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Development and *In vitro* Evaluation of Oral Controlled Release Formulations of Celecoxib Using Optimization Techniques

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The objective of this study was to develop controlled release matrix embedded formulations of celecoxib (CCX) as candidate drug using hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC), either alone or in combination, using optimization techniques like polynomial method and composite design. This would enable development of controlled release formulations with predictable and better release characteristics in lesser number of trials. Controlled release matrix tablets of CCX were prepared by wet granulation method. The *in vitro* release rate studies were carried out in USP dissolution apparatus (paddle method) in 900 ml of sodium phosphate buffer (pH 7.4) with 1% v/v tween-80. The *in vitro* drug release data was suitably transformed and used to develop mathematical models using first order polynomial equation and composite design techniques of optimization. In the formulations prepared using HPMC alone, the release rate decreased as the polymer proportion in the matrix base was increased. Whereas in case of formulations prepared using EC alone, only marginal difference was observed in the release rate upon increasing the polymer proportion. In case of formulations containing combination of HPMC and EC, the release of the drug was found to be dependent on the relative proportions of HPMC and EC used in the tablet matrix. The release of the drug from these formulations was extended up to 21 h indicating they can serve as once daily controlled release formulations for CCX. Mathematical analysis of the release kinetics indicates a near approximate Fickian release character for most of the designed formulations. Mathematical equation developed by transforming the *in vitro* release data using composite design model showed better correlation between observed and predicted $t_{50\%}$ (time required for 50% of the drug release) when compared to first order polynomial equation model. The equation thus developed can be used to predict the release characteristics of the drug from matrix embedded formulations depending upon the proportion of HPMC and EC used in the formulation.

Key words——celecoxib; optimization; controlled release; matrix embedding

INTRODUCTION

Celecoxib (CCX), (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-H-pyrazol-1-yl) benzene sulfonamide), is a member of the new generation of non-steroidal antiinflammatory drugs used for the symptomatic treatment of osteoarthritis and rheumatoid arthritis for long term therapy. It selectively inhibits cyclooxygenase–2 (COX–2), the main cyclooxygenase isomer expressed during inflammation.[1—4] As celecoxib specifically inhibits the COX–2 pathway, it has a lesser chance to cause gastropathy and GI bleeding.[1,3] For this reason amongst all the selective COX–2 inhibitors CCX is considered to be the safest. CCX has also been reported to have chemo preventive activity in case of colon cancer,[4] UV light induced skin cancer[5] and breast cancer.[6]

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The benefits of administering NSAIDs in a controlled release system have been established and demonstrated by different workers.[7,8] CCX has a long half-life of 21 h but has a poor oral bioavailability of 64—88% from solution formulations and 22—40% from capsule formulations. The oral bioavailability of CCX is lesser from solid dosage forms because of its poor solubility and poor dissolution rates.[9] Therefore, larger doses of CCX are to be administered to overcome poor bioavailability, which leads to local (gastrointestinal tract) as well as systemic side effects. Controlled release formulations of CCX would be effective in overcoming the dissolution limitation by slowing supplying the drug from the intact matrix base during its sojourn in the gastrointestinal tract and is thus expected to increase bioavailability and improve patient compliance with fewer side effects. Various workers have developed controlled release formulations for oral use either by incorporat-

ing drug in hydrophilic polymer matrix[10,11] or in hydrophobic polymeric matrix.[12,13] Hydroxy propyl methyl cellulose (HPMC) has been widely used as hydrophilic matrix base for design of controlled release formulations of various types of drugs.[10,11,14] Our group has earlier reported the suitability of using ethyl cellulose (EC) for manufacturing controlled release matrix embedded oral formulations by wet granulation method of diclofenac sodium[13] and also for ciprofloxacin and theophylline.[12] EC has also been widely used for microencapsulation of a number of water-soluble drugs to retard the release or to improve the stability.[15—17]

In the development of extended-release dosage form, an important issue is to design an optimized pharmaceutical formulation with appropriate release kinetics within the shortest possible time period and with minimum number of trials. Optimization techniques can be used effectively to design controlled release tablet formulations with desired release characteristics based on one or more attributes like, release rate, retardant polymer proportion, hardness, etc. Several workers have applied optimization techniques based response surface methodology (RSM) utilizing polynomial equation or composite design for the design of controlled release formulations.[18—20] The optimization procedure involves systematic formulations designs to minimize the number of trials, and analyze the response surfaces in order to realize the effect of causal factors and to achieve appropriate formulations with target goals.

