ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Design and Evaluation of Famotidine Matrix Tablet Using 3^2 Factorial Design.

Jadhao UT*, Thakare VM, Chaudhari KP, Tekade BW, Chaudhari CS, and Patil VR

Department of Pharmaceutics T.V.E. S H.L.M.C.College of Pharmacy Faizpur, India.

ABSTRACT

The Aim of current study was to design an oral sustained release matrix tablet of Famotidine and to optimize the drug release profile using responce surface methodology.Tablets were prepared by wet granulation method using HPMCK100M and Xanthan gum as matrix forming polymer.A central composite design for 2 factor at 3 levels each was employed to systematically optimize drug release profile.HPMCK100M (X1)and Xanthan gum(X2) were taken as the indepndent variables.The dependent variables selected were % of drug release in 2 hr (Q_2),% drug release in 8 hr (Q_8) and time to 50% drug release ($t_{50\%}$).plots were drawn,and optimum formulation were selected by feasibility and grid searches. The granules was evaluated for the bulk density, tapped density, angle of repose, compressibility index and Hausner ratio. The values indicate good flow and compression properties. The compressed tablets were evaluated in terms of their physical characteristics, *in vitro* release, swelling property. All the observations are within the prescribed limits. . The in vitro data were fitted to different Kinetic order. The formulated tablets exhibited Non–fickian drug release kinetics approaching Zero–order as the value of release rate exponent (n) varied between 0.6024 and0.7354.

Keywords: Sustained Release; Matrix Tablet; Hydroxyl propyl methyl cellulose (HPMC K100); Xanthan gum; Central composite design.

Corresponding author
umj81@rediffmail.com

ISSN: 0975-8585

INRODUCTION

Sustained or controlled release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half – life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance [1]. Matrix type sustained delivery systems are popular because of their ease of manufactures. It excludes complex production procedure such as coating and pellitization during manufacturing and drug release from the dosage form is controlled mainly by the type and proportion of the polymers used in the preparation. Hydrophilic polymer matrix is widely used for formulating a sustained release dosage forms [2].Hydrophilic polymer matrix system are widely used for designing oral sustained release delivery systems because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The hydrophilic polymer selected for the present study was HPMCK-100. HPMCK–100 forms transparent tough and flexible films from aqueous solution[2] the films dissolve completely in the gastrointestinal tract at any biological pH and provide good bioavailability of the active ingredient.xanthan gum was also used along with the HPMC K-100 to get the required sustained release of the drug. [3]

Famotidine [4] is a potent H2 receptor antagonist used in the management of benign gastric and duodenal ulceration, zollinger-Ellison syndrome and gastro oesophageal reflux disease. Conventional oral formulations of Famotidine are administered multiple times a day. Treatment of gastric acid secretion using conventional formulations of Famotidine is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multi dose therapy and poor patient compliance. Controlled release formulations of Famotidine can overcome some of these problems.

MATERIALS AND METHODS

Famotidine was obtained as gift sample by IPCA Pharmaceutical laboratories Ltd,Indore indore.(MM.P) India. HPMC-K100M and xanthan gum were obtained as a gift sample from the Colorcon Asia Pvt. Ltd., Goa, India. All other materials and solvents used were of analytical grade.

Preparation of Sustained Release Matrix Tablets:

The composition of different sustain release formulations prepared using varying amounts of the polymers (HPMC K 100 and Xanthan gum) and granulated using Povidone in Iso-propyl alcohol along with the fixed quantity of magnesium stearate as the lubricant. Drug and the excipient were homogeneously blended and subsequently compressed using Eight station tablet machine, equipped with flat punch 8 mm punch (Jaguar JMD-8).

Experimental Design:

A 3 randomized full factorial design was used, in this design 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of HPMCK100 (X_1) and amount of xanthan gum (X_2) were selected as independent variables. The time required for 50% drug(t_{50}) dissolution percentage drug release at 2 hours (Q_2) and percentage release at 8 hours (Q_8) Given in table no-2 were selected as dependent variable [4,5].

Physical Evaluation of Granules:

The flow properties of granules were characterized in terms of angle of repose, Carr index and Hausner's ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner's ratio were calculated [6-9].

