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FORMULATION AND OPTIMIZATION OF CONTROLLED RELEASE PAROXETINE HYDROCHLORIDE TABLETS USING RESPONSE SURFACE METHODOLOGY

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ABSTRACT

Controlled drug delivery has taken an important position in pharmaceutical development due to improving the tolerability and patient compliance with prescribed dosing regimens. Paroxetine IR antidepressant efficacy may compromised by early discontinuation of treatment secondary to common, treatment-emergent side effects, including nausea, agitation and somnolence. This study is to develop a generic controlled release Paroxetine hydrochloride matrix tablet, which is stable, robust and an acceptable formulation when compared to Paxil CR a reference listed drug (RLD). A central composite design (CCD) with α =1 was employed as per the standard protocol. HPMC K4M (x_1), HPMC K100 (x_2) and ethyl cellulose 7CPS (x_3) are selected as independent factors, studied at two levels each. In case of dissolution at 60 minutes time point the model F-value of 30.44 implies the model is significant. In case of dissolution at 240 minutes time point the model F-value of 483.88 implies the model is significant. All the runs compared for dissolution profiles against the pealed Paxil CR to check the similarity factor. Out of the 12 runs, run 2 (F2) has shown higher similarity factor when compared against pealed Paxil CR and the same has been confirmed with the reproducible run 10 (F10). Acryl-EZE coating weight build-ups of 6.0%, 7.0% and 8.0% w/w were given on the run 2 composition. It can be highly postulated that the Higuchi model could best express in vitro release profile of all the matrix formulations. Formulation F14 was finalized, 30's count were filled into HDPE bottle 75cc/ 33 mm screw neck and loaded for stability along with RLD bottles. No difference in the dissolution profile between the initial and 3 months accelerated stability samples with Paxil CR and F14 formulations. The results from the in vitro alcohol study showed that alcohol increased the release of the drug from the formulation, but a dose dumping effect per se was not observed.

INTRODUCTION

Controlled release is a term referring to the presentation or delivery of compounds in response to stimuli or time. Time-release is a mechanism used in several dosage forms to dissolve a drug over time in order to be released slower and steadier into the blood stream while having the advantage of being taken at

less frequent intervals than immediate-release (IR) formulations of the same drug.

Paroxetine hydrochloride[1-3] is an orally administered psychotropic drug. It is the hydrochloride salt of a phenylpiperidine compound. Paroxetine is a selective serotonin reuptake inhibitor, chemically unrelated to tricyclic, tetracyclic, or other antidepressants; presumably, the inhibition of serotonin reuptake from brain synapse stimulated serotonin activity in the brain. Paroxetine IR antidepressant efficacy may be compromised by early discontinuation of treatment secondary to common, treatment-emergent side effects, including nausea, agitation and somnolence. Paroxetine controlled release (CR) was developed to improve general tolerability and in particular, gastrointestinal tolerability. Matrix-based CR tablet formulations are the most popular and easiest to formulate on a commercial scale. The matrix tablets can be prepared via wet granulation[4] or by direct compression[5-6]. Many polymers have been used in the formulation of matrix-based CR drug delivery systems. Reports were found on usage of hydrophilic polymers such as hydroxypropyl methyl cellulose (HPMC), methyl cellulose, sodium carboxy methyl cellulose, carbopols etc., for the purpose of controlled release[7-11] formulations of different drugs. In this study as Paroxetine hydrochloride is a water soluble drug, mixture of hydrophilic polymer HPMC and hydrophobic polymer ethyl cellulose were used to control the drug release and coated with Acryl-EZE[12-14] coating which contains methacrylic acid copolymer type C, sodium carbonate, talc, silica, sodium lauryl sulfate and triethyl citrate so as to minimize/ prevent initial drug release in stomach that will reduce the possible gastro irritant effects of the drug. A normal conventional optimization process, a single independent variable is varied while all others are kept constant at a specific set of conditions. It is not possible to change more than one parameter at a time during the formulation development. This method may lead to unreliable results and improper conclusions besides wastage of production cost and man power. A computer based factorial design is an alternative to overcome the above mentioned difficulties. A response surface methodology[15] (RSM) is a widely practiced approach in the development and optimization of drug delivery devices. Based on the principal of design of experiments (DOE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations, and mapping of the response over the experimental domain to determine the optimum formulation(s). The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms. A central composite design (CCD) can be run sequentially because it can be naturally partitioned into two subsets of points; the first subset estimates linear and two-factor interaction effects while the second subset estimates curvature effects. The second subset need not be run when analysis of the data from the first subset points indicates the absence of significant curvature effects. CCDs are very efficient, providing much information on experiment variable effects and overall experimental error in a minimum number of required runs. CCDs are very flexible. The availability of several varieties of CCDs enables their use under different experimental regions of interest and operability.

The objective of the present study is to prepare Paroxetine hydrochloride core tablets by using HPMC K4M, HPMC K100M, ethyl cellulose and Povidone as release controlling polymers by using factorial study[16-19]. Coating optimization was done with Acryl-EZE to evaluate the dissolution rate of Paroxetine hydrochloride tablets in comparison with Paxil CR. In vitro release kinetic study[20-22] and stability studies were performed for the prepared Acryl-EZE coated Paroxetine hydrochloride CR tablet. This study is to develop a generic Paroxetine hydrochloride CR tablet which is stable, robust and an acceptable formulation when compared to Paxil CR.

MATERIALS AND METHODS

Materials

Paroxetine hydrochloride was procured from Milton Drugs Pvt. Ltd., Puducherry, spray dried lactose and hydroxylpropyl methyl cellulose (HPMC) were obtained from Dow Chemical Company, USA, ethyl cellulose 7CPS (Ethocel), aerosil and magnesium stearate were obtained from Rankem Limited, Mumbai, Povidone K30 was purchased from Signet Chemical, Mumbai, Acryl-EZE from Rohm GmbH, Thane.

