Formulation and Evaluation of Cephalexin Extended Release Matrix Tablets Using 3² Factorial Design

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ABSTRACT

The aim of the present investigation was to prepare extended release film coated matrix tablets of cephalexin using binary mixture of two grades of hydrophilic polymer, hydroxypropyl methyl cellulose (HPMC), by direct compression method. Results of the preliminary trials indicated that the polymers used have significant release retarding effect on the formulation. To study the effect of concentration of polymers on drug release from matrix tablets, 3² full factorial design was applied. The concentration of HPMC K15M and HPMC 15cps were used as independent variables, while percentage drug release was selected as dependent variable. The dissolution data were fitted into zero-order, first-order, Higuchi and Korsemeyer–Peppas models to identify the pharmacokinetics and mechanism of drug release. Comparative study of dissolution profile of final batch F3 with market preparation (Sporidex AF 375) was done by similarity factor (f_2) determination and it was concluded that final formulation F3 (10% HPMC K15M, 17.5% HPMC 15cps) shows good similarity with the market product. The results of the accelerated stability study of final formulation F3 for 1 month revealed that storage conditions were not found to have made any significant changes in final formulation F3. The release of cephalexin was prolonged for 6 h by using polymer combinations of HPMC and a twice daily matrix tablet was formulated.

Key words: Cephalexin, factorial design, hydroxypropyl methyl cellulose, matrix tablets, release kinetics, similarity factor (f_2)

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. Extended release oral drug formulations have been used since 1960s to enhance performance and increase patient compliance.[1] By incorporating the dose for 24 h into one tablet from which the drug is slowly released, peaks of high plasma concentration and troughs of low plasma concentration can be prevented.[2] This helps to avoid the side effects associated with high concentrations and the lack of activity associated with low concentrations, giving better overall therapy. In biopharmaceutics, scientists generally are faced with an engineering problem: To develop drug delivery systems that hit a desired target. The target in pharmacokinetics

is generally a plasma/blood drug concentration that lies between the minimum effect concentration (MEC) and minimum toxic concentration (MTC). Cephalexin is a semisynthetic antibiotic derived from cephalosporin C and is almost completely absorbed from the gastrointestinal tract, with a bioavailability of 95%. Cephalexin has a half-life of around 1.1 h.[3-5] To maintain therapeutic range, the drug should be administered 3–4 times a day, which leads to sawtooth kinetics and resulting in ineffective therapy.[6] Addressing this problem, we attempted to formulate extended release tablets of cephalexin, which can provide constant effective drug level for 6 h, based on calculations considering pharmacokinetic parameters.

MATERIALS AND METHODS

Materials

The chemicals used in the experiment were: Cephalexin monohydrate (Aurobindo Pharma Ltd., Hyderabad, India), microcrystalline cellulose PH102 (Weiming Industries, China), lactose anhydrous (DMV-Fonterra Excipients, Germany), hydroxypropyl methyl cellulose (HPMC) 15cps and HPMC K15M (Feicheng Ruitai Fine chemicals, China), colloidal silicon dioxide (Degussa India Pvt. Ltd., Mumbai, India), magnesium stearate (Ferro Corporation, USA), Sporidex AF 375 (Ranbaxy laboratories Pvt. Ltd., Gurgaon, India). All the other reagents used were of analytical grade.

Methods

Preparation and evaluation of cephalexin monohydrate granules[7]
Accurately weighed quantities of drug and excipients were passed through sieve no: 20 and 40, respectively. Drug and excipients (excluding lubricant) were added in geometric proportions and mixed thoroughly for 15 min. The blend was mixed finally with lubricant to get the granules of cephalexin monohydrate. The flow properties of granules were characterized in terms of angle of repose, Carr's index and Hausner's ratio. The bulk density and tapped density were determined using USP bulk density apparatus (Veego Industries, Mumbai, India). The data summarized in Table 1.

Formulation of cephalexin matrix tablets using direct compression method[8]
The prepared granules of cephalexin monohydrate were compressed in 15 × 8.5 mm punches of 27 station rotary tablet compression machine (CMB4D Cadmach, Ahmadabad, India). The formulae for batches F1–F9 are shown in Tables 2 and 3.