Evaluation of Famotidine Matrix Tablets:

Tablets from all the formulations were evaluated for various properties like hardness, Friability and weight variation.

Content Uniformity:

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100 ml of pH 7.4 phosphate buffer saline. Followed by stirring for 30 min. Dilute suitably and the absorbance of resultant solution was measured spectrophotometrically at 265 nm using pH 7.4 phosphate buffer saline as a blank.

***In-vitro* Drug Release studies:**

The release rate of famotidine from controlled release tablets was determined using USP dissolution testing apparatus 2 (paddle method). The dissolution test performed using 900 ml of pH 7.4 phosphate buffer saline at 37±0.5^{0}C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The sample were filtered through a 0.45 µ membrane filter and dilute to a suitable conc. with pH 7.4 phosphate buffer saline. Absorbance of these solutions was measured at 265 nm using UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.

Swelling Characteristic

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume [10, 11]. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule the liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting

ISSN: 0975-8585

in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet. From each formulation, one tablet was weighed and placed in a dissolution test apparatus, in900 ml of enzyme free simulated gastric fluid at 37 ±0.5°C. After predetermined time interval the tablet was removed from apparatus, blotted to remove excess water and weighed. The swelling characteristics were expressed in terms of the percentage water uptake (WU %) according to following equation

$$\text{Swelling Index (S.I.)} = \{(W_t - W_o)/W_o\} \times 100$$

Where, S.I. = swelling index
W_t = weight of tablet at time t
W_o = weight of tablet before immersion.

Kinetic Modelling of Drug Release:

Analysis of drug release from swellable matrices must be performed with a flexible model that can identify the contribution to overall kinetics The dissolution profile of all the batches was fitted to various models such as zero-order Higuchi, Korsmeyer and Peppas to ascertain the kinetic modelling of drug release [12, 14].

Table no.1-Composition of Famotidine matrix tablet.

Ingredient	Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Famotidin	40	40	40	40	40	40	40	40	40
Hpmck100m	20	30	40	20	30	40	20	30	40
Xanthan gum	20	20	20	30	30	30	40	40	40
Lactose	110	100	90	100	90	80	90	80	70
PVPK30M	10	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10

Table 2: Formulation and Dissolution Characteristics of Batches in 3^2 Factorial Designs

Batch code	Coded value		$t_{50\%}$	% Release at (Q_2)	% Release at(Q_8)	n	r^2
	X1	X2					
F1	-1	-1	260	27.74	81.78	0.6845	0.9962
F2	0	-1	279	23.55	75.11	06984	0.9918
F3	+1	-1	301	21.27	71.08	0.6935	0.9934
F4	-1	0	356	24.82	78.81	0.6947	0.9949
F5	0	0	291	19.66	68.21	0.6984	0.9822
F6	+1	0	297	17.07	63.42	0.7354	0.9527
F7	-1	+1	367	20.11	76.82	0.7000	0.9927
F8	0	+1	371	21.21	71.40	0.6806	0.9786
F9	+1	+1	378	18.20	65.70	0.6024	0.9735

ISSN: 0975-8585

Coded value	Actual value	
	X1	X2
-1	20	20
0	30	30
+1	40	40

where X1 –amount of HPMCK100M, X2-amount xanthan gum ($t_{50\%}$)- time required for 50% of drug release, (Q_{2})-Percentage release at 2 hr,(Q_{8})-percentage drug release at 8 hr. n= Release component obtained from Koresmeyer Equation, r2 = regression coefficient.

Table No.3. Charesterastic of Precompression.

Batches	Parameters				
	Bulk Density(gm/cc)	Tapped Density(gm/cc)	Angle of Repose	Compressibility Index (%)	Hausner Ratio
F1	0.465	0.502	29.72	9.01	1.19
F2	0.487	0.515	31.21	5.66	1.17
F3	0.440	0.465	30.32	5.57	1.12
F4	0.422	0.453	28.85	7.24	1.18
F5	0.462	0.494	30.19	6.91	1.15
F6	0.417	0.441	30.15	5.57	1.13
F7	0.462	0.496	33.58	7.44	1.10
F8	0.417	0.439	29.37	5.26	1.23
F9	0.372	0.391	31.38	5.08	1.18

Table No.4 Evaluation of Famotidine Matrix Tablet Fomatidine Matrix Tablet.