METHODS

Formulation design of controlled release matrix tablets

For preparation of Paroxetine hydrochloride CR matrix tablets direct compression method was adopted. All the formulations were prepared according to CCD model and the respective compositions were shown in Table 1& 2. Accurate quantities of all the ingredients were weighed and passed through sieve #40. The sieved materials were mixed thoroughly by tumbling method in a polythene bag and the dry blend was lubricated with aerosil and magnesium stearate. After lubrication, the formulations were evaluated for flow properties like angle of repose, bulk density, compressibility index prior to compression. Then the lubricated dry blends were subjected to punching using a tablet punching machine with punch size: 8.3 mm round concave punches having upper punch embossed with 'N' and lower punch embossed with '37.5'. Tablet weight was adjusted to 230 mg and hardness was adjusted to 5-7 kg/cm^2. Then the prepared tablet formulations were evaluated for post compression parameters like thickness, weight variation, hardness, friability, drug content and in vitro dissolution studies.

Acryl-EZE coating of Paroxetine hydrochloride CR matrix core tablets

A 20% w/w of Acryl-EZE in water was prepared with continuous stirring for 1 hour. It contains methacrylic acid copolymer type C, sodium carbonate, talc, silica, SLS and triethylcitrate. The final solution was passed through #100 and pH of the final solution was 5.3. Enteric coating was done by using standard 24-inch Accela-cota make with spray nozzle of 0.040 inch fluid orifice. The speed of the pan was 22-26 rpm and speed of the pump was 1-3 rpm, temperature of 55^{0}C with spray rate of 1.2 kg/cm^2. After spraying the total volume of solution, compressed air was stopped and the tablets were rolled for another 10 minutes for complete drying. Average weight of the coated tablets was calculated. The enteric coated tablets were evaluated for various post compression parameters.

EVALUATION

Particle size of pure drug

Mechanical sieve shaker (Make: Electrolab, Mumbai) was used to measure the particle size of the active pharmaceutical ingredient (API). A series of standard sieves were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves with smaller pore size (greater sieve number towards the bottom). Particle size was calculated based on the percent drug retained.

FTIR spectral studies

FTIR study was performed to verify any physical or chemical interaction between drug and excipients used in the formulation. FTIR spectra of the pure drug Paroxetine hydrochloride, pure polymers and mixture of both drug and polymers were carried out by comparing the obtained spectra for the presence of functional groups. It was done by potassium bromide (KBr) pellet method. Formulations were taken in a KBr pellet using BOMEN MB SERIES FTIR instrument. Approximately 5 mg of samples were mixed with 50 mg of spectroscopic grade KBr; samples were scanned in the IR range from 500 to 3500 cm^{-1}, with a resolution of 4 cm^{-1}.

Evaluation of pre compression parameters

Micromeritic properties like angle of repose, bulk density, tapped density and compressibility index (Carr's index) were performed to know the flow properties of powder blend.

Evaluation of Paroxetine hydrochloride matrix core tablets

As part of In-process tests and quality control checks weight variation, thickness, diameter, hardness and friability tests of Paroxetine hydrochloride matrix core tablets were performed. As the formulations are of controlled release matrix tablets there is no scope for disintegration test.

Assay of Paroxetine hydrochloride matrix core tablets

Twenty tablets were weighed and crushed in to dry powder by using mortar and pestle. A 100 mg equivalent quantity was taken and transferred into 100 mL volumetric flask and diluted with methanol. After sonication for 15 minutes the diluted solution was filtered. The total amount of drug for each tablet was analyzed using HPLC Dvelosil C8 (33x 4.6 mm) column at a flow rate of 2.0 mL/minute, column temperature 30^{o}C, run time 5 minutes at a wave length of 295 nm. The same procedure was used for identifying assay of Paxil CR.

***In vitro* release study**

In vitro release studies were carried out using dissolution test apparatus USP type II (n=6). For each sample, dissolution was performed in 750 mL of 0.1N hydrochloric acid at 150 rpm using USP type II apparatus for 2 hours followed by 1000 mL of Tris buffer pH 7.5 maintained at 37°C ± 0.5°C with 150 rpm. Aliquot samples were withdrawn for a period of 6 hours, filtered through a 0.45 µm millipore filter and replaced by an equivalent volume of fresh dissolution medium. The amount of drug dissolved was determined by HPLC method using HPLC Dvelosil C8 (33x4.6 mm) column at a flow rate of 2.0 mL/minute, column temperature 30ºC, run time 5 minutes at a wave length of 295 nm.

Optimized core formulation by central composite design

The optimization of controlled release formulation of Paroxetine hydrochloride was done by using design expert software. A central composite design (CCD) with α =1 was employed as per the standard protocol. HPMC K4M (x_1), HPMC K100 (x_2) and ethyl cellulose (x_3) were selected as the independent factors, studied at two levels each. All the other formulation and processing variables were kept invariant throughout the study. Table 1 summarizes an account of the 12 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. Percent of drug release in 60 minutes (rel_{60min}) and drug release in 240 minutes (rel_{240min}) were taken as the responsible variables.

Release kinetic study

To study the mechanism of drug release from the optimized formulation of matrix tablets, the release data were fitted to following equations:

Zero- order equation: $Q_t = Q_0 + k_0 t$

Where, Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and k_0 is the zero order release rate.

First- order equation: $\ln Q_t = \ln Q_0 + k_1 t$

Where, Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the solution and k_1 is the first order release rate constant.

Higuchi's equation: $\ln Q = k_H t^{1/2}$

Where, Q is the amount of drug release at time t, and k_H is the Higuchi diffusion rate constant.

Korsmeyer–Peppas equation: $Mt/M\infty = Kt^n$

Where, Mt is the amount of drug released at time t, $M\infty$ is the amount of drug released after infinite time, and K is a kinetic constant incorporating structural and geometric characteristics of the tablet and n is the diffusion exponent indicative of the drug release mechanism. The mechanism of drug release was dependent on the value of *'n'*.