Table 1: Pre-compression parameters of final batches F1–F9

Code	Angle of repose (θ)*	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index (%)	Hausner's ratio
F1	32°21′ ± 0.57	0.58 ± 0.41	0.72 ± 0.18	19.22 ± 0.31	1.23 ± 0.43
F2	34°16′ ± 0.32	0.57 ± 0.54	0.68 ± 0.23	16.22 ± 0.58	1.19 ± 0.38
F3	33°35′ ± 0.64	0.56 ± 0.27	0.67 ± 0.45	16.14 ± 0.19	1.19 ± 0.87
F4	34°45′ ± 0.87	0.57 ± 0.36	0.70 ± 0.52	17.75 ± 0.72	1.21 ± 0.66
F5	32°31′ ± 0.49	0.58 ± 0.19	0.72 ± 0.31	19.97 ± 0.54	1.24 ± 0.33
F6	34°43′ ± 0.71	0.54 ± 0.32	0.65 ± 0.49	16.67 ± 0.27	1.20 ± 0.18
F7	35°17′ ± 0.36	0.56 ± 0.67	0.68 ± 0.48	18.10 ± 0.16	1.22 ± 0.25
F8	35°26′ ± 0.25	0.56 ± 0.22	0.68 ± 0.14	16.88 ± 0.23	1.20 ± 0.55
F9	34°43′ ± 0.68	0.55 ± 0.12	0.66 ± 0.65	16.19 ± 0.69	1.19 ± 0.79

*The values are expressed as Mean ± SD; *n*=3

Table 2: Composition of optimization batches F1–F5

Ingredients	Quantity used (mg/tab)				
	F1	F2	F3	F4	F5
Cephalexin monohydrate	401.25	401.25	401.25	401.25	401.25
Microcrystalline cellulose	22.15	36.65	7.65	33.75	48.25
HPMC K15M	58.00	58.00	58.00	46.40	46.40
HPMC K15cps	87.00	72.50	101.50	87.00	72.50
Colloidal silicon dioxide	5.80	5.80	5.80	5.80	5.80
Magnesium stearate	5.80	5.80	5.80	5.80	5.80
Average tablet weight	580.00	580.00	580.00	580.00	580.00

Table 3: Composition of optimization batches F6–F9

Ingredients	Quantity used (mg/tab)			
	F6	F7	F8	F9
Cephalexin monohydrate	401.25	401.25	401.25	401.25
Microcrystalline cellulose	19.25	45.35	59.85	30.85
HPMC K15M	46.40	34.80	34.80	34.80
HPMC K15cps	101.50	87.00	72.50	101.50
Colloidal silicon dioxide	5.80	5.80	5.80	5.80
Magnesium stearate	5.80	5.80	5.80	5.80
Average tablet weight	580.00	580.00	580.00	580.00

Evaluation of tablet properties[8,9]
The prepared cephalexin matrix tablets were evaluated for thickness, hardness, friability, uniformity of weight and drug content. The thicknesses of tablets were measured using vernier caliper (Aerospace, China). Hardness of tablets was tested using a validated modified dial type hardness tester (Shivani Scientific Industries, Mumbai, India). Friability of tablets was determined by using Roche Friabilator (Electrolabs, Banglore, India). The drug content of each batch was determined as per USP assay of cephalexin using high performance liquid chromatography (HPLC; SCL-10AVP, Shimadzu Corporation, Japan).[10] The results are shown in Table 4.

In vitro drug release study
The drug release studies of cephalexin matrix tablets were performed using dissolution testing apparatus USP type I (Basket type; Electrolabs, Banglore, India). The dissolution

testing was performed using 900 ml of 0.01 N HCl for the 1st h and phosphate buffer, pH 6.8, from 2nd h to 6th h at 37 ± 0.5°C temperature and speed 100 rpm for 6 h. A sample (5 ml) of the solution was withdrawn from the dissolution testing apparatus at 1st, 2nd, 4th and 6th h and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 μm membrane filter and diluted to a suitable concentration with the corresponding medium. Absorbance of these solutions was measured at 262 nm using UV-1650 spectrophotometer (Shimadzu Corporation, Japan).[11] The *in vitro* drug release specification was 20–40% at 1st h, 40–60% at 2nd h, 60–80% at 4th h and >80% at 6th h, determined from theoretical drug release and dissolution pattern of the marketed product. The *in vitro* drug release data is a singular term which shows a single set of grouped data shown in Table 5 and also graphically represented in Figures 1 and 2.