Batches	Parameters				
	Hardness	Weight Variation	Friability	Drug content	Thickness
F1	4.6± 0.21	0.220±0.49	0.036	98.96±0.62	1.92±0.05
F2	4.2±0.20	0.220±0.42	0.049	97.93±1.50	1.91±0.01
F3	5.7±0.17	0.219±0.44	0.061	97.98±1.47	1.9±0.06
F4	5.9±0.20	0.220±0.38	0.061	98.23±1.61	1.91±0.04
F5	4.2±0.21	0.219±0.38	0.062	98.45±1.12	1.89±0.05
F6	5.6±0.15	0.220±0.39	0.048	98.26±0.96	1.92±0.03
F7	5.0±0.21	0.219±0.37	0.076	98.96±0.96	1.9±0.06
F8	5.7±0.12	0.220±0.26	0.061	98.49±0.84	1.91±0.04
F9	5.9±0.10	0.220±0.37	0.037	98.18±1.31	1.92±0.05

Table 5: Summary of Results of Regression Analysis

Model	T50%		Q2		Q8	
	coeficent	p-value	coeficent	p-value	coeficent	**p-value**
Intercept	291.00	**0.0012**	19.66	0.0290	68.21	**0.0001**
X1	-1.45	0.8086	-0.53	0.4209	-3.67	**0.0001**
X2	42.98	**0.0001**	-1.78	0.0247	-6.12	**0.0001**
X1X2	-7.50	0.3869	0.37	0.6876	-1.66	0.0342
$X1^2$	26.25	**0.0039**	0.64	0.3699	2.57	**0.0010**
$X2^2$	13.25	0.0700	2.65	**0.0055**	2.13	**0.0030**
R^2	0.9163		0.7808		0.9776	

- R2 value for Q6, Q12 and T50% are 0.9197, 0.9425 and 0.8299 respectively indicating good correlation between dependent and independent variables. The terms with P<0.05 were considered statistically significance.

RESULT AND DISCUSION

All the tablets of factorial design batches showed good physical property The bulk density of granules was found to be between 0.372 ± 0.04 to 0.487 ± 0.073 g/cm. This indicates good packing capacity of granules. Carr's index was found to be between 5.08 ± 0.03 to 9.01 ±0.10 showing good flow characteristics. Hausner ratio low range was indicates good flow ability. The angle of repose of all the formulations within the range of 28.85 ±0.08 to 33.58 ± 0.12 i.e. granules were of good flow properties. The hardness of tablet was in range of 4.2± 0.21 to 5.9 ± 0.40 measured by Monsanto hardness tester. The friability was in range of 0.036 ± 0.02 to 0.061± 0.01. The values of average weight are within limit. Drug content was in range of98.93 ± 0.62 to 98.96± 0.13 indicating good content uniformity in the prepared formulation results shown in table no-3& 4.

A 3^2 factorial design was constructed to study the effect of the amount of HPMCK100 (X1) and Xanthan gum (X2) on the drug release from matrix tablet of Famotidine respectively. The dependent variables chosen were times required for 50% drug release (t_{50}), percentage drug 50% release at 8 hours (Q_8) and percentage drug release at 2 hours (Q_2) given in **.** A statistical model incorporating interactive and polynomial term was used to evaluate the responses.Shown in table No.2

Where, Y is dependent variable, b0 is the arithmetic mean response of the 9 runs, and b1 (b1 b2, b12, b11 and b22 is the estimated coefficient for the factor X1 the main effect. (X1 and X2) represents the average results of changing one factor at a time from its low to high values. The interaction term (X1 X2) show how the response changes, when 2 factors are changed simultaneously. The polynomial term (X_1^2 and X_2^2) are included to investigate nonlinearity. The $t_{50\%}$, Q_2 and Q_8, for 9 batches (F1- F9) showed a wide variation (i.e. 260-378 min, 18.21-27.74, 65.70-81.78% respectively). The2 responses of formulation prepared by 3 factorial designs are indicated in Table 2. The data clearly indicate that the t_{50}, Q_2 and Q_8 were strongly dependent on the selected independent variables. The fitted equation relating the response $t_{50\%}$, Q_2 and Q_8 to the transformed factors are,

