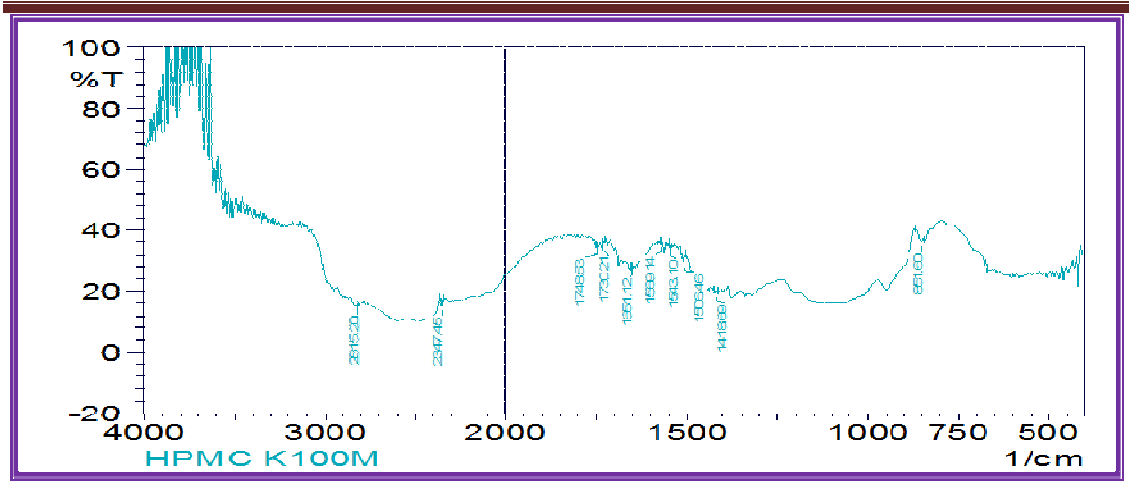

Figure 6 FTIR spectrum of HPMC K100M

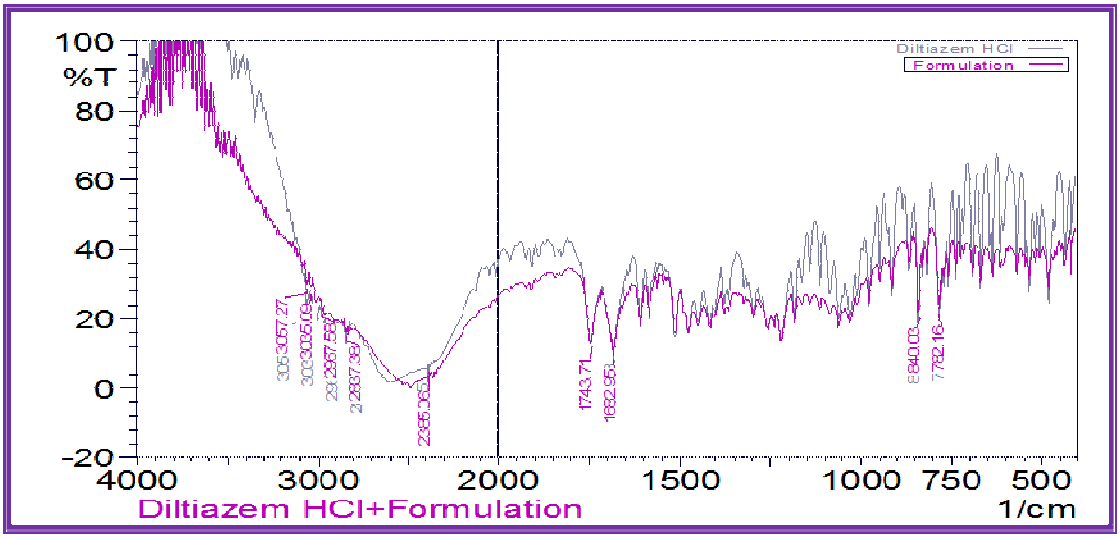

Figure 7 FTIR spectrum of Diltiazem HCl and Formulation

b) OPTIMIZATION OF VARIABLES USING STATISTICAL DESIGN

Pre-compression parameters of Statistical Design batches:

The evaluation was carried out using the parameters like bulk density, tapped density, Hausner's ratio, Carr's index, and angle of repose as per the procedure described in Preformulation study. The results are given in table 7.

The tablet blend of all the batches were evaluated for different derived properties viz.-angle of repose (between 20-30), Bulk density (between 0.43-0.46 gm/cm3), Tapped Density (0.54–0.57 gm/cm3), Compressibility index (between 16-22, and

flowability (good). The results of Angle of repose and compressibility indicated that the flowability of blend is significantly good. So the flow of the prepared mass from the hopper was able to fill the die completely for compression. After the lubrication the blend ready for compression had good flow property and excellent compressibility.