The objective of the present study was to design and compare the release characteristics of controlled release oral formulations of CCX prepared using HPMC and EC either alone or in combination. Effect of varying proportion of the retardant material in matrix tablet on the release kinetics was studied. Batch reproducibility and the effect of storage on the stability and release profile were also investigated. It was also envisaged to apply optimization models (first order polynomial equation and composite design) to design and develop controlled release formulations with predictable and better release characteristics in less number of trials.

EXPERIMENTAL

Materials Celecoxib was obtained as gift sample from IPCA laboratories, Mumbai, India. HPMC, EC and all other reagents and chemicals used were of pharmaceutical or analytical grade.

Characterization of the Bulk Drug Bulk drug was characterized by various tests of identification according to the certificate of analysis given by the supplier and analyzed by in-house developed and validated UV–visible spectrophotometric method (Jasco, Tokyo, Japan; UV–visible spectrophotometer, model V570, with 1 cm quartz cell) at 251 nm in aqueous medium.[21] The IR spectrum obtained (Jasco Infrared spectrophotometer; model IR Report 100) was compared with that of the standard given by the supplier. Effects of various formulation excipients such as HPMC, EC, talc, magnesium stearate and isopropyl alcohol on the stability of CCX were also studied by the above UV method.

Preparation of Matrix-embedded Tablets Matrix embedded controlled release tablet formulations of CCX was prepared using varying proportions (5, 10, 15 and 20% w/w of the drug) of EC and HPMC as the retarding polymer either alone or in combination. The tablets were manufactured by wet granulation process using isopropyl alcohol as the binding agent. Pulverized drug was mixed with the polymer (s) and granulated with isopropyl alcohol and dried in a tray drier at 50°C and then passed through mesh #20. The final granules were blended with talc and magnesium stearate at 3% and 1% w/w of the granule weight respectively. The final blend was compressed on a single station tablet compression machine (Cadmach, Ahmedabad, India). Compositions of the matrix embedded tablets are given in Table 1.

Physical Characterization of the Designed Tablets The drug content of the manufactured tablets of each batch was determined. For each batch 20 tablets were taken, weighed and finely ground. An aliquot amount of this powder equivalent to 10 mg of CCX was accurately weighed, suitably dissolved, diluted in sodium phosphate buffer (pH 7.4) with 1% tween–80, and analyzed by UV spectrophotometric method[21] at 251 nm. The weight variation was evaluated taking 20 tablets using an electronic balance (Afcoset, Type ER182A). Tablet hardness was determined for 10 tablets using a Monsanto (standard type) tablet hardness tester. Friability was determined by testing 10 tablets (Campbell Electronic friabilator) for 4 min at 25 rpm.

Release Rate Studies *In vitro* release rate studies were carried out using USP dissolution apparatus (USP XXIII) type 2 (paddle method) in 900 ml of

Table 1. Components and Physical Properties of Various Matrix Tablets of Celecoxib

Formulations	CE0H1	CE0H2	CE0H4	CE1H0	CE2H0	CE4H0	CE3H1	CE2H2	CE1H3	CE2H4	CE4H2	CE4H4
Components[a]												
CCX (in mg)	250	250	250	250	250	250	250	250	250	250	250	250
EC[b]	0	0	0	5	10	20	15	10	5	10	20	20
HPMC[b]	5	10	20	0	0	0	5	10	15	20	10	20
Physical properties												
Drug content (mg/tablet)[c]	257.5 (±1.1)	254.6 (±0.9)	254.9 (±0.7)	255.5 (±1.0)	253.8 (±0.9)	252.5 (±0.7)	257.3 (±0.6)	254.6 (±1.0)	252.5 (±0.6)	253.9 (±1.1)	251.5 (±0.8)	253.6 (±0.4)
Weight variation (%)[d]	±3.0	±2.5	±2.2	±2.9	±2.7	±2.1	±2.0	±2.8	±2.3	±2.9	±2.6	±2.5
Hardness (Kg/cm^2)[e]	5.5 (±0.3)	5.4 (±0.2)	5.6 (±0.3)	5.3 (±0.3)	5.6 (±0.3)	5.5 (±0.4)	5.4 (±0.3)	5.7 (±0.2)	5.5 (±0.4)	5.6 (±0.3)	5.4 (±0.2)	5.3 (±0.2)
Friability (%)	<0.5%	<0.5%	<0.5%	<0.5%	<0.5%	<0.5%	<0.5%	<0.5%	<0.5%	<0.5%	<0.5%	<0.5%

a) Also contains 3% w/w talc and 1% w/w magnesium stearate as manufacturing additives. *b*) % w/w of the drug content. *c*) Mean of triplicate with SD. *d*) ±max. variation from the mean value. *e*) Mean of 10 tablets with SD.