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X1X1 + b22X2X2$$

$$T_{50\%}=291.00-1.45X_1+42.98X_2-7.50X_1X_2+26.25X_1^2+13.25X_2^2 . (R^2=0.9163)$$

$$Q6=19.66-0.53X_1-1.78X_2+0.37X_1X_2+0.64X_1^2+2.65X_2^2. (R^2=0.7808)$$

$$Q12=68.21-3.67X_1-6.12X_2-1.66X_1X_2+2.57X_1^2+2.13X_2^2. (R^2=0.9776)$$

The values of the correlation coefficient indicate a good fit. (Fig 1-6.) Shows the plot of the amount of HPMC K100M (X1) and amount of xanthan gum (X2) versus $t_{50\%}$ Q_2 and Q_8 respectively. The data demonstrate that both X1 and X2 affect the drug release ($t_{50\%}$, Q_2 and Q_8). It was concluded that the low level of X1 (amount of HPMCK-100M) and the low level of X2 (amount of xanthan gum) favour the preparation of sustained release Matrix tablets. The high value of X1X2 coefficient also suggests that the interaction between X1 and X2 has a significant effect on t50% An increase in the concentration of HPMCK100M (X1) and amount of xanthan gum (X2), decrease rate of release of sustained release Matrix tablet respectively.

The fitted equations relating the responses, Q_2, Q_8, $T_{50\%}$ to the transformed factor are shown in the Table No.5The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive). Table No. 5 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Data were analyzed using Microsoft Excel.

The swelling index was calculated with respect to time. the % swelling index was initially more up to 1 hr. but then swelling was slowed down. This occurs because, at first hydration of polymer at surface take place fastly so the swelling is more but afterwards the diffusion path length is increased causing slow penetration of water and slow swelling of polymer. The gel layer thickness depends on water penetration, polymer chain disentanglement and mass transfer in water. After some time when diffusion path is more, water penetrates slowly and there is little change in gel thickness because water penetration and chain disentanglement rates are similar.

From the dissolution study of batch F1 to F9, it was concluded that release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The drug release study was carried out up to 12 hrs. The percentage drug release from batch F1 to F9 vary from 79.98 to 97.42 %. Large concentration of high viscosity polymer induces the formation of strong viscous gel layer that slowed down the rate of water diffusion into the tablet matrix, which may result in the retardation or decreases the drug release. Dissolution profiles for all batches were shown in (Fig. 7). The effect of Xanthan gum on drug release from matrices, increasing the concentration of Xanthan gum in matrix showed somewhat retardation of drug release. The drug release profile of tablets with combination of xanthan gum and HPMC K 100 M. The combinations of polymers significantly retard the release for more than12 hrs. As the concentration of HPMC K100 M increased the release rate decreased. An increase in the polymer i.e. HPMC K100M and Xanthan gum concentration causes the increase in viscosity of gel and also the formation of gel layer with longer diffusional path. This may decrease the effective diffusion coefficient of drug and therefore there is reduction in drug release rate.