Dissolution equivalency

The similarity factor (f_2) was employed to evaluate the release profiles of various formulations compared with the ideal release profile.

$$f_2 = 50 + \log \{[1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} * 100\}$$

***In vitro* alcohol dose dumping study**

An *in vitro* study was conducted to evaluate if alcohol had an effect on the release characteristics of the test CR formulation and Paxil CR. Testing conditions were used are apparatus II, 150 rpm, 750 mL of 0.1 N hydrochloric acid mixed with 5.0% and 40.0% v/v alcohol at 37°C.

Stability of optimized formulation

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. Stability studies were conducted at different conditions of 40ºC/ 75% RH and 25ºC/ 60% RH for about 3 months in stability chamber (Thermo Lab). Samples were collected at 1, 2 and 3 months intervals.

RESULTS AND DISCUSSION

From the particle size distribution curve the d90 value of the pure drug was 297 microns. Bulk density (g/cm^3) and tapped density of pure API were observed to be 0.206± 0.02 and 0.466± 0.009. Carr's index (%) and Hausner's ratios were found to be 55.682% and 2.256 respectively. From the above data, flow properties of API were found to be poor. Different blends were prepared as per the CCD runs and their angle of repose and compressibility index were around 25° and 13.0-15.5% respectively. Bulk density and tapped density of blends of CCD runs were observed to be 0.58- 067 g/cm^{3}and 0.69- 0.78 g/cm^3. The flow properties of the CCD blends were improved and not varying much with respect to the design run.

The FTIR of Paroxetine hydrochloride pure drug stretching's at 3402.68 cm^{-1}, 1606.26 cm^{-1}, 2954.94 cm^{-1} corresponding to the functional groups, NH, C=C and C-H bending as shown in Figure 1. The FTIR of drug and excipients shown intense bands at 3403.24 cm^{-1}, 1606.37 cm^{-1}, 2923.51 cm^{-1} indicates no change in the functional groups NH, C=C and C-H as shown in Figure 2. The FTIR of placebo shown that there are no intense bands at groups NH, C=C and C-H this shows that drug peaks are missing in it as shown in Figure 3. From the above stretching's there is no major shifting in the frequencies of above said functional groups. Drug and polymers are compatible with each other.

As part of In-process test specifications quality control checks like weight variation, thickness, diameter, hardness and friability tests of Paroxetine hydrochloride matrix core tablets were performed. All the In process specifications were fixed stringently to have an advantage at scale up stage. Assay of Paroxetine hydrochloride matrix core tablets prepared as per CCD were in the range of 95.0- 105.0%. In process test specifications for Paroxetine hydrochloride CR matrix core tablets were given in Table 3. For the statistical approach drug release in 60 and 240 minutes were chosen as the dissolution profile impact was more significant and distinguish at these time points. A response surface methodology (RSM) with central composite design, quadratic process order and manual selection were chosen. Utilizing the equation to make predictions about the response for given levels of each factor. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

In vitro drug release studies for the uncoated CR matrix tablets were done in 1000 mL of pH 7.5 Tris buffer. As the tablets were not coated with delayed release polymer, the acid stage testing was skipped. The data was incorporated in to the software and below are the observations.

In case of dissolution at 60 minutes time point the model F-value of 30.44 implies the model is significant. There is only a 3.22% chance that an F-value this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant. In this case A is a significant model term. There is 8.16% chance that a "Lack of Fit F- value" this large could occur due to noise. The "Pred R-Squared" of 0.1407 is not as close to the "Adj R-Squared" of 0.9601 as one might normally expect i.e. the difference is more than 0.2. All empirical models should be tested by doing confirmation runs. "Adeq Precision" measures the signal to noise ratio. A ratio of 19.329 indicates an adequate signal. This model can be used to navigate the design space. ANOVA data was given in Table 5, contour and response plots were represented in Figures 5& 6.

In case of dissolution at 240 minutes time point the model F-value of 483.88 implies the model is significant. There is only a 0.21% chance that an F-value this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant. In this case A, C, AB and A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve this model. The "Lack of Fit F-value" of 1.50 implies the Lack of Fit is not significant relative to the pure error. There is a 43.59% chance that a "Lack of Fit F-value" this large could occur due to noise. Non-significant lack of fit is good, want the model to fit. ANOVA data was given in Table 6, contour and response plots were represented in Figures 7& 8.

The "Pred R-Squared" of 0.9663 is in reasonable agreement with the "Adj R-Squared" of 0.9975 i.e. the difference is less than 0.2. "Adeq Precision" measures the signal to noise ratio. A ratio of 72.053 indicates an adequate signal. This model can be used to navigate the design space.

Mathematical relationship in the form of polynomial equation for the measured (release in 60 and 240 minutes) were obtained with the statease software. The polynomial equation relating the different response and independent variables are given below:

Dissolution@ 60 minutes= +6.32 -4.88 *A -0.18 *B -1.27 *C -1.30*AB +0.15*AC -1.00 *BC +0.73 *A^2 -0.24 *B^2 -0.27 *C^2

Dissolution@ 240 minutes= +22.03 -9.19 *A -0.78 *B -3.04 *C -3.09*AB +0.37*AC -0.64 *BC +0.90 *A^2 +0.30 *B^2 +0.50 *C^2

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels of the factors are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

From the response surface plots of 60 and 240 minutes time points, it was observed that with the increase in concentration of HPMC K4M and HPMC K100M the dissolution rate was decreased. In contour and response surface plots ethyl cellulose was taken as actual factor at a concentration of 10 mg. AC & BC interaction effects were also shown the same observation and their corresponding contour and response surface plots were not represented in this paper.

From the optimization part, numerical data as per criteria has shown several solutions. Among those, a solution of HPMC K4M (A): 40 mg, HPMC K100M (B): 10 mg and ethyl cellulose 7CPS (C): 10 mg was shown a desirability of 1.000.