Experimental design[12,13]

A 3^2 full factorial design was adopted and the amount of polymers, HPMC K15M (X_1) and HPMC K15cps (X_2), were taken as independent variables and cumulative percentage drug release at 1st h (Y_1), 2nd h (Y_2) and 4th h (Y_3) was taken as dependent variables as shown in Table 6. The factors were studied at three levels (−1, 0, +1) indicating

Table 4: Post-compression parameters of optimization batches F1–F9

Formulation	Weight variation (%)*	Thickness (mm)*	Hardness (kg/cm²)*	Drug content (%)	Friability (%)**
F1	1.32 ± 1.34	5.46 ± 0.05	10.26 ± 1.11	97.19	0.03 ± 0.35
F2	2.37 ± 2.16	5.54 ± 0.06	12.59 ± 2.20	95.66	0.04 ± 0.51
F3	2.13 ± 1.48	5.52 ± 0.04	11.23 ± 1.25	96.12	0.03 ± 0.82
F4	2.74 ± 2.79	5.43 ± 0.08	11.46 ± 1.74	96.64	0.04 ± 0.53
F5	1.55 ± 3.13	5.57 ± 0.07	10.28 ± 2.28	97.23	0.02 ± 0.67
F6	2.31 ± 2.42	5.43 ± 0.05	12.22 ± 2.35	95.16	0.06 ± 0.18
F7	1.12 ± 3.19	5.56 ± 0.06	10.61 ± 1.76	94.89	0.03 ± 0.52
F8	2.07 ± 3.67	5.54 ± 0.04	11.55 ± 2.22	98.48	0.05 ± 0.76
F9	2.72 ± 2.43	5.45 ± 0.02	10.57 ± 2.36	96.53	0.02 ± 0.84

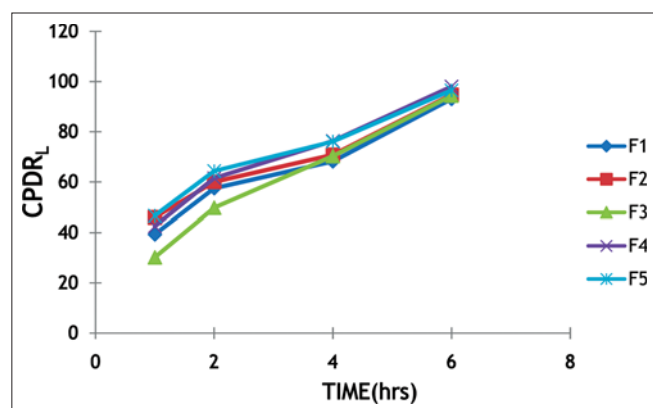*Values are expressed as mean ± SD; n=20. **Values are expressed as mean ± SD; n=3

low, medium and high, respectively, as represented in Table 7. The statistical optimization procedure was performed with the help of optimization softwares like Design Expert 8 (Stat-Ease Inc., Minneapolis, MN, USA)

Table 5: Dissolution profiles of optimization batches F1–F9

Formulation code	Cumulative percentage drug release (%)*			
	1st h	2nd h	4th h	6th h
F1	39.31 ± 0.73	57.48 ± 0.99	68.16 ± 0.99	93.07 ± 1.10
F2	45.96 ± 0.72	59.99 ± 1.02	70.82 ± 0.99	94.74 ± 1.29
F3	30.18 ± 1.12	49.74 ± 1.54	70.24 ± 1.50	94.38 ± 0.76
F4	42.51 ± 0.73	61.47 ± 1.30	76.33 ± 0.73	98.00 ± 1.24
F5	46.64 ± 0.62	64.36 ± 0.89	76.09 ± 0.80	96.48 ± 1.08
F6	33.64 ± 0.89	55.22 ± 0.74	73.21 ± 0.90	97.34 ± 0.80
F7	43.96 ± 1.02	64.34 ± 1.69	82.41 ± 1.01	97.12 ± 0.92
F8	48.68 ± 0.65	68.49 ± 0.78	84.39 ± 1.15	98.45 ± 0.59
F9	35.13 ± 1.35	58.76 ± 0.81	81.85 ± 0.93	98.34 ± 0.89

