DESIGN AND EVALUATION OF CONTROLLED RELEASE TABLETS OF PAROXETINE HYDROCHLORIDE

Namrata Vaidya^{1*}, Ravikumar Nayak¹, Raja Benhar¹, Narayanswamy VB²¹Department of Pharmaceutics, Karavali College of Pharmacy, Mangalore, India²Department of Pharmacognosy, Karavali College of Pharmacy, Mangalore, India

*Corresponding Author Email: vainamrata@gmail.com

Article Received on: 13/08/13 Revised on: 07/09/13 Approved for publication: 14/09/13

DOI: 10.7897/2230-8407.04917

IRJP is an official publication of Moksha Publishing House. Website: www.mokshaph.com

© All rights reserved.

ABSTRACT:

The present study aimed at Formulation Development and Evaluation of controlled release tablets for the programmed release of Paroxetine hydrochloride for the treatment of Major Depression. The matrix tablets of Paroxetine hydrochloride were prepared using wet granulation. Physical characterization of tablet and powder blends used to form the matrix tablet was under taken using a range of experimental techniques. Instacoat EN II was used as enteric coat polymer for coating the matrix tablet. The ratio of Methocel K100M and Methocel K4M, concentration of Compritol 888 ATO and percentage of coating with Instacoat EN II was optimized using Design of experiment software and effect of factors on *in-vitro* drug release at Q2 and Q9 Studied. Dissolution studies of paroxetine hydrochloride controlled release tablets in media with different dissolution media 0.1 N HCl, pH (7.5). The study showed that, drug release in 2 h was highly affected by the coating level. Optimization enabled formulation of Paroxetine hydrochloride CR tablets shown that formulation F 12 with Methocel K100M and Methocel K4m (1:2 ratio), Compritol 888 ATO (12 mg) and (10 %) coating of Instacoat EN II met the desired release profile. Formulation F12 was compared with marketed brand in same dissolution medium. Stability study of the optimized formulation indicates no significant difference in release profile after a period of one month.

Keywords: Paroxetine hydrochloride, Depression, Methocel K4M and K100M, Compritol 888 ATO, Instacoat EN II.

INTRODUCTION

Oral route has been the most popular and successfully used for controlled delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system.¹ The United States Pharmacopoeia (USP) defines the modified-release (MR) dosage form as the one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms^{2,3}. The rationale for the Controlled Delivery of drugs is to promote therapeutic benefits while at the same time minimizing toxic effects. Controlled, sustained drug delivery can reduce the undesirable fluctuation of drug levels, enhancing therapeutic action and eliminating dangerous side effects.⁴ Paroxetine hydrochloride is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate. It is selective serotonin reuptake inhibitor. It is used as an anti-panic agent and anti-depressant. Tablets were formulated as controlled release of the drug because of advantages like ease of the drug administration, patient compliance. Avoid the adverse effect, which was caused by conventional dosage form. Maintain the blood therapeutic concentration, which avoid suicidal tendency as compared to conventional dosage form.

MATERIALS AND METHODS

Paroxetine hydrochloride was gifted by Alkem Labs, Mumbai, India. HPMC K4M, HPMC K100M, HPMC E5, HPMC K100 LV were procured from Zydus Candila, Kundaaim Goa, India. Lactose Monohydrate was purchased from S. D. Finechem Ltd, Mumbai, India. PVP K30, Isopropyl alcohol was purchased from Ranchem Ltd. Compritol 888 ATO, Sodium starch glycolate, Aerosil 200, InstacoatTM EN were purchased from Gattefosse pharmaceuticals, FMC biopolymer, Grase Davison Ltd, Ideal

Cures Pvt. Ltd respectively. All other ingredients used were of analytical grade.

Preformulation studies of pure drug

Identification of pure drug

Identification of Paroxetine hydrochloride was carried out by Infrared Absorption Spectroscopy.

Melting point determination

Melting point of Paroxetine hydrochloride was determined by Open capillary method.

Drug - excipient Compatibility Studies

A successful formulation of a stable and effective solid dosage form depends on careful selection of excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. If the excipients are new and not been used in formulation containing the active substance, the compatibility studies are of paramount importance. Compatibility of Paroxetine hydrochloride hemihydrate with the respective polymers that individual excipients and physical mixture of main formulation was established by Infrared Absorption Spectral Analysis (FTIR). Any changes in the chemical composition after combining with the excipients were investigated with IR spectral analysis.

Formulation of Paroxetine hydrochloride tablets:

Paroxetine hydrochloride controlled release tablets were prepared by wet granulation technique and prepared tablets were coated by using Instacoat EN II Shown in Table 1.