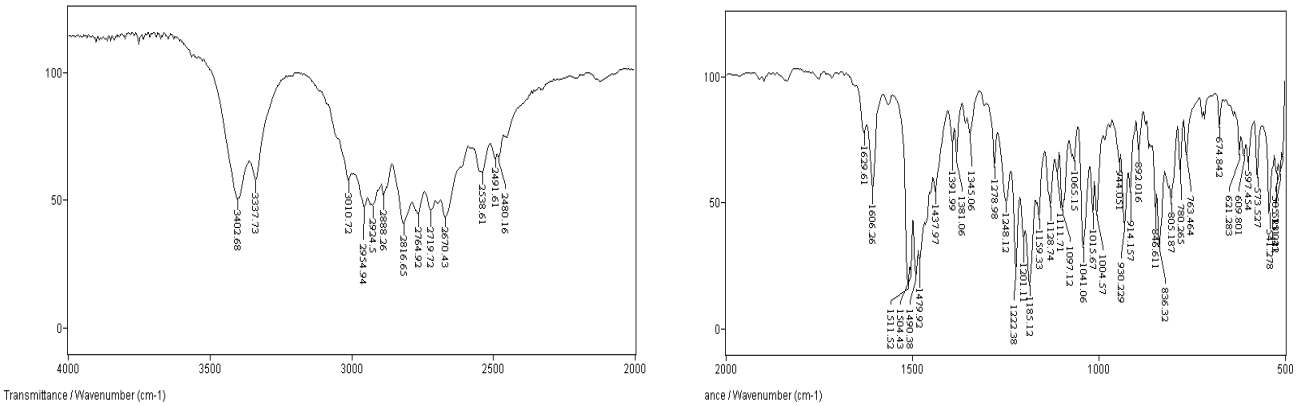

Figure 1: FTIR spectra of pure drug (spectra divided in to two portions)

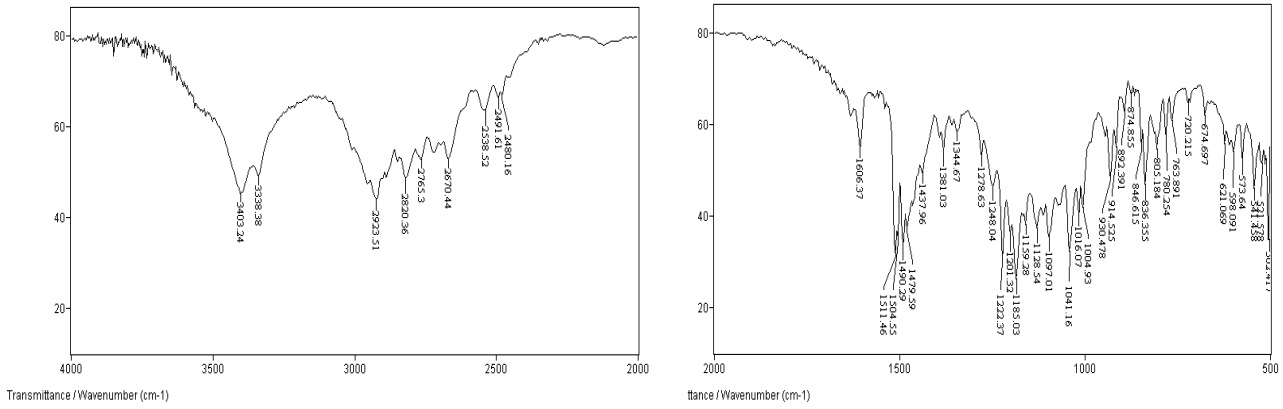

Figure 2: FTIR spectra of API +Excipients (spectra divided in to two portions)

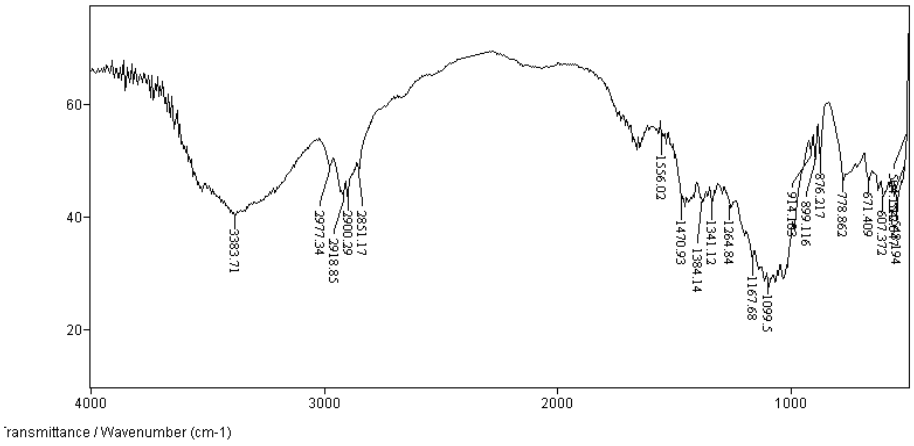

Figure 3: FTIR spectra of placebo (with all excipients excluding pure drug)

Table 1: Central composite design

Std	Run	Factor 1 A: HPMC K4M (mg)	Factor 2 B: HPMC K100M (mg)	Factor 3 C: Ethyl cellulose 7CPS (mg)
3	1	30	15	15
11	2	40	10	10
8	3	40	17.07	10
7	4	40	2.93	10
1	5	50	15	5
9	6	40	10	2.93
6	7	54.14	10	10
2	8	50	5	15
10	9	40	10	17.07
12	10	40	10	10
5	11	25.86	10	10
4	12	30	5	5

Table 2: Formula of preliminary Paroxetine hydrochloride matrix core tablets as per central composite design

Ingredient (mg/tab)	RUN											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Paroxetine hydrochloride*	42.66	42.66	42.66	42.66	42.66	42.66	42.66	42.66	42.66	42.66	42.66	42.66
HPMC K4M	30.00	40.00	40.00	40.00	50.00	40.00	54.14	50.00	40.00	40.00	25.86	30.00
HPMC K100M	15.00	10.00	17.071	2.93	15.00	10.00	10.00	5.00	10.00	10.00	10.00	5.00
Ethyl cellulose 7CPS	15.00	10.00	10.00	10.00	5.00	2.93	10.00	15.00	17.07	10.00	10.00	5.00
Povidone	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Spray dried lactose	111.34	111.34	104.27	118.41	101.34	118.41	97.198	101.34	104.27	111.34	125.48	131.34
Aerosil	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Magnesium stearate	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
Total weight (mg)	230.00	230.00	230.00	230.00	230.00	230.00	230.00	230.00	230.00	230.00	230.00	230.00