*Values are expressed as mean ± SD; n=6

Table 6: Factors and responses evaluated in 3^2 factorial design

Formulation code	Factors in coded form		Responses (%)		
	HPMC K15M (X_1)	HPMC 15cps (X_2)	Drug release at 1st h (Y_1)	Drug release at 2nd h (Y_2)	Drug release at 4th h (Y_3)
F1	0.0	0.0	42.51	61.47	76.33
F2	0.0	1.0	33.64	55.22	73.21
F3	1.0	1.0	30.18	49.74	70.24
F4	1.0	0.0	39.31	57.48	68.16
F5	−1.0	1.0	35.13	58.76	81.85
F6	1.0	−1.0	45.96	59.99	70.82
F7	−1.0	0.0	43.96	64.34	82.41
F8	0.0	−1.0	46.64	64.36	76.09
F9	−1.0	−1.0	48.68	68.49	84.39

Table 7: Correlation of actual and coded factors

Factor level	Coded form	Actual value (mg)		Actual value (%)	
		HPMC K15M	HPMC K15M	HPMC K15M	HPMC 15cps
Low	−1	34.80	72.50	6.00	12.50
Medium	0	46.40	87.00	8.00	15.00
High	+1	58.00	101.50	10.00	17.50

Figure 1: Cumulative percentage drug release of F1–F5
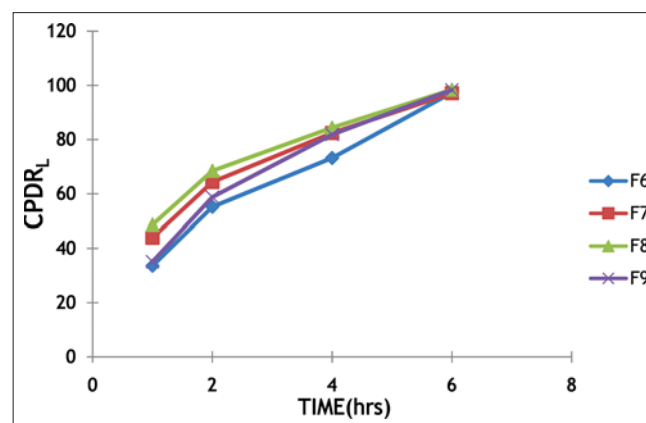

Figure 2: Cumulative percentage drug release of F6–F9

and Statgraphics Centurion XVI (StatPoint Technologies, Inc. Warrenton, Virginia, USA). The software performs the multiple regression analysis (MRA), analysis of variance (ANOVA) and statistical optimization.

Multiple regression analysis[12]

The use of regression analysis in 3^2 factorial design generates polynomial equations for different models, with interacting terms and regression coefficients, useful in evaluating the responses. The software generates two models, particularly, full model (non-significant terms included) and reduced model (excluding non-significant terms). In the full model study, the responses were analyzed using the quadratic equation below:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

where Y is the response evaluated, b_0 is the arithmetic mean response of 9 runs and b_i is the estimated coefficient of X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) were included to investigate nonlinearity.

In the reduced model study, the non-significant terms in the quadratic equation are removed using backward regression procedure to generate a reduced model which is more important in studying the influence of factors on the responses evaluated. The value and sign of regression coefficient (b_i) indicates the magnitude of influence of the particular term on the response. The regression coefficients give the average change in a response when the particular factor is changed by a unit, when all the other terms remain constant. A positive sign on the regression coefficient indicates the factor has a positive effect on the response and negative sign indicates a negative effect.

ANOVA study[13]

The software performs the individual analysis of responses and calculates the sum of squares (SS), mean square (MS), Fischer's ratio (F statistics) and *P* value. The F statistics and *P* value give the significance level of each term, considering the null hypothesis (H_0) is true. The terms with a *P* value less than 0.05 are considered significant at a level of significance $\alpha = 0.05$. When the F value obtained is greater than the critical F value from the F distribution table, the factor becomes significant and the null hypothesis is rejected.