Post-compression parameters of Statistical Design batches:

All the prepared tablets showed acceptable pharmaceutical properties. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness were shown in the range of 4.0–6.0 kg/cm2 in all the formulations which indicated good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations, the friability value was less than 1% and meets the official limit. All the batches exhibited appropriate floating lag time and showed total floating time of more than 12 hrs. The percentage drug content of all the tablets was found to be between 98.5-101.5 % of Diltiazem HCl which was within acceptable limit

***In vitro* release studies of Statistical Design batches:**

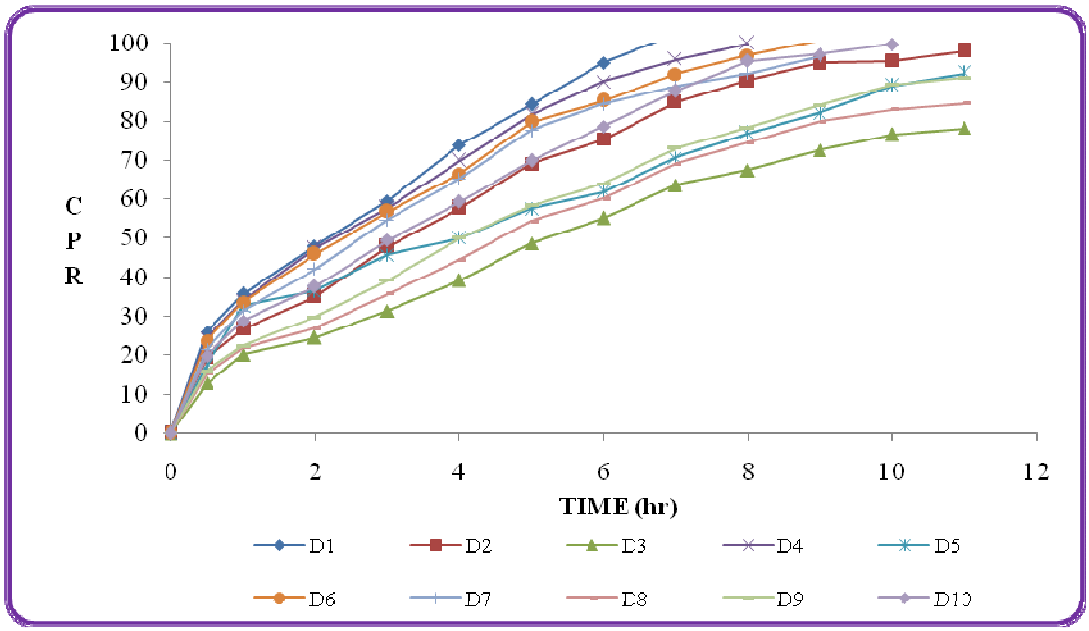

Figure 8 *In vitro* release studies of Statistical Design batches

From the dissolution profile of all the batches it was found that there was fast drug release at initial state of dissolution. The initial rise in the drug release was due to burst effect i.e release of drug from surface of tablet. Here to check the combination effect of different polymers on drug release profile. Formulations D1, D2, D4, D6, D7 and D10 showed 100% of drug release before 12 hrs, whereas in formulation D3, D8, D9 showed 85-90% of drug release in 12 hrs, whereas batch D5 showed 100% release in 12 hrs. Among ten batches, batch D5 is selected as optimized batch because of its good floating lag time and 100% drug release at 12 hrs. Stability study was performed on formulation batch D5.

c) STATISTICAL ANALYSIS OF STATISTICAL DESIGN BATCHES

* All batches contained 120 mg of Diltiazem HCl, X_1 indicates the concentration of HPMC K4M (mg), X_2 indicates the concentration of HPMC K15M(mg), X_3 indicates the concentration of HPMC K100M(mg),. Q_2, Q_6 and Q_{10} indicate percentage drug released after 2, 6 and 10 hours, respectively. n and k indicates diffusion coefficient and release rate constant respectively.

d) RESULTS OF SIMPLEX LATTICE DESIGN

A simplex lattice design was employed to study the effect of combination of independent variables i.e. HPMC K4M (X_1), HPMC K15M (X_2), HPMC K100M (X_3) on dependent variables floating lag time, release at 2, 6, 10 hrs, diffusion co-efficient and release rate constant. A statistical model incorporating interactive and polynomial terms was used to evaluate responses.

$$\mathbf{Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_{12} + b_{13}X_{13} + b_{23}X_{23} + b_{123}X_{123}} \quad \mathbf{\ldots\ldots 5.1}$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the ten runs and b_1 is the estimated coefficient for factor X_1. The main effect (X1, X2, and X3) represents effect produced by only one factor individually. The interactive terms (X_{12}, X_{13}, X_{23}, and X123) show how the response changes when two or more factors are simultaneously changed. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). Table 12 shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors. The high values of correlation coefficient for all variables

(Table 11) indicate a good fit, i.e., good agreement between the dependent and independent variables.

i) Full and Reduced Model for Floating Lag Time

The significance levels of the coefficients b_1, b_{12}, b_{13}, and b_{23} were found to be P= 0.3454, 0.357, 0.7562 and 0.4491 respectively (Table 11), so they were omitted from the full model to generate a reduced model. The results of statistical analysis are shown in Table 12. The coefficients b_2 and b_3 were found to be significant at P< 0.05; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_1, b_{12}, b_{13} and b_{23} contribute significance information to the prediction of floating lag time. The results of model testing are shown in Table 12. The critical value of F for α =0.05 is equal to 9.01 (df=5,3). Since the calculated value (F= 0.46) is less than critical value (F=9.01), it may be concluded that the interaction term b_1, b_{12}, b_{13} and b_{23} do not contribute significantly to the prediction of floating lag time and can be omitted from the full model to generate the reduced model.