Application of factorial design

A 2³ factorial design was selected and the 3 factors were evaluated at 2 levels, respectively. The statistical treatment and interpretation of data was done by Stat Ease Design Expert 8.0.7.1 software. The analysis of Test of variance (ANOVA) was calculated. The data were also subjected to contour Plot

and 3-D response to study the interaction of independent variables and dependent variables. Optimization was carried out using 2^3 factorial designs after evaluating the preliminary data obtained from six batches of formulations (F1 to F6). The ratio of polymers Methocel K100M and HPMC K4M (X1), the amount of Compritol (X2) and percentage of coating with instacoat EN(X3) were selected as independent variables. % Drug Release in 2 h and % Drug Release in 9 h were selected as dependent variables. The three factors were evaluated, each at 2 levels and experimental trials were performed at all 8 possible combinations. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses. Based on factorial design, 8 different formulations were prepared and evaluated shown in Table 2.

Evaluation pre-compression parameters

The pre-compression evaluation parameters such as angle of repose, bulk density, carr's consolidation index and hausner's ratio were studied.

Evaluation post Compression parameters

The post compression evaluation parameters such as hardness, friability, weight variation and content uniformity were studied.

In-vitro drug release studies of tablets

Drug release studies of coated tablets were carried out using a USP XXIII dissolution rate test apparatus (Apparatus 2, 100 rpm, 37°C) for 2 h in 0.1 M HCl (900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with pH-7.5 Tris buffer (900 ml) for 7 h tested for drug release up to complete drug release. At the end of the time period 10 ml of the samples were taken and analyzed for Paroxetine hydrochloride content. A 10 ml Volume of fresh and filtered dissolution medium was added to make the Volume after each sample withdrawal. Sample was analyzed using UV spectrophotometer at 276 nm.

Stability study of optimized formulation

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, to establish re-set period for drug substances or a shelf life for the drug product and recommended storage conditions. The formulation F12 under storage condition used for stability studies are 40°C, 75 % $\pm$ 5 % RH, for two months¹⁹. The tablets were withdrawn for analysis of following parameters:

- Physical characteristics
- Assay
- Dissolution

Tablets were evaluated for Physical characteristics; Assay, and *in-vitro* drug release after one month.

RESULTS AND DISCUSSION

Paroxetine hydrochloride is an odorless, off-white powder 5.4 mg /ml in water (slightly soluble in water, freely soluble in methanol, sparingly soluble in alcohol and in methylene chloride). Melting point of Paroxetine hydrochloride was found by using capillary method and it was found to be 120° to 138° C. FTIR spectra of pure drug and physical

mixtures are shown in Figure 1 and 2. By comparing the FTIR spectra of pure Paroxetine hydrochloride and its physical mixture with excipients, it was observed that the drug remains intact in the presence of excipients as there were no considerable differences in their spectra's. This was justified by the presence of five peaks –CH₂, NH strec and C-F strec, aromatic group and phenoxy C-O group strec (present in pure drug) in the mixture. Hence, there were no drug-excipients interactions. FTIR studies conducted on pure drug and physical mixtures showed that there is no marked interaction between drugs and selected polymers.

Evaluation of Tablets

Pre Compression Evaluation Parameters

The powder blend of the formulations (F1 to F14) was evaluated for the flow properties such as angle of repose, bulk density, tapped density, % compressibility and hausner's ratio (Table 3).

Flow properties

Granules of all the formulations were subjected for various pre compression evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's Ratio. Results of all the pre-compression parameters performed on the granules of batches are shown in Table 3. The result of angle of repose 33 and 34, Compressibility index 28.21 and 30.05, Hausner's ratios 1.34 and 1.36 of F1 and F2 respectively. The result clearly indicate that flow of granules were very poor from this we conclude that formulation F1 and F2 were difficult to compress. The result of angle of repose was found to be 27 to 30 for batches F3 to F14 respectively. Compressibility index was found to be 13.49 to 15.12 for batches F3 to F14 respectively. The results of Hausner's ratios were found to be 1.17 to 1.213 respectively for batch F3 to F14 respectively. The results of angle of repose (< 30) indicate good flow properties of the powder based on Table 3. This was further supported by lower compressibility index values. Generally, compressibility index values up to 15 % results in good flow properties.