Comparison of dissolution profiles[14]

The similarity in drug release pattern of the marketed product (Sporidex AF 375) and the formulation developed was compared by similarity factor (f_2) determination. The two products are said to be similar if the value of f_2 lies between 50 and 100. The similarity factor and a similarity testing have been recommended for dissolution profile comparison in the Food and Drug Administration (FDA)'s Guidance for Industry. The f_2 is calculated using the formula given below:

$$f_2 = 50 \log\{1 + 1/n\sum_{t}^{n=1}(Rt - Tt)2] - 0.5*100\},$$

where R_t is the percentage of reference product dissolved at a specified time, T_t is the percentage of test product dissolved at a specified time, and n is the number of sampling points.

Pharmacokinetic study[14,15]

To study the release kinetics, the data obtained from *in vitro* drug release studies were plotted in various kinetic models as follows:

1. Zero order: Cumulative % of drug released versus time ($Q_t = Q_0 - K_0t$);
2. First order: Log cumulative % of drug remaining versus time ($\ln Q = \ln Q_0 - K_1t$);
3. Higuchi: Cumulative % of drug released versus square root of time ($Q = Kt^{1/2}$); and
4. Korsmeyer–Peppas: Log cumulative % of drug released versus log time ($M_t/M_\alpha = Kt^n$),

where Q_i and K_i stand for the amount of drug release and kinetic release constant, respectively. M_t/M_α indicates the fractional drug release and "*n*" is the diffusional exponent which gives the mechanism of drug release. When *n*<0.5, the drug diffuses through the polymeric matrix by a Fickian (case I) diffusion mechanism. For 0.5 < *n*<1, an anomalous (non-Fickian) mechanism occurs; *n*=1 indicates a zero-order (case II) and *n*>1 indicates non-Fickian super case II release mechanism.

The plots were drawn using Microsoft excel 2007 and the regression equations were obtained for each plot. The linearity of the plots was obtained from the value of regression coefficient (R). The model with the highest linearity (R value approaching unity) was chosen as the best fit kinetic model.

Accelerated stability studies[16]

Short-term accelerated stability studies were performed on the optimized tablet formulations of blister packed cephalexin extended release tablets. The tablets were subjected to stability studies at 40°C/75% relative humidity (RH) in a stability chamber (Servewell Instrument Pvt. Ltd., Bengaluru, India) for a period of 1 month. Initial evaluation

of the tablets was done, and at the end of first month the tablets were again analyzed for their physical appearance, water content and *in vitro* drug release profile.

RESULTS AND DISCUSSION

The bulk density of granules was found to be between 0.54 ± 0.32 and 0.58 ± 0.41 g/cm³. This indicates good packing capacity of granules. Carr's index was found to be between 16.14 ± 0.19 and 19.97 ± 0.54, showing good flow characteristics. Hausner's ratio ranged from 1.19 ± 0.38 to 1.24 ± 0.33, which indicates good flowability. The angle of repose of all the formulations was within the range of $32°21' \pm 0.57$ to $35°26' \pm 0.25$, i.e. the granules of cephalexin have fair flow properties.

The thickness ranged from 5.43 ± 0.08 mm to 5.57 ± 0.07 mm, and the hardness ranged from 10.26 ± 1.11 kg/cm² to 12.59 ± 2.20 kg/cm². The friability ranged from 0.02 ± 0.67 to 0.06 ± 0.18. The values of percentage weight variation ranged from 1.12 ± 3.19 to 2.74 ± 2.79. Drug content ranged from $98.48 \pm 0.12\%$ w/w to $94.89 \pm 0.13\%$ w/w, indicating good content uniformity among the prepared formulations.

Multiple regression analysis

Backward regression analysis technique was used to generate the best fit models for the analyzed responses. The equations were obtained both for coded and actual values of factors. The final equation of reduced model contains only the significant factor terms corresponding to the response analyzed.