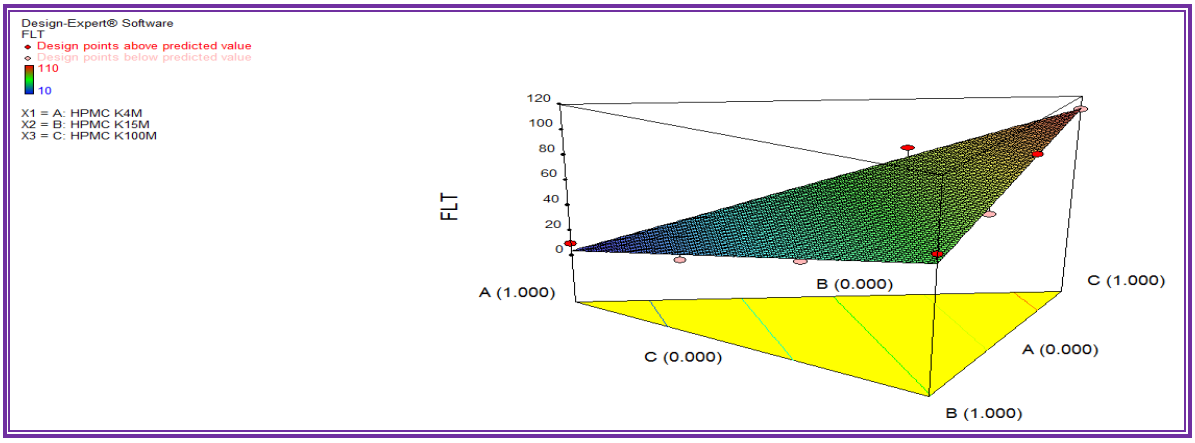

Figure 9 3D Surface Plot for Floating Lag Time

ii) Full and Reduced Model for Q_2

The significance levels of the coefficients b_{12}, b_{13}, and b_{23} were found to be P= 0.542, 0.606 and 0.521 respectively (Table 11), so they were omitted from the full model to generate a reduced model. The results of statistical analysis are shown in Table 12. The coefficients b_1, b_2, and b_3 were found to be significant at P< 0.05; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{12}, b_{13} and b_{23} contribute significance information to the

prediction of Q_2. The results of model testing are shown in Table 12. The critical value of F for α =0.05 is equal to 9.12 (df=4,3). Since the calculated value (F=0.22) is less than critical value (F=9.12), it may be concluded that the interaction term $b_{12,}$ b_{13} and b_{23} do not contribute significantly to the prediction of Q_2 and can be omitted from the full model to generate the reduced model

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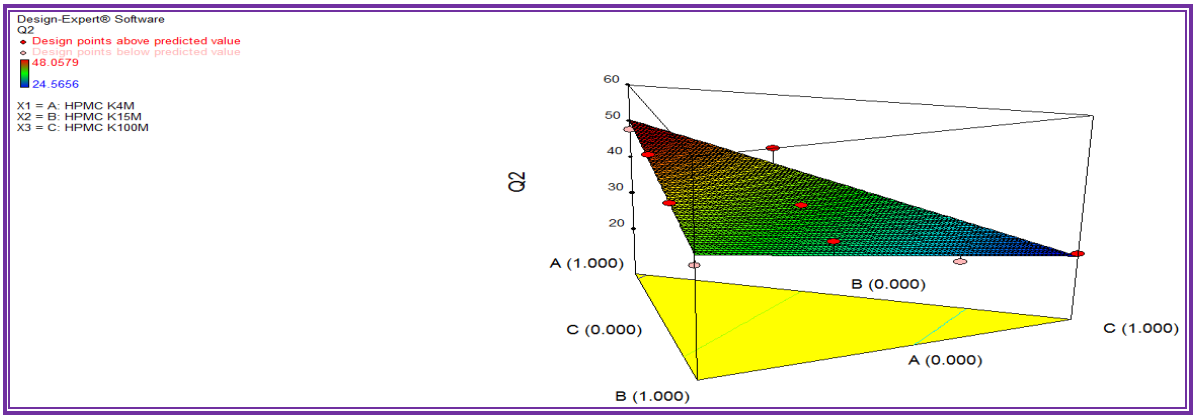

Figure 10 3D Surface Plot for Q_2

iii) Full and Reduced Model for Q_6

The significance levels of the coefficients $b_{12,}$ $b_{13,}$ and b_{23} were found to be P=0.511, 0.994 and 0.470 respectively (Table 11), so they were omitted from the full model to generate a reduced model. The results of statistical analysis are shown in Table 12. The coefficients b_1, b_2, b_3 were found to be significant at P< 0.05; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient $b_{12,}$ b_{13} and b_{23} contribute significance information to the prediction of Q_6. The results of model testing are shown in Table 12. The critical value of F for α =0.05 is equal to 9.12 (df=4,3). Since the calculated value (F=0.7) is less than critical value (F=9.12), it may be concluded that the interaction term $b_{12,}$ b_{13} and b_{23} do not contribute significantly to the prediction of Q_6 and can be omitted from the full model to generate the reduced model.