*Paroxetine hydrochloride 42.66 mg is equal to Paroxetine 37.5 mg (As is basis calculations were included), weights were rounded for convenience

Table 3: In-process test specifications for Paroxetine hydrochloride matrix core tablets

S. No.	In-process Test	Sample quantity	Specification*
1	Description	20 tablets	Round, biconvex, film coated, upper punch embossed with 'N'and lower punch embossed with'37.5'
2	Average mass	50 tablets	230.0 mg ± 3.0% (223.1- 236.9 mg)
3	Mass of 50 tablets	50 tablets	11.500 g ± 3.0% (11.155- 11.845 g)
4	Friability	Eq. to 6.5 g of tablets	Not more than 1.0% w/w
5	Thickness	10 tablets	4.02 ± 0.30 mm (3.72- 4.32 mm)
6	Hardness	10 tablets	5.0- 7.0 kg/cm^2

*Target value indicated for reference purpose only and not restricted

Table 4: *In vitro* drug release study of Paroxetine hydrochloride matrix core tablets as per central composite design

Time (h)	RLD	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
% Drug release in buffer stage													
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1.0	5.1 ±2.01	9.8 ±1.20	5.9 ±2.35	5.9 ±1.21	6.4 ±2.89	2.0 ±2.31	7.9 ±2.34	1.2 ±2.58	2.7 ±1.96	4.3 ±3.46	6.1 ±2.13	15.0 ±2.75	10.4 ±3.21
2.0	7.2 ±1.45	13.4 ±1.11	8.2 ±2.10	7.7 ±0.97	9.6 ±1.12	4.0 ±1.70	11.4 ±1.98	3.0 ±2.54	4.2 ±2.01	5.9 ±2.48	8.3 ±2.02	20.2 ±2.11	18.3 ±2.78
3.0	8.9 ±1.64	24.7 ±0.96	10.1 ±1.56	9.0 ±1.56	12.4 ±2.01	8.1 ±1.82	13.6 ±1.85	4.6 ±2.63	7.7 ±1.54	7.8 ±2.01	9.9 ±2.34	29.8 ±1.95	26.5 ±2.11
4.0	21.7 ±0.86	31.3 ±0.98	21.9 ±1.89	21.4 ±1.89	23.6 ±1.84	14.1 ±1.12	27.2 ±1.11	10.7 ±2.01	16.5 ±1.67	18.6 ±2.05	22.4 ±2.01	36.7 ±1.85	33.5 ±1.69
6.0	55.9 ±1.24	64.9 ±1.35	57.3 ±1.56	52.7 ±1.56	60.7 ±0.89	40.7 ±1.34	61.4 ±1.08	39.4 ±1.88	43.6 ±1.58	49.1 ±2.00	58.7 ±1.54	66.9 ±1.64	67.8 ±1.98
8.0	80.7 ±1.44	82.9 ±1.54	82.0 ±1.45	79.2 ±1.34	83.1 ±0.75	64.9 ±1.58	84.0 ±1.67	62.0 ±1.94	64.7 ±1.34	75.6 ±2.45	80.9 ±1.36	84.7 ±1.94	83.4 ±1.65
(f2)		53.76	92.65	88.34	76.83	52.30	68.62	48.53	54.62	71.98	89.40	45.36	49.16

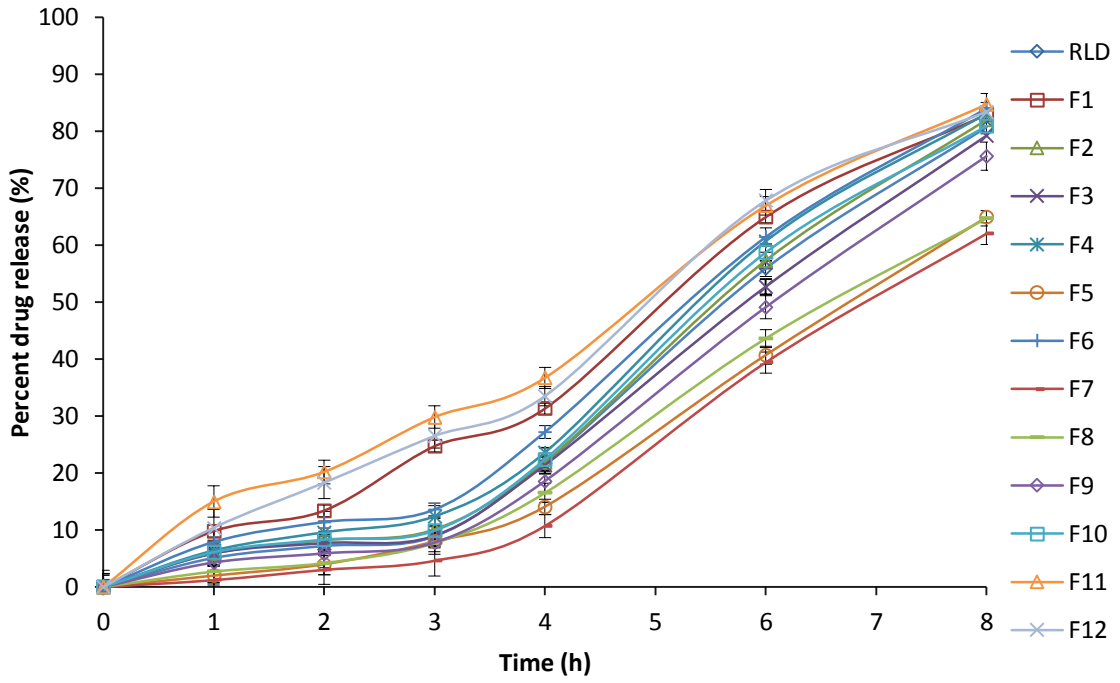

Figure 4: Percent drug release profile of Paroxetine hydrochloride matrix core tablets prepared as per central composite design