Reduced model equation for responses in terms of actual factors:
1. Release at 1st h (Y_1) = $24.49 - 0.18$ HPMC K15M + 1.08 HPMC 15cps − 0.009 HPMC 15cps²
2. Release at 2nd h (Y_2) = $46.35 - 0.35$ HPMC K15M + 1.047 HPMC 15cps² − 0.008 HPMC 15cps²
3. Release at 4th h (Y_3) = $102.2 - 0.5665$ HPMC K15M

Reduced model equation for responses in terms of coded factors:
1. Release at 1st h (Y_1) = $41.93 - 2.05 X_1 - 7.05 X_2 - 1.89 X_2^2$
2. Release at 2nd h (Y_2) = $61.10 - 4.06 X_1 - 4.85 X_2 - 1.67 X_2^2$
3. Release at 4th h (Y_3) = $75.94 - 6.57 X_1$

The inferences from reduced model analysis are: The release at 1st and 2nd h is influenced by both the polymers. The reduced model equation in actual factors indicates that

HPMC K15M decreases the drug release from the tablet during 1st, 2nd and 4th h as the coefficients carry a negative sign. It also indicates that the HPMC 15cps increases the drug release from the tablet during 1st and 2nd h as the coefficients carry a positive sign and the polymer has no effect at the 4th h as it is a non-significant term.

ANOVA (Analysis of variance) studies

The ANOVA of 1st h from Table 8 indicates that both HPMC K15M and HPMC 15cps are significant terms as the F values are above the critical F values, thus making the *P* values less than 0.05 (threshold level). Thus, the null hypothesis H_0 is rejected and the alternate hypothesis that the two polymers used significantly influence the rate of drug release from the cephalexin matrix tablets is found to be true.

The ANOVA of 2nd h from Table 9 shows that both HPMC K15M and HPMC 15cps are significant terms, indicating that both the polymers influence the rate of drug release at the 2nd h from the cephalexin matrix tablets and the alternate hypothesis holds good in this case.

The ANOVA of 4th h from Table 10 indicates that the only term significant is HPMC K15M, and HPMC 15cps was found to have no influence in the 4th h release from cephalexin matrix tablets. The polymer HPMC 15cps with a low viscosity is found to have rate-controlling effect only in the initial hours and HPMC K15M with a higher viscosity grade has rate-controlling effects even in the 4th h.

The 3D response surface plots give a representation of

Table 8: Analysis of variance for 1st h

Source	Sum of squares	DF	Mean square	F ratio	*P* value
A: K15M	25.2971	1	25.2971	55.09	0.0051*
B: 15CPS	298.638	1	298.638	650.40	0.0001*
AA	0.309422	1	0.309422	0.67	0.4719
AB	1.24323	1	1.24323	2.71	0.1984
BB	7.13161	1	7.13161	15.53	0.0291*
Total error	1.37749	3	0.459162		
Total (corr.)	333.997	8			

*Significant values. "DF" stands for degree of freedom

Table 9: Analysis of variance for 2nd h

Source	Sum of squares	DF	Mean square	F ratio	*P* value
A: K15M	99.0641	1	99.0641	205.77	0.0007*
B: 15CPS	141.329	1	141.329	293.57	0.0004*
AA	0.605	1	0.605	1.26	0.3439
AB	0.0676	1	0.0676	0.14	0.7328
BB	5.5778	1	5.5778	11.59	0.0423*
Total error	1.44427	3	0.481422		
Total (corr.)	248.088	8			

*Significant values. "DF" stands for degree of freedom

the variations in each response when the two factors are simultaneously changed from lower level to higher level. They also give a three-dimensional curvature of the change in response at different factor levels and also give the variation in design points from the predicted response value. The response plots are shown in Figures 3–5.

Pharmacokinetic report

The kinetic summary from Table 11 reveals that cephalexin extended release tablets follow zero-order kinetics as the regression coefficients approach unity, indicating that the drug release is independent of drug concentration. The *n* values from Korsemeyer–Peppas model show that the drug release pattern follows mainly Fickian diffusion mechanism, but erosion too plays a significant role as the formulations F3, F6, F9 show n values above 0.5. The Higuchi plots also show good linearity, indicating that the drug release is proportional to the square root of time and the drug release is at a slower rate as the distance of diffusion increases.

Comparison of dissolution profiles

The similarity factor (f_2) shown in Table 12 indicates that F3 gave the most similar dissolution profile to that of the marketed product. Thus, F3 was determined as the optimized product and is preferred for scale-up batches. The drug release pattern of optimized product F3 and theoretical release pattern were compared to determine the similarity and is shown in Figure 6. The graph shows good

correlation between the dissolution profiles of marketed product F3 and the theoretical release pattern.