sodium phosphate buffer (pH 7.4) with 1% v/v tween−80 at 37.5±0.5 ℃. The stirring speed was set at 100 rpm. At predetermined time intervals, a 10 ml sample was withdrawn and replaced with fresh dissolution media up to 24 h. After appropriate dilutions, the samples were analyzed by the UV spectrophotometric method[21] at 251 nm. Cumulative percent of the drug released was calculated and the mean of three tablets each from three different batches was used in data analysis.

Characterization of Release Kinetics The release mechanism and the release rate constant (% h^{-1}) were elucidated by the method given by power equation[22,23] This was done by fitting the dissolution data obtained after 1 h up to time point of complete release or 24 h which ever is shorter in Eq. (1).

$$M_t/M_a = K.t^n \quad (1)$$

Where, M_t/M_a is the fraction of drug released at any time 't'; K is the release rate constant incorporating the structure and geometric characteristics of the tablets; n is the diffusional exponent, indicative of the release mechanism. (The value of n for a cylinder is less than 0.45 for Fickian release, 0.45 to less than 0.89 for non-Fickian release, 0.89 for case II release and greater than 0.89 for super II release.) The values of K, n, $t_{50\%}$ (time required for 50% of drug release *in vitro*), $t_{70\%}$ (time required for 70% of drug release *in vitro*), $t_{90\%}$ (time required for 90% of drug release *in vitro*) and r (correlation coefficient) as obtained from the dissolution data are presented in Table 2. For cylindrical shaped matrix formulation a combination 'K' and 'n' determine the overall rate and duration of drug release.

Application of Optimization Techniques The *in vitro* drug release rate study data was suitably transformed and used to develop mathematical equation using first order polynomial and composite techniques of optimization. The proportion of retardant polymers (HPMC and EC) was taken as variable for computation.

(a) Polynomial Method In this method a first order polynomial equation is constructed where the coefficients in the equation are related to the effects and interactions of the factors. The fitting of an empirical first order polynomial equation to the experimental results facilitates the optimization procedure.[24,25] The equation constructed from 2^n factorial experiments, where n=2, is of the following form:

$$Y = B_O + B_1X_1 + B_2X_2 + B_{12}X_1X_2 \quad (2.1)$$

Where, Y is the measured response, X_i is the level of the i^{th} factor (e.g., concentration of EC or HPMC), and B_i and B_{ij} are the coefficients computed from the responses of the formulations in the design. For this method the transformation done by applying the relationship as given below:

Transformed value = (X_i−Average of two levels) /0.5 (Difference of the two levels) (2.2)

Where the two levels are 20% w/w of the drug as maximum level and 0% w/w of the drug as the minimum level. The coefficients in the polynomial equation are given by the equation:

$$B_o = \Sigma Y_i/N \quad (2.3)$$

$$B_i = \Sigma x_i Y_i/2^n \quad (2.4)$$

Table 2. Release Rate Parameters of Designed Matrix Tablets of Celecoxib

Parameters	CE0H1	CE0H2	CE0H4	CE1H0	CE2H0	CE4H0	CE3H1	CE2H2	CE1H3	CE2H4	CE4H2	CE4H4
r[a)]	0.9681	0.9856	0.9952	0.9836	0.9924	0.9962	0.9633	0.9960	0.9542	0.9892	0.9855	0.9964
K[b)]	53.09	47.82	37.76	39.57	37.34	36.14	45.24	33.29	32.57	38.12	42.30	41.67
n[c)]	0.2726	0.3026	0.3309	0.1320	0.1304	0.1337	0.2602	0.3772	0.5063	0.3133	0.2723	0.2507
$t_{50\%}$[d)]	0.80	1.16	2.34	5.89	9.52	11.34	1.48	2.94	2.32	2.39	1.85	2.07
$t_{60\%}$[e)]	2.75	3.53	6.45	75.23	125.42	140.11	5.38	7.17	4.51	6.99	6.36	7.91
$t_{90\%}$[f)]	6.93	8.10	13.80	—	—	—	14.13	13.97	7.41	15.59	16.02	21.57

a) Correlation coefficient. *b*) Release rate constant. *c*) Diffusional exponent indicative of release mechanism. *d*) Time for 50% of the drug release, *e*) Time for 70% of the drug release, *f*) Time for 90% of the drug release.