Table 5: ANOVA for response surface quadratic model dissolution@ 60 minutes

Analysis of variance table [Partial sum of squares- Type III]						
Source	**Sum of squares**	**d. f.**	**Mean square**	**F value**	**p-value Prob> F**	
Model	167.58	9	18.62	30.44	0.0322	Significant
A- HPMC K4M	95.22	1	95.22	155.67	0.0064	
B- HPMC K100M	0.13	1	0.13	0.20	0.6955	
C- Ethyl cellulose 7CPS	6.48	1	6.48	10.59	0.0828	
AB	3.37	1	3.37	5.51	0.1435	
AC	0.044	1	0.044	0.072	0.8138	
BC	2.02	1	2.02	3.30	0.2111	
A^2	3.23	1	3.23	5.28	0.1485	
B^2	0.35	1	0.35	0.57	0.5281	
C^2	0.43	1	0.43	0.70	0.4915	
Residual	1.22	2	0.61			
Lack of Fit	1.20	1	1.20	60.17	0.0816	Not Significant
Pure Error	0.020	1	0.020			
Cor Total	168.81	11				

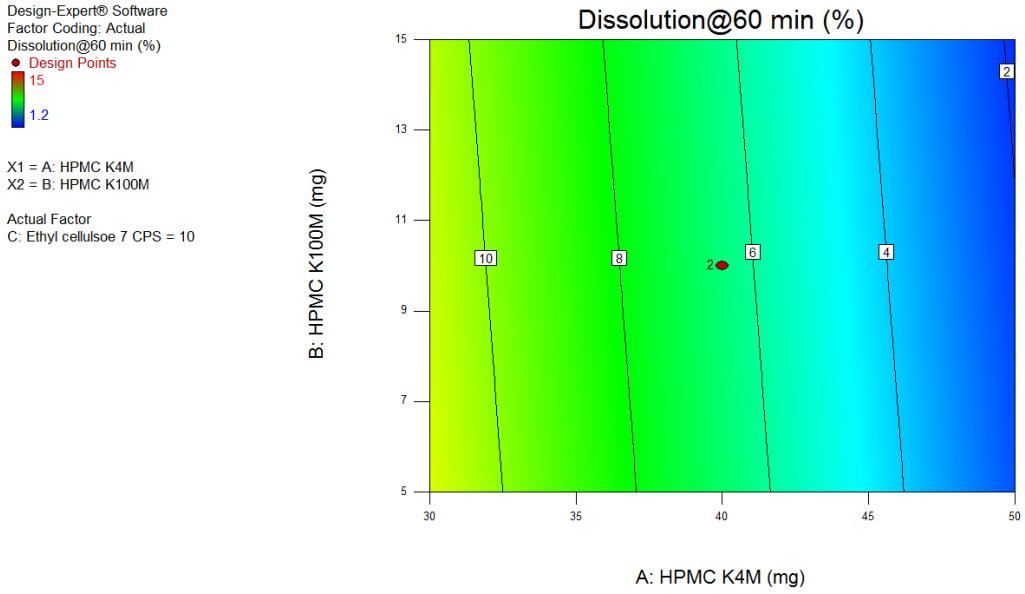

Figure 5: Contour plot showing the effects of the amount of polymer HPMC K4M and HPMC K100M on drug release at 60 minutes from Paroxetine hydrochloride matrix core tablets

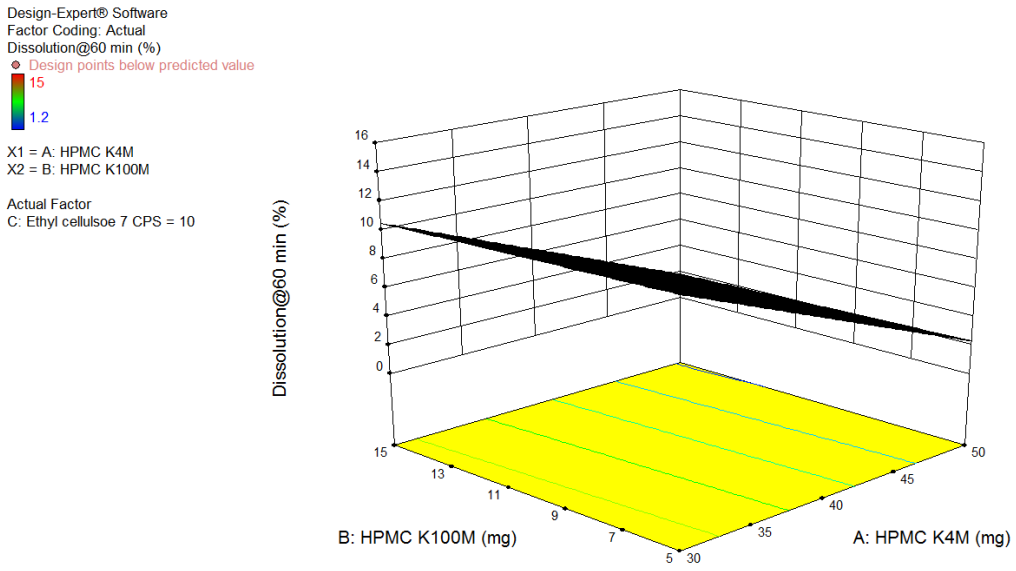

Figure 6: Response surface plot showing the effects of the amount of polymer HPMC K4M and HPMC K100M on drug release at 60 minutes from Paroxetine hydrochloride matrix core tablets