Accelerated stability study report

The accelerated stability study report shown in Table 13 reveals that the formulation has not undergone any physical or chemical degradation during the period. There are no significant differences in the *in vitro* drug release and the drug content of the optimized formulation.

Table 10: Analysis of variance for 4th h

Source	Sum of squares	DF	Mean square	F ratio	P value
A: K15M	259.121	1	259.121	127.28	0.0015*
B: 15CPS	6.0	1	6.0	2.95	0.1845
AA	2.42734	1	2.42734	1.19	0.3547
AB	0.9604	1	0.9604	0.47	0.5415
BB	0.435556	1	0.435556	0.21	0.6752
Total error	6.10751	3	2.03584		
Total (corr.)	275.052	8			

*Significant values "DF" stands for degree of freedom

Table 11: Kinetics modeling summary

Code	Kinetic model							
	Zero order		First order		Korsemeyer		Higuchi	
	R^2	K_0	R^2	K_1	R^2	n	R^2	K_H
F1	0.964	9.950	0.844	0.679	0.967	0.45	0.960	34.48
F2	0.970	15.71	0.876	0.439	0.963	0.38	0.958	31.58
F3	0.997	21.31	0.924	0.483	0.994	0.62	0.993	43.00
F4	0.976	10.45	0.877	0.635	0.986	0.45	0.984	36.48
F5	0.969	9.288	0.894	0.513	0.979	0.38	0.976	32.37
F6	0.997	20.90	0.889	0.612	0.987	0.57	0.988	42.09
F7	0.994	17.75	0.95	0.573	0.989	0.43	0.989	35.80
F8	0.993	16.52	0.924	0.67	0.988	0.38	0.985	33.27
F9	0.993	21.27	0.995	0.469	0.985	0.57	0.990	42.95

R^2 = regression coefficient, K_0 = zero-order release rate constant, K_1 = first-order release rate constant, n=diffusional exponent, K_H = Higuchi rate constant
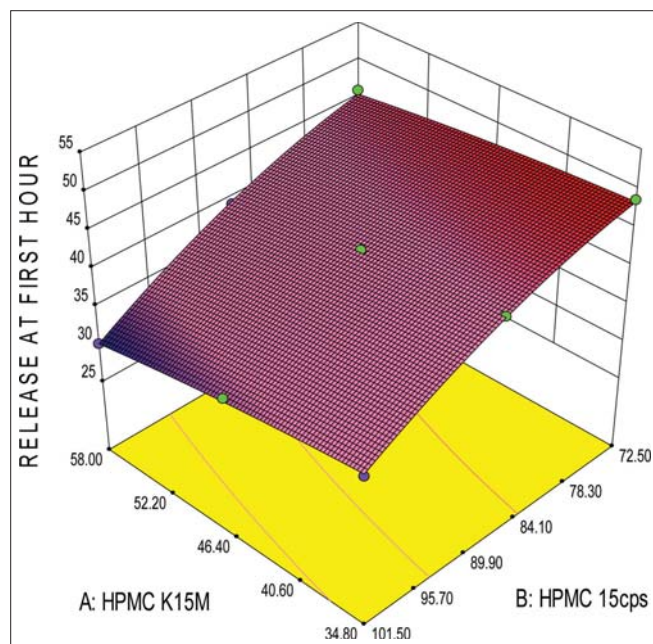

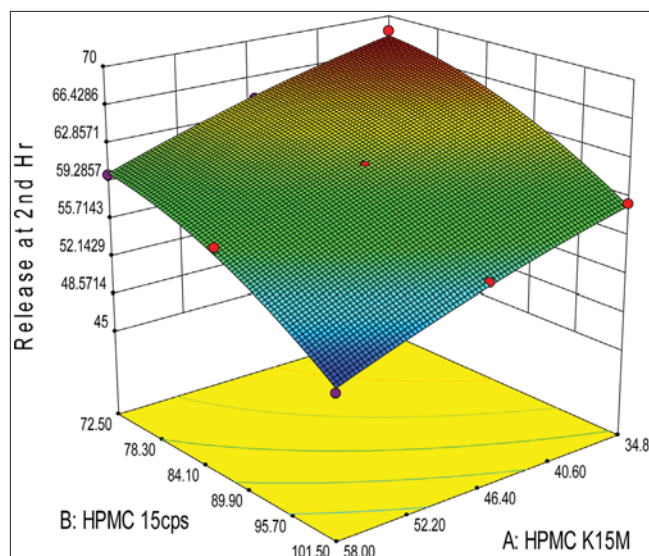**Figure 3:** 3D plot for percentage drug release at the 1st h