ISSN: 0975-8585

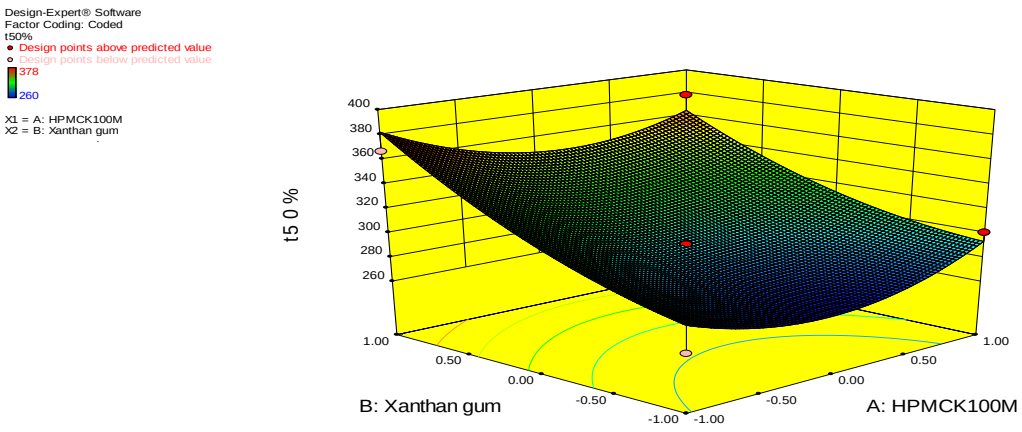

Fig plot

Fig-no-1 Responce surface plot for $t_{50\%}$ f

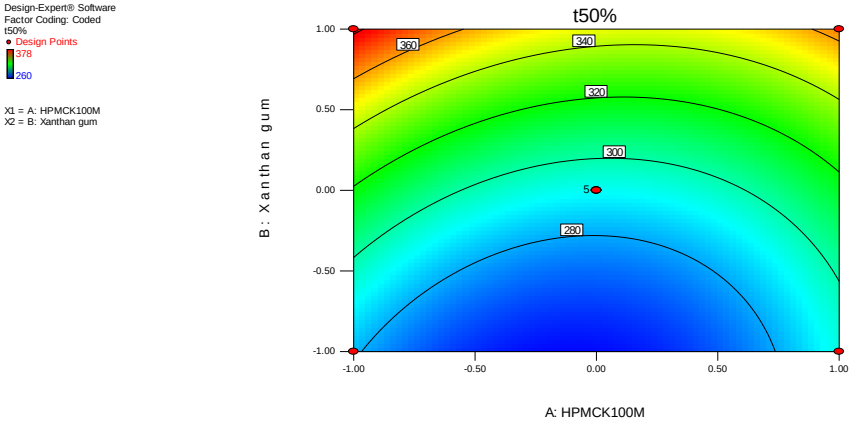

Fig-No-2. Counter Plot for $t_{50\%}$

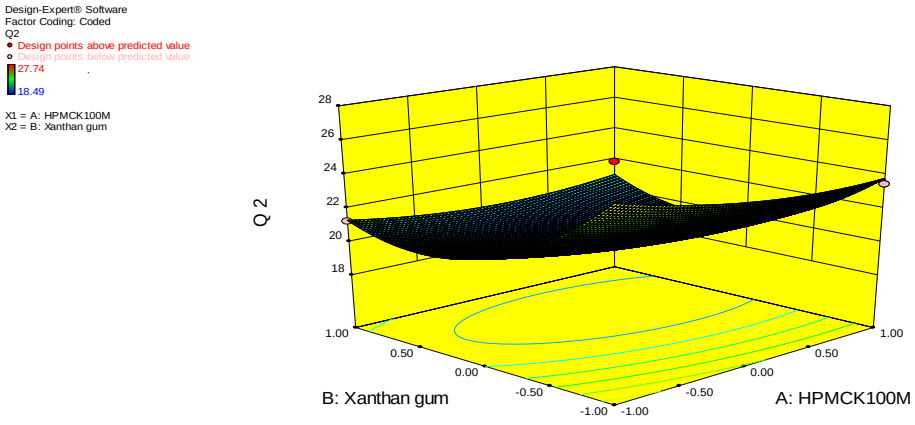

Fig-no-3 Responce surface plot for Q_2 Re splot fo

ISSN: 0975-8585

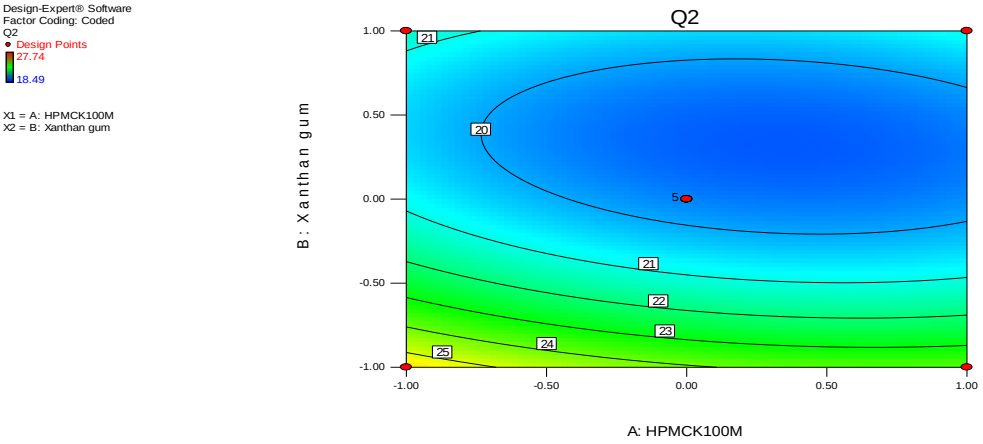

Fig-no-4.Counter plot for Q_2 Figfor

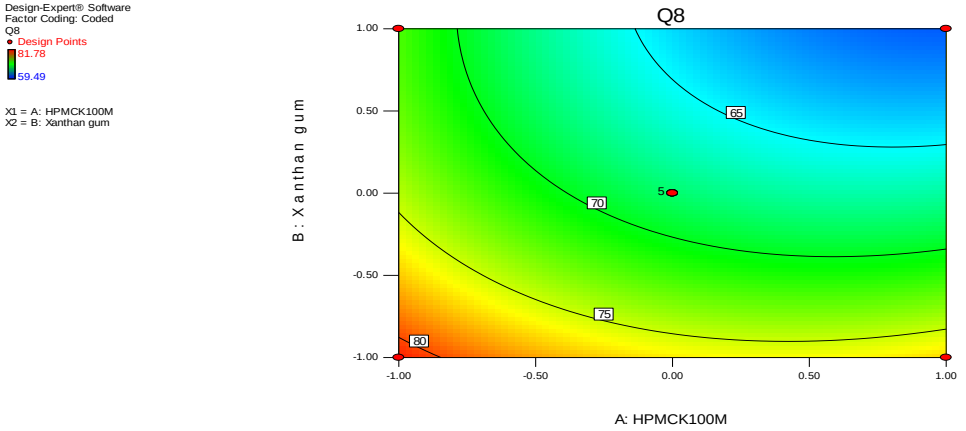

Fig Fig-no-5.Counter plot for Q_8

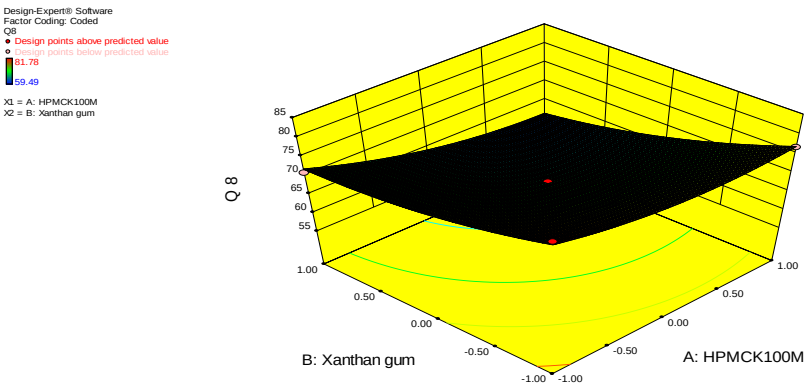

Fig-no-6 Responce surface plot for Q_8

ISSN: 0975-8585

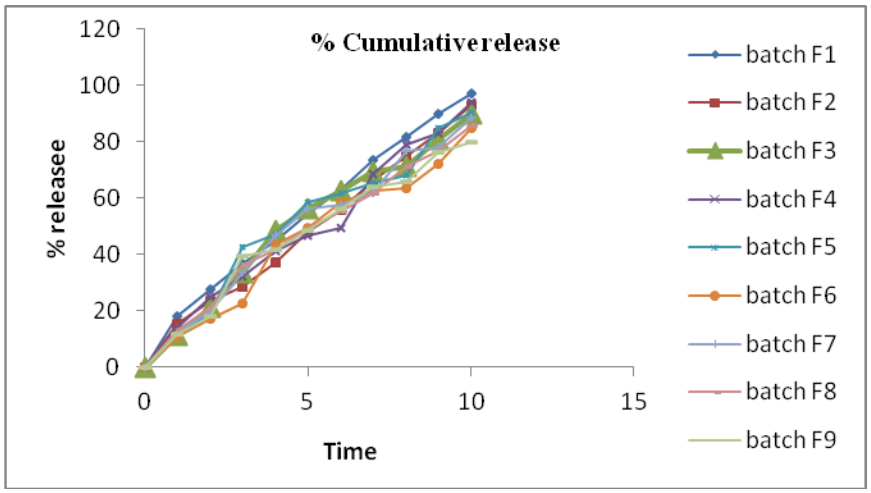

Fig Fig-no-7 Results of % drug release Vs time R

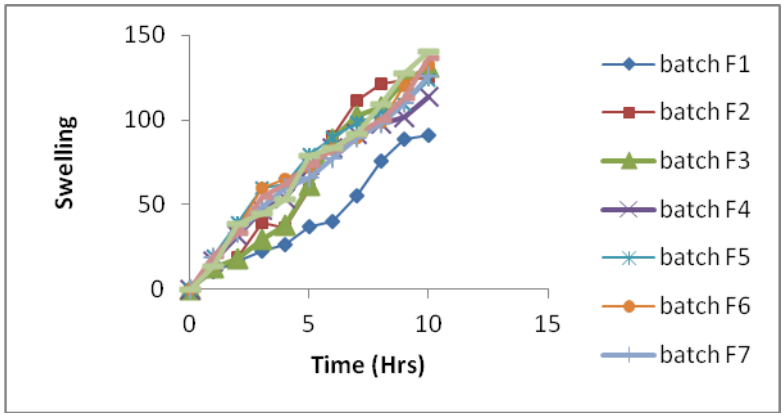