Table 6: ANOVA for response surface quadratic model for dissolution@ 240 minutes

Analysis of variance table [Partial sum of squares- Type III]						
Source	**Sum of squares**	**d. f**	**Mean square**	**F value**	**p-value Prob> F**	
Model	680.46	9	75.61	483.88	0.0021	Significant
A- HPMC K4M	338.00	1	338.00	2163.20	0.0005	
B- HPMC K100M	2.42	1	2.42	15.49	0.0589	
C- Ethyl cellulose 7CPS	36.98	1	36.98	236.67	0.0042	
AB	19.10	1	19.10	122.26	0.0081	
AC	0.28	1	0.28	1.77	0.3145	
BC	0.83	1	0.83	5.28	0.1483	
A^2	4.86	1	4.86	31.10	0.0307	
B^2	0.54	1	0.54	3.46	0.2041	
C^2	1.50	1	1.50	9.60	0.0903	
Residual	0.31	2	0.16			
Lack of Fit	0.19	1	0.19	1.50	0.4359	Not significant
Pure Error	0.13	1	0.13			
Cor Total	680.77	11				

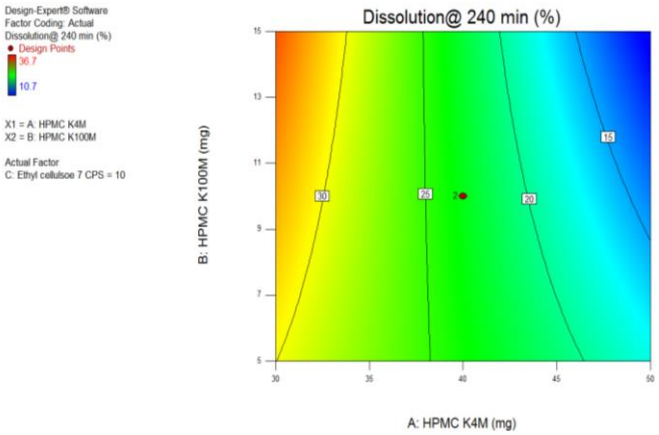

Figure 7: Contour plot showing the effects of the amount of polymer HPMC K4M and HPMC K100M on drug release at 240 minutes from Paroxetine hydrochloride matrix core tablets

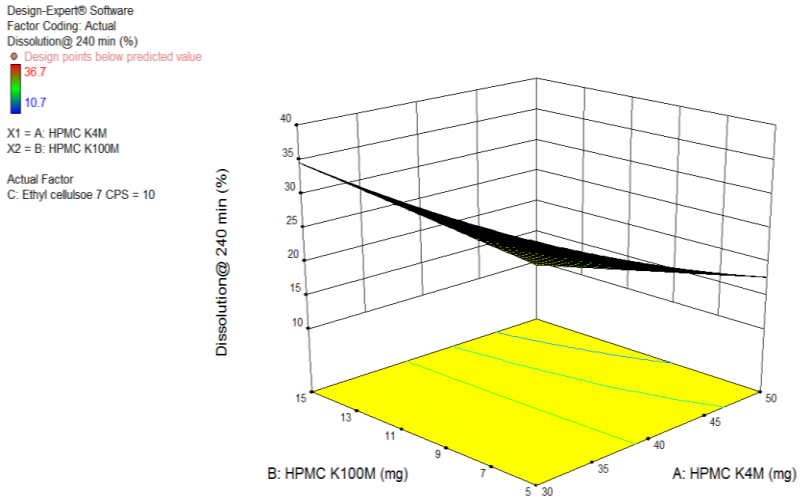

Figure 8: Response surface plot showing the effects of the amount of polymer HPMC K4M and HPMC K100M on drug release at 240 minutes from Paroxetine hydrochloride matrix core tablets

Table 7*: In vitro* drug release study of Acryl-EZE coated Paroxetine hydrochloride CR tablets

Time (h)	RLD	F13 (6.0% w/w)	F14 (7.0% w/w)	F15 (8.0% w/w)
% Drug release in acid stage				
0.0	0.0± 0.0	0.0± 0.0	0.0± 0.0	0.0± 0.0
2.0	0.0± 0.0	0.0± 0.0	0.0± 0.0	0.0± 0.0
% Drug release in buffer stage (acid+buffer)				
3.0	4.8± 2.8	6.9± 3.2	5.2± 1.98	3.2± 1.86
4.0	6.4± 2.4	8.2± 2.8	6.5± 2.04	5.6± 1.78
5.0	10.9± 1.9	14.5± 2.9	12.6± 2.01	8.5± 1.93
6.0	20.4± 1.87	25.2± 2.1	22.7± 1.98	15.4± 1.55
8.0	57.2± 1.54	64.1± 1.67	59.7± 1.99	45.3± 1.46
10.0	81.6± 1.67	89.3± 1.73	82.6± 2.04	72.3± 1.88
Similarity (f2)		66.19	87.27	60.38

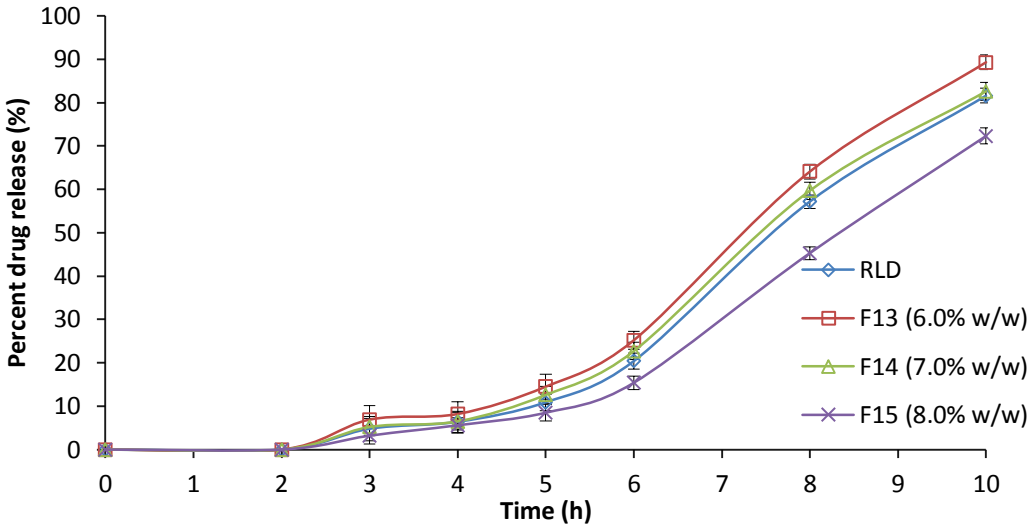

Figure 9: Percent drug release profile of Paroxetine hydrochloride CR formulations coated with Acryl-EZE of different weight build ups