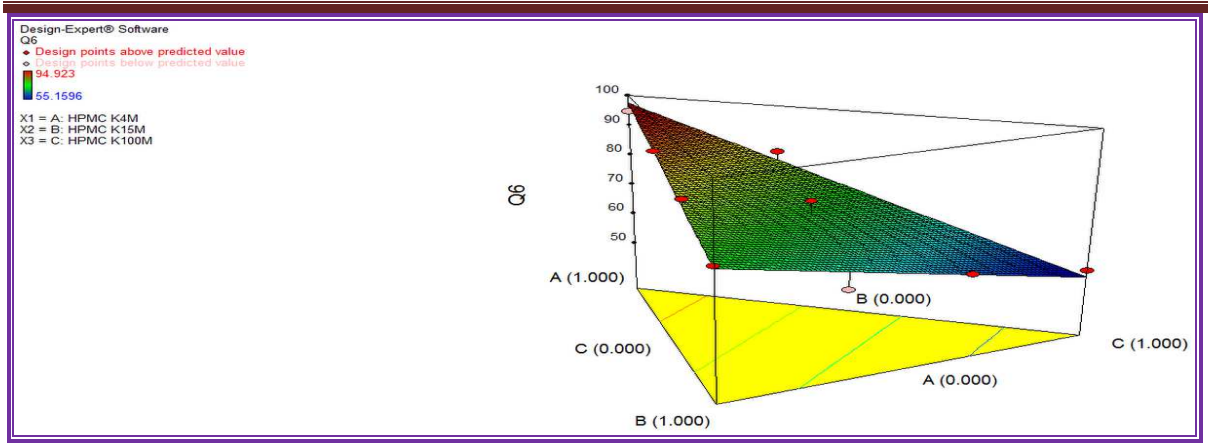

Figure 11 3D Surface Plot for Q_6

iv) Full and Reduced Model for Q_{10}

The significance levels of the coefficients b_{12} and b_{23} were found to be P=0.909 and 0.400 respectively (Table 11), so they were omitted from the full model to generate a reduced model. The results of statistical analysis are shown in Table 12. The coefficients b_1, b_2, b_3 and b_{13} were found to be significant at P< 0.05; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{12} and b_{23} contribute significance information to the prediction of Q_{10}. The results of model testing are shown in Table 12. The critical value of F for α =0.05 is equal to 9.27 (df=3,3). Since the calculated value (F=8.128) is less than critical value (F=9.27), it may be concluded that the interaction term b_{12} and b_{23} do not contribute significantly to the prediction of Q_{10} and can be omitted from the full model to generate the reduced model.

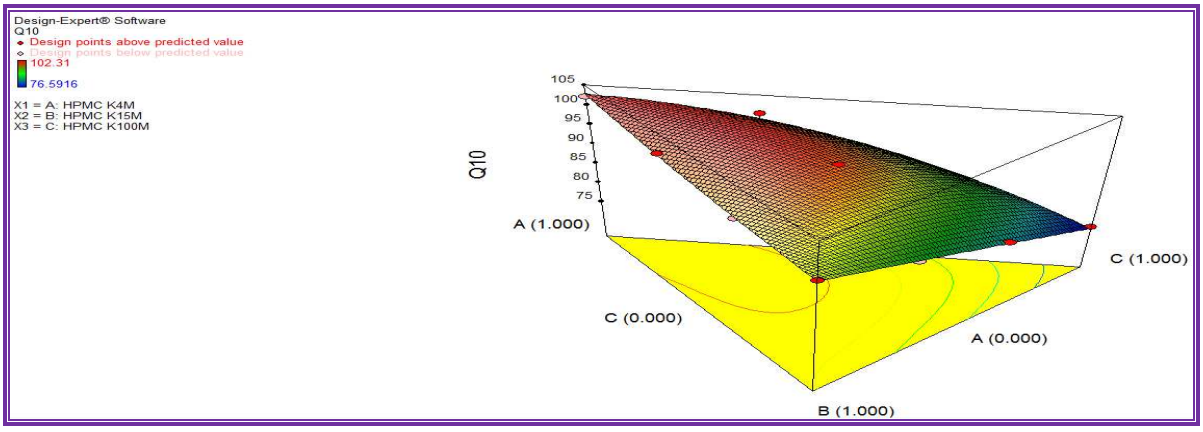

Figure 12 3D Surface Plot for Q_{10}

v) Full and Reduced Model for Release Rate Constant (k)

The significance levels of the coefficients b_{12}, b_{13}, and b_{23} were found to be P=0.700, 0.626 and 0.476 respectively (Table 11), so they were omitted from the full model to generate a reduced model. The results of statistical analysis are shown in Table 12. The coefficients b_1, b_2, b_3 were found to be significant at P< 0.05; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{12}, b_{13} and b_{23} contribute significance information to the prediction of k. The results of model testing are shown in Table 12. The critical value of F for α =0.05 is equal to 9.12 (df=4,3). Since the calculated value (F=0.5) is less than critical value (F=9.12), it may be concluded that the interaction term b_{12}, b_{13} and b_{23} do not contribute significantly to the prediction of k and can be omitted from the full model to generate the reduced model.