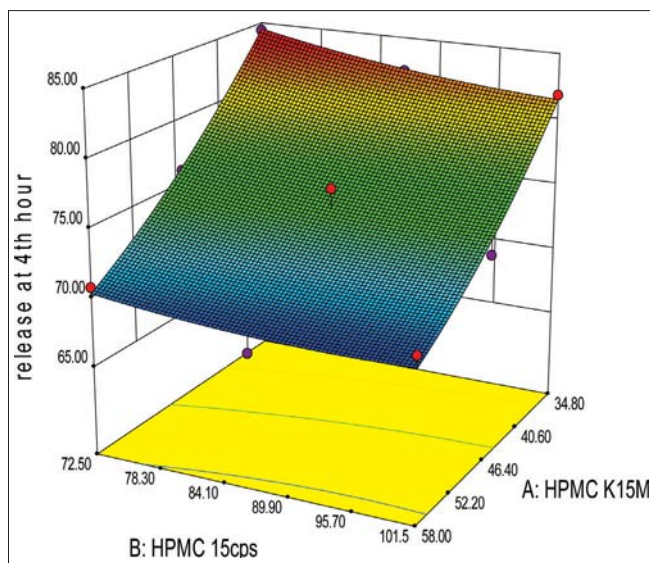**Figure 4:** 3D plot for percentage drug release at the 2nd h

Figure 5: 3D plot for percentage drug release at 4th h

Table 12: Similarity factor of formulations F1–F9

Code	Similarity factor (f_2)
F1	61.13
F2	52.72
F3	84.78
F4	54.66
F5	49.05
F6	78.53
F7	48.80
F8	42.97
F9	59.19

Period: 1 month. Study conditions: 40°C/75% RH

Table 13: Accelerated stability studies report of cephalexin ER 375

Period	Dissolution (%)				Assay (%)	Appearance
	1st h	2nd h	4th h	6th h		
Intial	30.18	49.74	70.24	94.38	96.12	Off white color
Final	32.54	53.46	71.69	96.51	95.47	Off white color

CONCLUSIONS

The major conclusions from the study are:

1. Improvement in the efficacy of cephalexin oral therapy was achieved by formulation of cephalexin extended release matrix tablets, as the frequency of dosing was decreased, thus improving patient compliance.
2. The sawtooth kinetics of conventional therapy was completely avoided by the development of new formulation.
3. The *in vitro* drug release profile of the newly developed tablets also shows good similarity with that of the innnovator product and ideal controlled release pattern.
4. There were no formulation problems associated with the optimized batch of cephalexin matrix tablets.
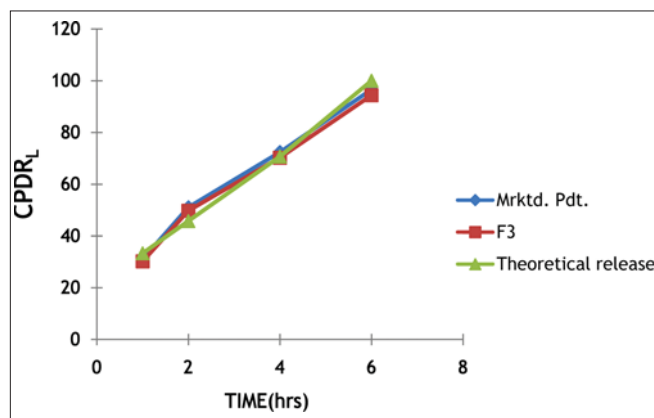5. The tablet also passed the short-term accelerated

Figure 6: Comparative dissolution profiles of marketed product, F3 and theoretical release profile

stability studies, indicating the physical and chemical stability of the product.

Future prospects of the study

The marketing of the product is possible only after bioequivalence studies with innovator's product. Particle size analysis of cephalexin monohydrate and pilot-scale studies of the formulation also need to be performed. Long-term stability studies as per ICH guidelines are also proposed.

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