Table 8: *In vitro* release kinetics of Paroxetine hydrochloride CR tablets

Trial No.	Zero order 'R^2'	First order 'R^2'	Higuchi 'R^2'	Korsmeyer–Peppas'R^2'
Paxil CR	0.8815	0.8226	0.9136	0.9753
F13	0.8947	0.8124	0.9283	0.9715
F14	0.8877	0.8312	0.9242	0.9665
F15	0.8723	0.8159	0.8959	0.9866

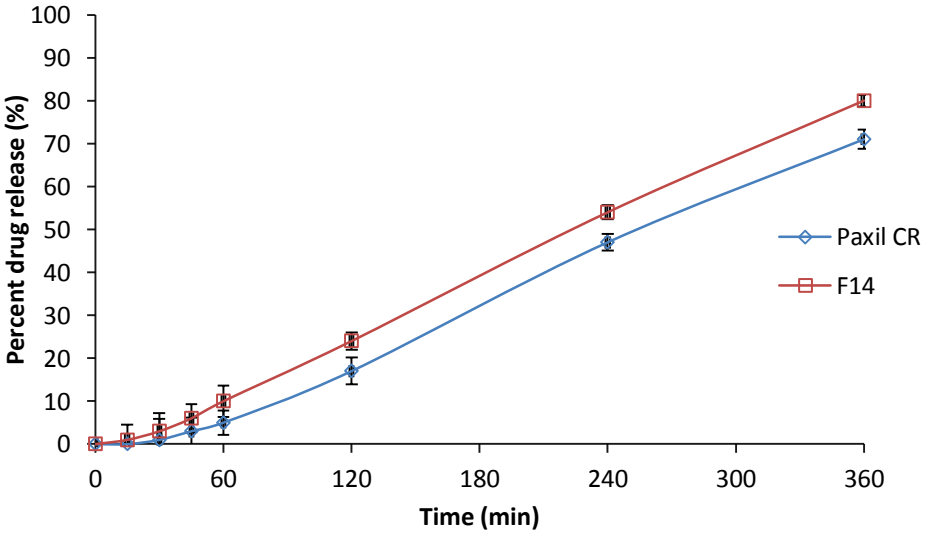

Figure 10: Alcohol dose dumping studies for Paxil CR and F14 in 0.1 N hydrochloric acid containing 40.0% alcohol

All the runs were compared for dissolution profiles against the pealed RLD to check the similarity factor. Out of the 12 runs, run 2 (F2) has shown higher similarity factor when compared against pealed RLD and the same has been confirmed with the reproducible run 10 (F10). Numerical solution from the software was confirmed by similarity factor. The dissolution profile data and graphs of Paroxetine hydrochloride CR matrix core tablets were illustrated in Table 4 and Figure 4. Run 2 (F2) composition was selected for Acryl-EZE coating trials. Acryl-EZE coating weight build ups of 6.0%, 7.0% and 8.0% w/w were given on the run 2 composition and named F13, F14 and F15 respectively. The dissolution profile data and graphs of Paroxetine hydrochloride CR matrix core tablets were illustrated in Table 7 and Figure 9. The release kinetics data were evaluated by applying the equation of zero order, first order, Higuchi and Korsmeyer- Peppas equation. The regression coefficient values of different release kinetic equations were evaluated from the dissolution profiles of developed formulations and were given in Table 8.

It can be highly postulated that in vitro release profile of all the matrix formulations could be best expressed by the Higuchi model. The plot showed high linearity in comparison to other release kinetic equations. Release of drug from CR matrix tablet generally follows diffusion for water soluble drug and erosion or relaxation for water insoluble drug. Paroxetine hydrochloride is a water soluble drug and follows diffusion mechanism. Formulation F14 was finalized as per the similarity factor and loaded in 40°C/75% RH condition for accelerated stability. F14 tablets of 30's count were filled into HDPE bottle 75cc/ 33 mm screw neck and loaded for stability as per the sampling requirement. Paxil CR bottles were also loaded in to stability chamber to check the stability performance. Test and Paxil CR samples were withdrawn at specified time intervals and observed for the physico chemical properties. There was no difference in the dissolution profile with respect to initial time points and 3 months accelerated stability. Alcohol dose dumping studies were performed to check the effect of alcohol concentration on the release profile. At 5.0% v/v concentration, no drug was release with Paxil CR and F14 formulations. At 40.0% v/v concentration F14 has shown a similarity factor of 67.2 with respect to Paxil CR. At the end of 6 hours 71.0% and 80.0% drug release was observed with Paxil CR and F14 formulations respectively. The results from the in vitro alcohol study showed that alcohol increased the release of the drug from the formulation, but a dose dumping effect per se was not observed. Alcohol dose dumping graphs were given in Figure 10.

CONCLUSION

Response surface methodology with central composite design was used to optimize and evaluate the Paroxetine hydrochloride controlled release tablets. Dissolution time points 60 and 240 minutes were shown that the model was highly significant. Numerical solution from the software was confirmed by similarity factor. Selected ranges of HPMC K4M, HPMC K100M and ethyl cellulose 7CPS were found to be significant with respect to release rate. In vitro release profiles of all the Acryl-EZE coated matrix formulations were following Higuchi model. Paxil CR and F14 samples were shown similarity in dissolution profile at initial and accelerated conditions. A generic Paroxetine hydrochloride CR tablet was developed.

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