Post compression evaluation parameters

All the tablet prepared formulations were subjected for evaluation according to various official specifications and other parameters: Shape, thickness, hardness, friability, weight variation, tablet dosage form assay. Tablets were white in color. The mean thicknesses of tablets lie between 4.08 ± 0.03 mm to 4.12 ± 0.07 mm. The standard deviation values indicated that all the formulations were within the range. The results lie between 198 ± 2 mg to 204 ± 1 mg. All the tablets passed the weight variation test, i.e., average percentage weight variation was found within the Indian pharmacopoeial limits of ± 7.5 %. Hardness or crushing strength of the tablets of all the formulation was found to be lies between 150 ± 5 N kg/cm² to 157 ± 2 N kg/cm² friability values for batch were found to be lies between 0.066 % to 0.0853 % respectively. The obtained results were found to be well within the approved range (< 1 %) in all the designed formulations. That indicated tablets possess good mechanical strength. Assay of formulations lies in between 97.90 % to 102.20 % drug content respectively. The results are tabulated in Table 4.

Table 1: Formula of preliminary trial batches

Ingredients (mg/tab)	Formulation Code					
	F1	F2	F3	F4	F5	F6
Paroxetine hydrochloride	25	25	25	25	25	25
HPMC E5	10	10	-	-	-	-
HPMC K100LV	20	-	11	-	-	-
HPMC K100M	-	-	9	11	11	11
HPMC K4M	-	20	9	14	14	14
Compritrol 888 ATO	-	-	-	10	10	10
Lactose monohydrate	139	139	134	128	122	122
PVP K30	4	4	4	4	4	4
Sodium starch glycolate	-	-	-	-	6	6
Aerosil 200	-	-	2	2	2	2
Talc	-	-	4	4	4	4
Magnesium stearate	2	2	2	2	2	2
Total weight (mg)	200	200	200	200	200	200
Coating %	-	-	4	6	4	6
Coated tablet weight	-	-	208	212	208	212

Table 2: Formula of Factorial batches

Ingredients (mg/tab)	Formulation Code							
	F7	F8	F9	F10	F11	F12	F13	F14
Paroxetine hydrochloride	25	25	25	25	25	25	25	25
HPMC K100M	11	11	11	11	11	11	11	11
HPMC K4M	16.5	16.5	16.5	16.5	22	22	22	22
Compritrol 888 ATO	14	12	14	12	14	12	14	12
Lactose monohydrate	115.5	117.5	115.5	117.5	110	112	110	112
PVP K30	4	4	4	4	4	4	4	4
Sodium starch glycolate	6	6	6	6	6	6	6	6
Aerosil 200	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2
Total weight (mg)	200	200	200	200	200	200	200	200
Coating %	10	8	8	10	8	10	8	10
Coated tablet weight	220	216	216	220	216	220	216	220

Table 3: Pre compression studies

Formulation	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio	LOD (%)
F1	33	0.6586	0.9976	28.21	1.34	2.02
F2	34	0.6576	0.997	30.05	1.36	1.98
F3	28	0.0669	0.8066	14.98	1.2	1.76
F4	27	0.6753	0.815	13.94	1.203	2.02
F5	29	0.669	0.8156	14.79	1.213	1.98
F6	27	0.6663	0.789	14.50	1.18	1.96
F7	29	0.6713	0.796	15.12	1.18	1.83
F8	28	0.6766	0.796	14.94	1.17	1.88
F9	30	0.6763	0.81	13.49	1.196	1.96
F10	27	0.6766	0.8113	15.09	1.176	2.12
F11	29	0.673	0.819	14.8	1.11	1.88
F12	28	0.6586	0.7976	14.81	1.2	2.02
F13	27	0.6576	0.797	13.5	1.2	1.98
F14	28	0.6586	0.7976	14.56	1.18	1.81

Table 4: Post-compression evaluation of the prepared Tablets

Formulation	Thickness (mm)	Weight of tablet (mg)	Friability (%)	Hardness (N Kg/cm ²)	Assay (%)
F1	Have not good flow property and compressibility index.				
F2					
F3	4.12 ± 0.04	200.33 ± 4.16	0.0853 ± 0.016	157 ± 2	98.56
F4	4.10 ± 0.07	199.33 ± 2.51	0.082 ± 0.006	157 ± 2	102.20 %
F5	4.12 ± 0.07	201.33 ± 3.21	0.074 ± 0.0041	151 ± 5	98.80 %
F6	4.10 ± 0.091	200 ± 3.21	0.0793 ± 0.013	155 ± 3	97.90 %
F7	4.13 ± 0.06	202 ± 3.464	0.0823 ± 0.005	152 ± 3	101.10 %
F8	4.08 ± 0.03	199.33 ± 3.21	0.079 ± 0.009	152 ± 4	100.10 %
F9	4.14 ± 0.07	198 ± 2	0.066 ± 0.005	152 ± 4	100.20 %
F10	4.09 ± 0.04	199 ± 2.51	0.074 ± 0.001	153 ± 2	99.50 %
F11	4.12 ± 0.04	204 ± 1	0.0659 ± 0.0063	150 ± 5	99.30 %
F12	4.11 ± 0.04	200.3 ± 1.52	0.077 ± 0.014	156 ± 4	99.50 %
F13	4.12 ± 0.05	201 ± 2.64	0.078 ± 0.0075	155 ± 3	99.80 %
F14	4.12 ± 0.07	203 ± 2	0.069 ± 0.005	154 ± 4	101.20 %