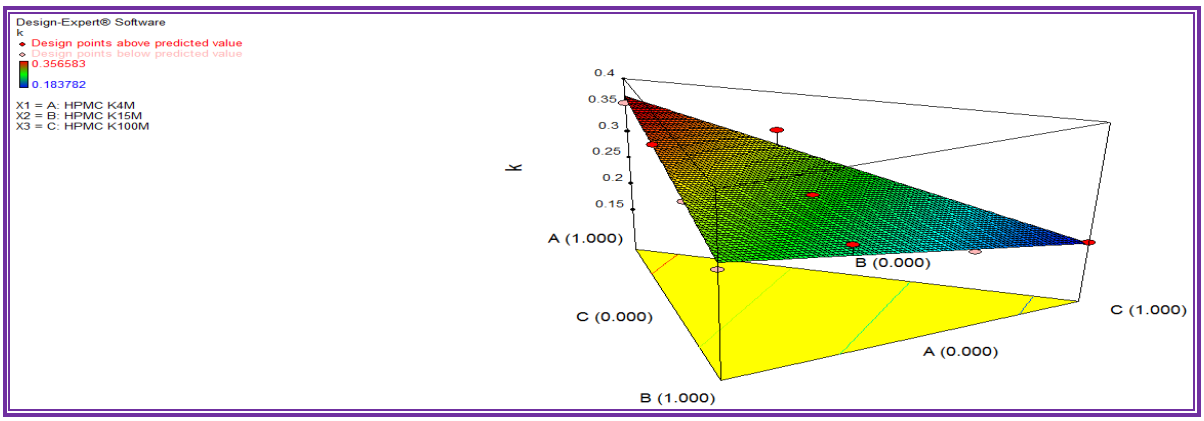

Figure 13 3D Surface Plot for Release Rate Constant (k)

vi) Full and Reduced Model for diffusion co-efficient (n)

The significance levels of the coefficients b_{12}, b_{13}, and b_{23} were found to be P=0.998, 0.719 and 0.321 respectively (Table 11), so they were omitted from the full model to generate a reduced model. The results of statistical analysis are shown in Table 12. The coefficients b_1, b_2, b_3 were found to be significant at P< 0.05; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{12}, b_{13} and b_{23} contribute significance information to the prediction of n. The results of model testing are shown in Table 12. The critical value of

F for α =0.05 is equal to 9.12 (df=4,3). Since the calculated value (F=0.55) is less than critical value (F=9.12), it may be concluded that the interaction term $b_{12,}$ b_{13} and b_{23} do not contribute significantly to the prediction of n and can be omitted from the full model to generate the reduced model.

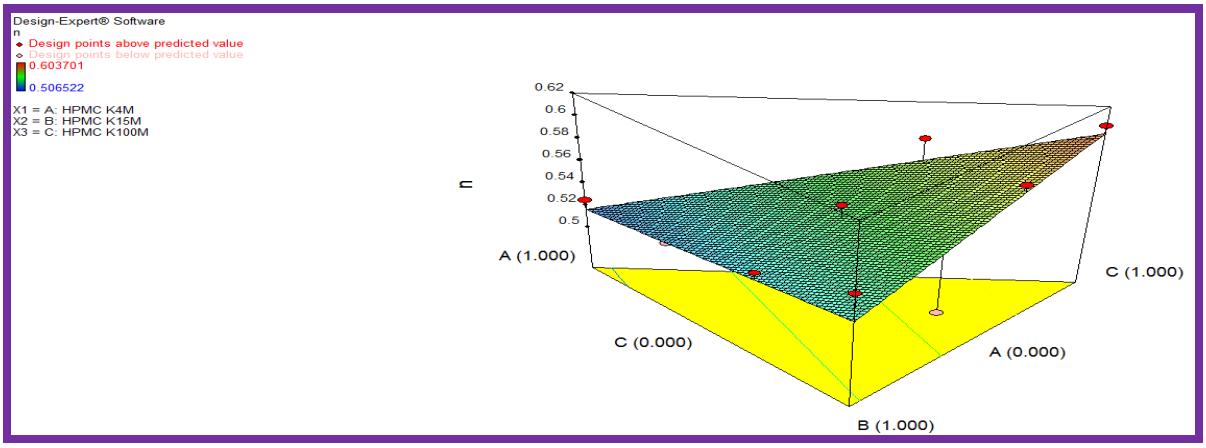

Figure 14 3D Surface Plot for diffusion co-efficient (n)

e) KINETIC MODELING OF DISSOLUTION DATA

The kinetics of the dissolution data were well fitted to zero order, Higuchi model and Krossmayer-Peppas model as evident from regression coefficients (Table 13). In case of the controlled release or sustained release formulations, diffusion, swelling and erosion are the three most important rate controlling mechanisms. Formulation containing swelling polymers show swelling as well as diffusion mechanism because the kinetic of swelling include relaxation of polymer chains and imbibitions of water, causing the polymer to swell and changing it from a glassy to rubbery state. The value of diffusion exponent n for D1 to D10 factorial formulations was between 0.5 and 1 (Table 13) indicating anomalous transport drug release from the formulations.