Where, x_i is the transformed coded levels for ith factor, Y_i is the response, N is the number of formulations and n is the number of factors (Here, $n=2$).

(b) Composite Design Composite designs are effective to estimate second-order terms giving orthogonal estimates of the polynomial coefficients.[24,25] The equation obtained in a composite design where there are only two factors is of the form:

$$Y=B_o+B_1X_1+B_2X_2+B_{12}X_1X_2+B_{11}(X_1^2-2/3)+B_{22}(X_2^2-2/3) \quad (3.1)$$

Where, Y is the measured response, X_i is the level of the i[th] factor (e.g., concentration of EC or HPMC), and B_i, B_{ii}, B_{jj}, and B_{ij} are the coefficients computed from the responses of the formulations in the design. For this method, the transformation of the release data was done by applying the relationship as given below:

$$\text{Transformed value}=(X_i-\text{Average of two levels})/0.5(\text{Difference of the two levels}) \quad (3.2)$$

Here, the two levels are 20% w/w of the drug as maximum level and 0% w/w of the drug as the minimum level. And the coefficients in the polynomial equation are given by the equation:

$$B_o=\Sigma Y_i/N \quad (3.3)$$

$$B_i=\Sigma x_i Y_i/\Sigma x_i^2 \quad (3.4)$$

Where, x_i is the transformed coded levels for ith factor, N is the number of formulations and Y_i is the response. These mathematical equations were then applied to design CCX controlled release tablet formulations with predictable release characteristics. The developed models were tested for their validity in predicting the $t_{50\%}$ using separate set (not used in model development) of formulations with varying levels of HPMC and EC.

Batch Reproducibility and Stability on Storage Three batches of each formulation were prepared and their respective dissolution rates were evaluated under the same conditions. Formulations were studied at 6 months and 1-year intervals for the effect of storage in ambient conditions on the stability and the release profile of CCX. The tablets were sealed in airtight cellophane packets and stored in ambient conditions (temperature 25°C, relative humidity 60%). The *in vitro* release profile was studied for all the formulations as discussed earlier and compared with their original release profile.

Statistical Analysis All values presented in this study are average of replicate experiments at the same time points. Least square regression equations, the correlation coefficients and *t*-test values were calculated using Microsoft Office 2000, Excel package at $p<0.05$. Difference between the observed and predicted $t_{50\%}$ values were tested statistically[24,25] using one-way analysis of variance $p<0.05$.

RESULTS AND DISCUSSION

Characterization of Bulk Drug and Effect of Various Formulation Excipients Supplied CCX passed the various tests of identification and analysis as per the certificate of analysis given by the supplier. The formulation excipients, in the concentration range used, did not affect the stability and UV absorbency profile of CCX.

Physical Characterization of the Designed Tablets The physical appearance, hardness, friability, weight variation and drug content uniformity of different tablet formulations were found to be satisfactory (Table 1). Tablet hardness varied between 5.0—6.0 kg/cm^2 and friability was less than 0.5% (w/w). The manufactured tablets showed low weight variation and a high degree of drug content uniformity due to good granulation, mixing and flowability, thus indicating that the wet granulation method is an acceptable method for preparing good quality controlled

release matrix tablets of CCX.

Release Rate Studies A plot of cumulative percentage released versus time for matrix embedded controlled release tablet formulations of CCX prepared using HPMC alone as the retarding polymer is shown in Fig. 1. It was observed that the initial percent released for the first hour was quite high (42—56 %) for all the formulations. However, in the later stages the release was found to be slower and more controlled in the tablets with higher proportion of the polymer. The release of the drug from the tablets extended from 8 h in case of CE0H1 to 15 h as in case of CE0H4 as the polymer proportion was increased from 5% to 20% w/w of the drug respectively.