Fig-no-8 Results of % Swelling Vs time R

REFERENCES

[1] Banker GS, Rhodes CJ, 1996 "Sustained & Controlled Release Drug delivery systems". New York: Marcel Dekker: 303-516.

[2] Chein YW. Novel drug delivery systems. 2nd ed. New York: Marcel Dekker Inc., 1997pp.142.

[3] Ritchel WA. Drug Dev Ind Pharm 1989; 15: 1073-103.

[4] Bolton S. Pharmaceutical Statistic, Practical and Clinical Applications, 1990, 2nd Edition, Marcel Dekker INC, New York and Basel, 308.

[5] Armstrong NA, James KC. Pharmaceutical Experimental Design and Interpretation, 1996, Taylor and Francis 131-136.

[6] Patel VF, Patel NM. AAPS Pharm Sci Tech 2006; 7:118-124.

[7] Jaimini M, Rana AC, Tanwar YS. Curr Drug Deliv 2007; 4:51-55.

[8] Dave BS, Amin AF, Patel MM. AAS Pharm Sci Tech 2004; 5:34-42.

[9] Umarunnisha AM, S Palanichamy, M Rajesh, S Jeganath and A Thangathirupathi. Archives of Applied Science Research 2010, 2 (3):212-220.
[10] Stops F, Fell JT, Collett JH. Int J Pharm 2006;308:8–13.
[11] Timmermans J, Moes A J. J Pharm Sci 1994; 83: 18-24.
[12] Billa N, Yuen KH. AAPS Pharmscitech 2000; 1(4):30.
[13] Wagner JG. J Pharm Sci 1969;58:1253-1257.
[14] Higuchi Mechanism of sustained action medicament, Theoretical analysis of rate release of solid drugs dispersed in solid matrices, J Pharmsci 1963;52:1145-1149.
[15] Korsmeyer RW, Gunny R, Peppas NA. Int J Pharmaceutics 1983;15: 25-35.