Kinetic Model Higuchi indicating that R^2 value of D1 to D10 was between 0.991 to 0.997, Shown that drug release type was diffusion type from gel network and extend drug release for longer period of time.

Kinetic Model Zero order indicating that R^2 value of D1 to D10 was between 0.976 to 0.996 that is near about 1.000, clearly mentioned that drug release from stiff gel networking was Zero order drug release that not depend on concentration of drug.

Kinetic Model First order indicating that R^2 value of D1 to D10 was between 0.928 to 0.966 that having less than Zero order release R^2 value, mentioned that drug release type was not first order release from gel network.

Table 1

List of materials used in present investigation

Ingredients	Supplier
Diltiazem HCl	Micro Labs. Ltd., Bangalore
Hydroxypropyl methylcellulose (HPMC K15M, K15M, K100M)	Colorcon Asia Pvt. Ltd., Goa.
Tablettose	Colorcon Asia Pvt. Ltd., Goa
Sodium bi carbonate	Finar chemical Pvt. Ltd., Ahmedabad
PVP K30	Orbicular Pharma. Tech. Ltd. Hyderabad
Aerosil	Orbicular Pharma. Tech. Ltd. Hyderabad

Table 2

Coding of actual values for simplex lattice design

Values	Levels			
Coded Value	0	0.33	0.66	1
Actual Value.(mg)	0	30	60	90

Table 3

Formulation layout for statistical design batches

Batch No.	Coded Value			Actual Value (mg) Polymer		
	A	B	C	A	B	C
1	1	0	0	90	0	0
2	0	1	0	0	90	0
3	0	0	1	0	0	90
4	0.66	0.33	0	60	30	0
5	0	0.66	0.33	0	60	30
6	0.66	0	0.33	60	0	30
7	0.33	0.66	0	30	60	0
8	0	0.33	0.66	0	30	60
9	0.33	0	0.66	30	0	60
10	0.33	0.33	0.33	30	30	30

Table 4

Composition of formulation of simplex lattice design

Ingredients	FORMULATION BATCH CODE									
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Diltiazem HCl	120	120	120	120	120	120	120	120	120	120
HPMC K4M	90	-	-	60	-	60	30	-	30	30
HPMC K15M	-	90	-	30	60	-	60	30	-	30
HPMC K100M	-	-	90	-	30	30	-	60	60	30
$NaHCO_3$	30	30	30	30	30	30	30	30	30	30
Tablettose	51	51	51	51	51	51	51	51	51	51
PVP K30	6	6	6	6	6	6	6	6	6	6
Aerosil	3	3	3	3	3	3	3	3	3	3
All weight is in mg. Each tablet weigh 300mg.										

Table 5

Interpretation of diffusional release mechanisms

Release exponent(n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5 < n < 1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero order release
> 1.0	Super case-II transport	t^{n-1}

Table 6

Graph plots for the kinetic model fitting

Kinetic model	X-Axis	Y-Axis
Zero Order	% Drug Release	Time
First Order	Log % Drug Release	Time
Higuchi model	% Drug Unreleased	$(Time)^{1/2}$
Hixon Crowell model	% Drug Unreleased	$(Time)^{1/3}$
Korsmeyer-Peppas	Log % Drug Release	Log Time

Table 7

Pre-compression parameters of Statistical Design batches

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose	Carr's index	Hausner's ratio
D1	0.44±0.01	0.54±0.044	25.41±0.41	18.51±0.77	1.22±0.52
D2	0.44±0.021	0.55±0.028	27.05±0.21	20.0±0.25	1.25±0.16
D3	0.46±0.014	0.57±0.012	28.19±0.18	19.29±0.16	1.23±0.23
D4	0.45±0.019	0.55±0.023	25.21±0.24	18.18±0.17	1.22±0.14
D5	0.45±0.023	0.54±0.042	30.18±0.34	16.66±0.45	1.20±0.16
D6	0.46±0.015	0.57±0.061	27.20±0.24	19.29±0.57	1.23±0.18
D7	0.45±0.021	0.56±0.034	27.22±0.34	19.64±0.43	1.24±0.21
D8	0.46±0.017	0.56±0.044	28.34±0.32	17.85±0.61	1.21±0.31
D9	0.43±0.023	0.55±0.041	26.65±0.55	21.81±0.45	1.27±0.17
D10	0.45±0.012	0.54±0.032	24.34±0.43	16.66±0.62	1.20±0.22
Results are the mean of three observations ± SD					