For matrix embedded controlled release tablet formulations of CCX prepared using EC alone as the retarding polymer the plot between cumulative percentage released and time is shown in Fig. 2. It was observed that the initial percentage released for the first hour was quite high (37—43%) for all the formulations. However, in the later stages the release was found to be slower and more controlled in the tablets with higher proportion of the polymer. The release of the drug from the tablets extended beyond 24 h from all the formulations with maximum percentage release ranging from 51% (CE4H0; 20% w/w of

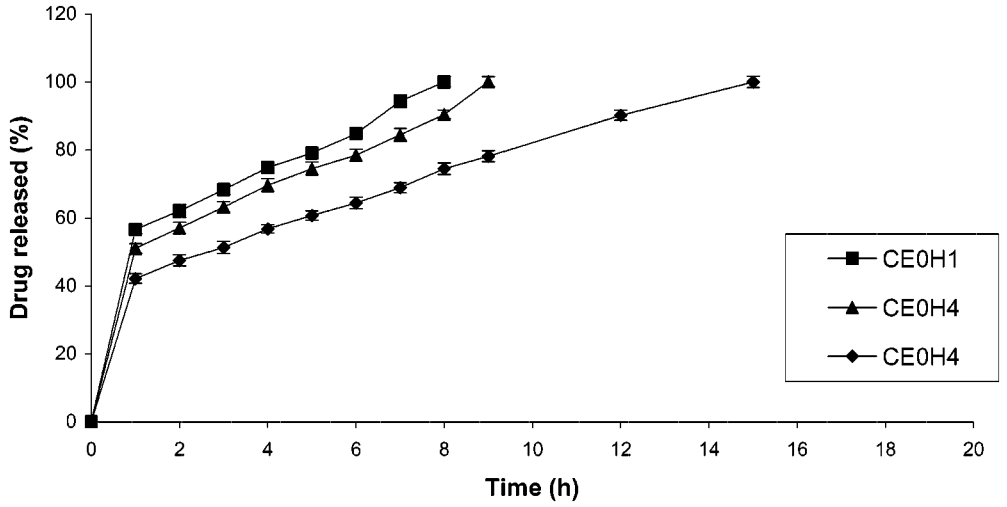

Fig. 1. Release Profile of CCX Controlled Release Matrix Tablet Formulations Prepared Using HPMC as the Retardant Base
Each data point represents the average of six tablets from three batches with SD.

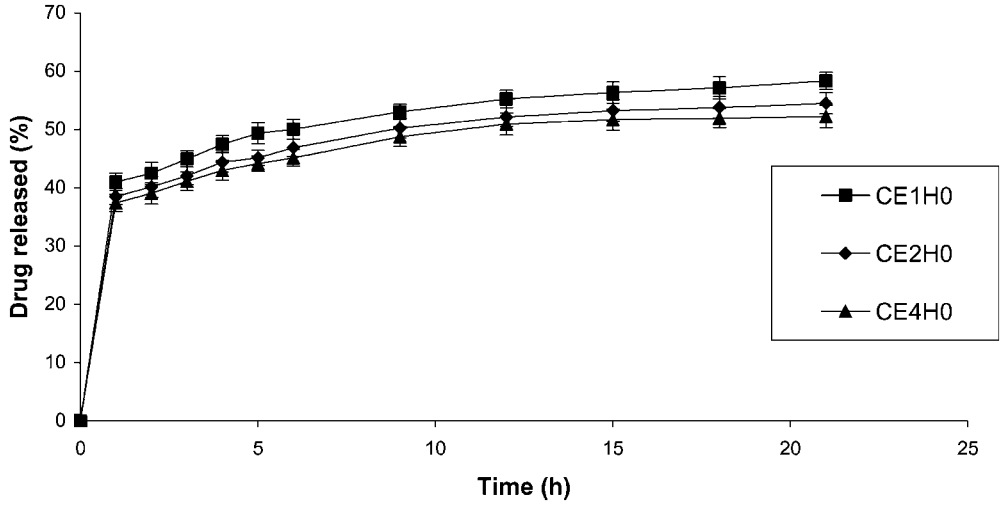

Fig. 2. Release Profile of CCX Controlled Release Matrix Tablet Formulations Prepared Using EC as the Retardant Base
Each data point represents the average of six tablets from three batches with SD.

EC) to 58% (CE1H0; 5% w/w EC) in 24 h. This indicates that though the proportion of EC was increased from 5% to 20% w/w of drug there is insignificant change in the extent of drug release from the designed formulations. Also the less than 5% drug was released from the formulations between 9th and 24th h.

In case of matrix embedded controlled release tablet formulations of CCX prepared using HPMC and EC in combination as the retarding polymers the initial percentage released for the first hour was also high with 34 to 45% drug release in first 1 h for all the formulations (Fig. 3). However, in the later stages the release was found to be slower and more controlled in tablets with higher proportion of the polymer. The release of the drug from the tablets extended from 9 to 21 h depending on the proportions of HPMC and EC used in the formulations. For tablets, when the total proportion of polymer was kept constant (20% w/w of the drug), as in case of CE3H1, CE2H2 and CE1H3, it was observed that with the increase in relative proportion of HPMC in the polymeric base the rate of release of the drug increased. While with EC the reverse of this phenomenon was observed. Therefore, it can be inferred that for a poorly soluble drug like, CCX in a hydrophilic-hydrophobic matrix base the hydrophilic component exerts a micro environmental solublization effect resulting in increased drug release rate. In the above formulations the initial rate of release was found to be faster when the relative proportion of EC was higher but better controlled in the later period of the release study. This observation can be attributed to poor solubility of EC in the granulating fluid (isopropyl alcohol) thereby leaving higher proportion of free drug in the formulation that is rapidly released in the initial period of release study. The rate of release was decreased and the duration of release enhanced when the total proportion of polymeric base (with constant HPMC: EC ratio of 1 : 1) was increased from 20% to 40% w/w of drug as in case of formulations CE2H2 and CE4H4.

Characterization of Release Kinetics The most possible mechanism of CCX release from the designed formulations appeared to be by diffusion due to swelling from HPMC based tablets, erosion from EC based tablets and a combination of the two mechanism when both are used as retardants. The results of the release rate and release mechanism elucidated from the power equation are given in Table 2. The values of n for the formulations of CCX prepared using HPMC alone as the retarding polymer ranged from 0.2726-0.3309, indicating a Fickian release mechanism when considering the shape of the matrix tablets to be cylindrical. The release rate of CCX from CE0H4 was slowest with a K value of 37.76% $h^{-0.3309}$ and $t_{50\%}$ of 2.34 h, whereas release of CCX from formulation CE0H1 was found to be fastest with a K value of 53.09% $h^{-0.2726}$ and $t_{50\%}$ of 0.80 h. The $t_{90\%}$ (time to 90% drug release *in vitro*)

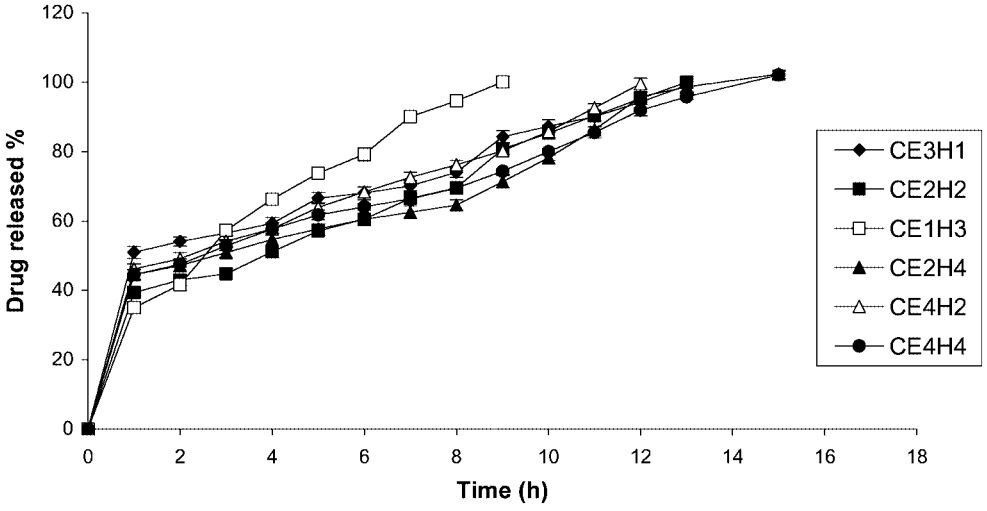

Fig. 3. Release Profile of CCX Controlled Release Matrix Tablet Formulations Prepared Using HPMC and EC in Combination as the Retardant Bases

Each data point represents the average of six tablets from three batches with SD.

was found to be 6.93 h, 8.10 h and 13.80 h for CE0H1 (5% w/w HPMC), CE0H2 (10% w/w HPMC) and CE0H4 (20% w/w HPMC) respectively (Table 2).