Table 8

Post-compression parameters of Statistical Design batches

Parameter / Batches	Floating Lag Time (sec)	Total Floating Time	Hardness Kg/cm^2	Content uniformity	Weight variation	Friability %
D1	10	>12 hrs	5.50±0.43	98.53±0.13	302±1.6	0.16±0.12
D2	66	>12 hrs	6.34±0.64	98.56±0.25	292±1.8	0.19±0.89
D3	110	>12 hrs	5.37±0.98	100.9±0.37	295±1.5	0.26±0.43
D4	18	>12 hrs	4.87±0.61	100.7±0.41	301±1.1	0.31±0.67
D5	71	>12 hrs	4.95±0.91	99.82±0.59	300±1.4	0.42±0.45
D6	33	>12 hrs	5.9±0.51	98.88±0.61	298±1.9	0.29±0.82
D7	39	>12 hrs	4.57±0.13	100.9±0.79	302±1.4	0.17±0.12
D8	94	>12 hrs	5.8±0.29	99.89±0.81	306±1.9	0.21±0.52
D9	82	>12 hrs	5.59±0.38	98.29±0.12	296±1.6	0.25±0.91
D10	57	>12 hrs	6.25±0.52	100.1±0.40	301±1.7	0.34±0.72

Results are the mean of three observations ± SD

Table 9
In vitro dissolution data of Statistical Design batches

Time (hr.)	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	35.69	26.76	20.15	33.98	32.69	33.69	31.31	21.90	22.50	28.86
2	48.06	35.07	24.57	47.49	36.42	45.90	42.15	26.91	29.74	37.64
3	59.42	47.81	31.40	57.73	45.80	56.74	54.72	35.63	39.14	49.48
4	73.77	57.71	39.23	69.85	50.14	66.49	65.19	44.46	49.99	59.28
5	84.18	69.00	48.63	81.62	57.49	79.78	77.63	54.41	58.42	69.88
6	94.92	75.35	55.16	90.12	61.84	85.21	84.44	60.17	64.01	78.59
7	102.3	84.92	63.54	95.68	70.69	92.06	88.79	68.97	73.11	87.77
8	-	90.39	67.50	99.78	76.80	96.87	92.12	74.48	78.23	95.33
9	-	94.90	72.59	-	82.12	100.6	96.63	79.89	84.07	97.13
10	-	95.45	76.59	-	88.99	-	-	82.96	89.39	99.74
11	-	97.91	78.22	-	92.22	-	-	84.51	91.11	-
12	-	-	80.06	-	99.98	-	-	86.74	93.90	-

Table 10

Formulation and Evaluation of Batches in Simplex Lattice Design

Batch Code	Variable Levels in Coded Form			FLT	Q_2	Q6	Q_{10}	n	K
	X_1	X_2	X_3						
D1	1	0	0	10	48.06	94.92	102.31	0.5252	0.3566
D2	0	1	0	66	35.07	75.35	95.45	0.5617	0.2686
D3	0	0	1	110	24.57	55.16	76.59	0.6037	0.1838
D4	0.66	0.33	0	18	47.49	90.12	99.78	0.5232	0.3411
D5	0	0.66	0.33	71	36.42	61.84	88.99	0.5065	0.2672
D6	0.66	0	0.33	33	45.90	85.21	100.62	0.5133	0.3331
D7	0.33	0.66	0	39	42.15	84.44	96.63	0.5369	0.3087
D8	0	0.33	0.66	94	26.91	60.17	82.96	0.5834	0.2097
D9	0.33	0	0.66	82	29.74	64.01	89.39	0.5892	0.2228
D10	0.33	0.33	0.33	57	37.64	78.59	99.74	0.5623	0.2808

Coded Values	**Actual Values**		
	X_1	X_2	X_3
0	0	0	0
0.33	30	30	30
0.66	60	60	60
1	90	90	90

Table 11
Summary of Results of Regression Analysis

Floating Lag Time							
Response	b_0	b_1	b_2	b_3	b_{12}	b_{13}	b_{23}
FM	0	7.37	65.15	113.47	-33.98	-10.64	-27.18
	P= 0	P=0.3454	P=0.0022	P=0.0004	P=0.357	P=0.7562	P=0.4491
RM	-	-	60.678	112.03	-	-	-
Q_2							
Response	b_0	b_1	b_2	b_3	b_{12}	b_{13}	b_{23}
FM	0	49.40	35.78	22.51	12.20	10.19	12.89
	P= 0	P=0.0009	P=0.002	P=0.009	P=0.542	P=0.606	P=0.521
RM	-	51.008	37.7395	24.213	-	-	-
Q_6							
Response	b_0	b_1	b_2	b_3	b_{12}	b_{13}	b_{23}
FM	0	95.95	74.74	54.72	12.76	0.12	-14.16
	P= 0	P=0.0001	P=0.0002	P=0.0006	P=0.511	P=0.994	P=0.470
RM	-	98.115	75.044	53.368	-	-	-
Q_{10}							
Response	b_0	b_1	b_2	b_3	b_{12}	b_{13}	b_{23}
FM	0	102.82	95.29	76.22	0.61	29.25	4.89
	P= 0	P=2.3E-6	P=3E-06	P=5.8E-6	P=0.909	P=0.009	P=0.400
RM	-	102.849	96.520	76.812	-	33.549	-
K							
Response	b_0	b_1	b_2	b_3	b_{12}	b_{13}	b_{23}
FM	0	0.36	0.27	0.17	0.044	0.056	0.084
	P=0	P=0.0004	P=0.001	P=0.004	P=0.700	P=0.626	P=0.476
RM	-	0.371	0.282	0.183	-	-	-
N							
Response	b_0	b_1	b_2	b_3	b_{12}	b_{13}	b_{23}
FM	0	0.51	0.55	0.61	-0.00025	-0.054	-0.16
	P=0	P=0.0003	P=0.0003	P=0.0002	P=0.998	P=0.719	P=0.321
RM	-	0.520	0.541	0.601	-	-	-