The values of n for the formulations of CCX prepared using EC alone as the retarding polymer ranged from 0.1320-0.1337, indicating a Fickian release mechanism when considering the shape of the matrix tablets to be cylindrical. The release rate of CCX from CE4H0 was slowest with a K value of 36.14% $h^{-0.1337}$ and $t_{50\%}$ of 5.89 h, whereas release of CCX from formulation CE1H0 was found to be relatively faster with a K value of 39.57% $h^{-0.1320}$ and $t_{50\%}$ of 11.34 h. The predicted $t_{70\%}$ (time to 70% drug release *in vitro*) was found to be 75.23 h, 125.42 h and 140.11 h for CE1H0 (5% w/w EC), CE2H0 (10% w/w EC) and CE4H0 (20% w/w EC) respectively (Table 2).

In case of CCX controlled release formulations prepared using combination of HPMC and EC the release mechanism was found to be Fickian with n value ranging from 0.2506 to 0.3772 except in case of CE1H3 where non-Fickian release characteristics was observed (n value of 0.5062). For this series of tablets, when the total proportion of polymer was kept constant (20% w/w of the drug), as in case of CE3H1, CE2H2 and CE1H3, maximum extension of release was observed in case of CE3H1 with a $t_{90\%}$ of 14.13 h and the least extension of release was observed in case of CE1H3 with a $t_{90\%}$ of 7.41 h. This result further establishes the micro environmental solublization effect of HPMC. In formulations where the total proportion of polymeric base was increased from 20% to 40% w/w of drug, keeping EC to HPMC ratio as 1 : 1, the release rate of CCX from CE2H2 was faster with a K value of 33.29% $h^{-0.3772}$ and $t_{90\%}$ of 13.97 h, whereas release of CCX from formulation CE4H4 was found to be slowest with a K value of 41.67% $h^{-0.2505}$ and $t_{90\%}$ of 21.57 h. As discussed earlier for cylindrical shaped matrix formulation a combination K and n determine the overall rate and duration of drug release.

Application of Optimization Techniques The transformation table for the data obtained from the *in vitro* release rate study of selected controlled release matrix tablet formulations using polynomial technique is shown in Table 3. The first order polynomial equation model developed using the transformed data of Table 3 and Eqs. (2.1) to (2.4) is represented by Eq. (4).

$$t_{50\%} = 3.79 + 2.82X_1 - 3.64X_2 - 2.78X_1X_2 \quad (4)$$

Where, $t_{50\%}$ (time required for 50% of the drug release) is the response variable, X_1 and X_2 are the level of EC and HPMC in the formulation. By using the developed first order polynomial equation $t_{50\%}$ values were predicted for all the formulations used in the development of model (Table 3). The correlation coefficient value (r) determined between the observed and the predicted $t_{50\%}$ using the polynomial equation was found to be 0.8427 and highly significant at $p < 0.05$ for N−2 degree of freedom.

The transformation table obtained from the *in vitro* release rate study of selected controlled release matrix tablet formulations using composite design is shown in Table 4. The composite design model developed using Eqs. (3.1) to (3.4) and transformed data of Table 4 is as follows Eq. (5).

$$t_{50\%} = 2.88 + 1.88X_1 - 1.76X_2 - 2.08X_1X_2 - 0.57(X_1^2 - 2/3) + 1.94(X_2^2 - 2/3) \quad (5)$$

Where, $t_{50\%}$ is the time required for 50% of the

Table 3. The Transformation Table for the Designed Controlled Release Matrix Embedded Formulations Using First Order Polynomial Equation Technique

Formulation	x_1	x_2	x_1x_2	Observed Y ($t_{50\%}$)	Predicted Y ($t_{50\%}$)
CE0H0	−1	−1	1	0.50	1.84
CE0H2	−1	0	0	1.16	0.98
CE0H4	−1	1	−1	2.34	0.11
CE2H0	0	−1	0	9.52	7.43
CE2H2	0	0	0	11.34	13.02
CE2H4	0	1	0	2.94	3.79
CE4H0	1	−1	−1	2.39	0.15
CE4H2	1	0	0	1.85	6.61
CE4H4	1	1	1	2.07	0.19

Table 4. The Transformation Table for the Designed Controlled Release Matrix Embedded Formulations Using Composite Design Technique