FM= Full model, RM= Reduced model

Table 12

Result of ANOVA

Floating Lag Time

	DF	SS	MS	F	R^2	
Regression						**Fcalc.= 0.46**
FM	7	43195.75	6170.822	128.337	0.9966	**Ftable=9.01**
RM	2	43085.43	21542.71	676.98	0.9941	**DF**(5,3)
Error						
FM	3	144.248	48.082			
RM	8	254.574	31.821			
Q_2						
	DF	**SS**	**MS**	**F**	**R^2**	
Regression						**Fcalc.=0.22**
FM	7	14587.74	2083.962	134.0702	0.9968	**Ftable=9.12**
RM	3	14574.02	4858.005	563.463	0.9958	DF (4,3)
Error						
FM	3	46.631	15.543			
RM	7	60.351	8.621			
Q_6						
	DF	**SS**	**MS**	**F**	**R^2**	
Regression						**Fcalc.=0.7**
FM	7	57918.98	8274.141	570.867	0.9992	**Ftable=9.12**
RM	3	57878.37	19292.79	1605.886	0.9985	DF (4,3)
Error						
FM	3	43.481	14.493			
RM	7	84.096	12.013			
Q_{10}						
	DF	**SS**	**MS**	**F**	**R^2**	
Regression						**Fcalc.= 8.128**
FM	7	87596.59	12513.8	10176.7	0.9999	**Ftable=9.27**
RM	4	87566.62	21891.66	3902.524	0.9996	**DF**(3,3)
Error						
FM	3	3.688	1.229			
RM	6	33.657	5.609			
K						
	DF	**SS**	**MS**	**F**	**R^2**	
Regression						**Fcalc.=0.5**
FM	7	0.797	0.113	212.604	0.9979	**Ftable=9.12**
RM	3	0.797	0.265	905.100	0.9974	DF (4,3)
Error						
FM	3	0.001	0.0005			
RM	7	0.002	0.0003			
N						
	DF	**SS**	**MS**	**F**	**R^2**	
Regression						**Fcalc.=0.555**
FM	7	3.038	0.434	467.342	0.9990	**Ftable=9.12**
RM	3	3.036	1.012	1606.515	0.9985	DF (4,3)
Error						
FM	3	0.002	0.0009			
RM	7	0.004	0.0006			

Table 13

Kinetic treatment of dissolution data

	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Zero order										
B	11.79	7.82	6.11	10.21	6.55	9.07	8.90	6.53	6.99	8.72
A	23.51	22.86	14.64	25.29	22.89	26.80	24.93	17.15	18.51	21.75
R^2	0.996	0.976	0.985	0.987	0.992	0.982	0.977	0.983	0.985	0.986
First order										
B	0.08	0.06	0.06	0.07	0.05	0.06	0.07	0.06	0.06	0.06
A	1.46	1.42	1.27	1.47	1.43	1.48	1.45	1.32	1.35	1.42
R^2	0.966	0.928	0.937	0.947	0.933	0.936	0.929	0.938	0.934	0.941
Higuchi										
B	40.07	32.99	26.55	37.15	28.27	34.91	34.38	28.46	30.46	34.96
A	-5.50	-6.62	-9.62	-3.50	-2.65	-1.77	-3.36	-8.93	-9.45	-7.87
R^2	**0.995**	**0.993**	**0.991**	**0.997**	**0.991**	**0.997**	**0.995**	**0.992**	**0.995**	**0.994**
Hixon Crowell										
B	-3.93	-2.60	-2.03	-3.40	-2.18	-3.02	-2.96	-2.17	-2.33	-2.90
A	25.49	25.71	28.45	24.90	25.70	24.39	25.02	27.61	27.16	26.08
R^2	-0.99	-0.97	-0.98	-0.98	-0.99	-0.98	-0.97	-0.983	-0.98	-0.98
Korsmeyer and Peppas										
A	-0.44	-0.57	-0.73	-0.46	-0.57	-0.47	-0.51	-0.67	-0.65	-0.55
n	**0.525**	**0.561**	**0.603**	**0.523**	**0.506**	**0.513**	**0.536**	**0.583**	**0.589**	**0.562**
R^2	0.995	0.995	0.992	0.998	0.988	0.998	0.997	0.992	0.995	0.996

B = slope, A= intercept, R^2= Square of correlation coefficient, n= diffusion exponent

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