Formulation	x_1	x_2	x_1x_2	$(x_1^2-2/3)$	$(x_2^2-2/3)$	Observed Y ($t_{50\%}$)	Predicted Y ($t_{50\%}$)
CE0H0	−1	−1	1	1/3	1/3	0.50	0.49
CE0H2	−1	0	0	1/3	−2/3	0.80	1.38
CE0H4	−1	1	−1	1/3	1/3	1.16	1.13
CE2H0	0	−1	0	−2/3	1/3	5.89	4.45
CE2H2	0	0	0	−2/3	−2/3	9.52	8.42
CE2H4	0	1	0	−2/3	1/3	1.48	3.26
CE4H0	1	−1	−1	1/3	1/3	2.32	0.93
CE4H2	1	0	0	1/3	−2/3	2.39	5.14
CE4H4	1	1	1	1/3	1/3	1.85	0.73

Table 5. Observed and Predicted $t_{50\%}$ Values for Test Formulations Using the Developed Models

Formulation	Observed $t_{50\%}$	Predicted $t_{50\%}$	
		Polynomial equation	Composite design
CE0H1	0.80	1.41	1.08
CE1H0	5.89	4.63	2.47
CE1H3	2.32	1.26	1.82
Correlation coefficient (r) between observed and predicted $t_{50\%}$		0.9446	0.9655

drug release, X_1 and X_2 are the level of EC and HPMC in the formulation. By using the developed composite design model $t_{50\%}$ values were predicted for the formulations and presented in Table 4. The correlation coefficient value (r) determined between the observed and the predicted $t_{50\%}$ using composite design was found to be 0.8661. The correlation coefficient value obtained for this model also found to be highly significant at 5% level of significance (i.e. pass the test of zero correlation) for N-2 degree of freedom. Also a one-way ANOVA test[24,25] was performed for observed and predicted $t_{50\%}$ values. The calculated F-value using the data was found to be less than the critical F-value for both the models, at $p<0.05$, indicating that statistically insignificant difference exist between the observed and predicted values obtained.

The developed models were further validated and tested using variables corresponding to the formulations other than the one used for generating them. The observed $t_{50\%}$ and predicted values for these formulations using the developed models are presented in Table 5. For this set of formulations the correlation coefficient values of 0.9446 and 0.9655 obtained for the developed first order polynomial equation and composite design model respectively were found to be highly significant at 5% level.

More significant correlation coefficient value was obtained from the composite design compared to the first order polynomial method indicating that the polymers proportions in the formulations have a parabolic relationship with $t_{50\%}$. It also indicates that the composite design is a better method to develop a model correlating release rate (expressed in terms of $t_{50\%}$) and independent variables like proportion of retardant polymers in the formulation.

Batch Reproducibility and Stability on Storage

No significant difference was observed in the release profile of different batches of each CR matrix tablet formulation, indicating that the manufacturing process employed was reliable and reproducible. Also, the release kinetics were unaltered after up to 6 months and 1 year of storage, suggesting that CCX was stable in HPMC and EC matrices and there was no change in tablet characteristics.

CONCLUSIONS

Good quality CCX controlled release matrix em-

bedded tablet formulations were successfully prepared using HPMC alone and HPMC–EC combination as the retarding polymers by wet granulation method. The reproducible tablet physical properties and release kinetics indicate that wet granulation method is an acceptable method for the design of good quality matrix tablets of CCX. The rate of release of the drug from the designed tablets was observed to decrease as the proportion of HPMC and EC is increased. The initial release of the drug, during the first hour, from all the designed controlled release formulations is sufficiently high and so no loading dose is required to be added in the formulations.

Mathematical analysis of the release kinetics indicate a near approximate Fickian release character. The most plausible mechanism of release from the matrix tablet is by leaching of the drug from the tablet by the dissolution fluid, which penetrates the drug-matrix phase through pores, cracks and intergranular spaces and/or by erosion of the matrix base. The drug release characteristics were reproducible for different batches of the formulations and were also unaltered on storage for 1 year at ambient condition.

The optimization models developed by applying the first order polynomial and composite design techniques can be used effectively for designing controlled release matrix embedded formulations of CCX with predictable release characteristics of the drug with fewer number of trials. A better correlation was obtained between the observed and predicted $t_{50\%}$ values for composite design than that of first order polynomial equation technique. The designed controlled release matrix tablet formulations of CCX, which extend the release beyond 21 h, can overcome the problems (like, side effects, drug wastage and patient non-compliance) associated with conventional tablet formulations of CCX.

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