Table 5: *In-vitro* drug release study of tablets F3 - F6

Dissolution medium	Time (h)	% Cumulative drug release			
		F3	F4	F5	F6
0.1 N HCL	1	9.54	7.84	4.08	3.44
	2	17.46	14.8	9.02	7.8
7.5 Tris Buffer	3	21.6	27	18.4	15.8
	4	38.8	31.5	31.5	22
	5	49.21	47.5	44.5	39.5
	6	62.32	69	60.5	54.5
	7	86.12	84.31	73	71.09
	8	97.35	98.01	83.5	87.06
	9	-----	-----	96.09	98.73

Table 6: *In-vitro* drug release study of factorial batches

Dissolution medium	Time (h)	% Cumulative Drug Release							
		F7	F8	F9	F10	F11	F12	F13	F14
0.1 N HCL	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0
	2	4.89	6.76	6.06	3.52	5.78	4.21	4.84	5.12
7.5 Tris buffer	3	14.32	18.38	17.60	15.45	16.87	14.7	13.07	14.31
	4	26.87	32.63	28.34	23.93	31.33	29.15	21.53	22.23
	5	40.65	54.47	46.40	41.0	48.24	40.27	42.49	39.64
	6	59.29	62.61	61.51	59.16	63.12	59.25	58.35	57.85
	7	70.05	75.85	74.6	77.59	72.41	73.1	76.41	71.49
	8	82.90	87.7	89.30	82.21	85.34	88.44	87.63	83.42
	9	96.42	98.5	97.09	94.45	98.34	99.13	95.14	99.66

Table 7: Result of ANOVA at Q2 h for selected factorial model

Column1	Sum of	Column2	Mean	F	p-value	Column3
Source	Squares	Df	Square	Value	Prob > F	
Model	8.04125	3	2.680417	66.63559	0.0007	significant
A-ratio of methocel K100 M and K4M	2.7378	1	2.7378	68.06215	0.0012	
B-conc of compritol	0.9522	1	0.9522	23.67185	0.0082	
C-% of coating	4.35125	1	4.35125	108.1728	0.0005	
Residual	0.1609	4	0.040225			
Cor Total	8.20215	7				

Table 8: Result of ANOVA at Q2 hr for selected factorial model Classical sum of squares - Type II

Column 1	Column 2	Column 3	Column 4	Column 5
Std. Dev.	0.20056171		R-Squared	0.98038319
Mean	5.1725		Adj R-Squared	0.96567059
C.V. %	3.87746179		Pred R-Squared	0.92153277
PRESS	0.6436		Adeq Precision	23.5159652

Table 9: Result of ANOVA at Q9 h for selected factorial model

Column 1	Sum of	Column 2	Mean	F	p-value	Column 3
Source	Squares	Df	Square	Value	Prob > F	
Model	24.66126	5	4.932253	1346.69	0.0007	Significant
A-ratio of methocel K100 M and K4M	2.892013	1	2.892013	789.628	0.0013	
B-conc of compritol	19.00361	1	19.00361	5188.7	0.0002	
C-% of coating	0.078012	1	0.078012	21.30034	0.0439	
AB	1.147613	1	1.147613	313.3413	0.0032	
BC	1.540013	1	1.540013	420.4812	0.0024	
Residual	0.007325	2	0.003662			
Cor Total	24.66859	7				

Table 10: Result of ANOVA at Q9 h for selected factorial model Classical sum of squares - Type II

Column 1	Column 2	Column 3	Column 4
Std. Dev.	0.06051859	R-Squared	0.99970306
Mean	97.31625	Adj R-Squared	0.99896072
C.V. %	0.06218755	Pred R-Squared	0.99524902
PRESS	0.1172	Adeq Precision	98.5009947

Table 11: Effect on Physical Properties of Tablet at 40°C / 75 % RH Storage Conditions

S. No	Properties	Initial	Storage Conditions 40°C / 75 % RH		
			10 days	20 days	30days
1	Appearance	White coloured, capsular shaped tablets	White coloured, capsular shaped tablets	White coloured, capsular shaped tablets	White coloured, capsular shaped tablets
2	Hardness NKg/Cm ²	150 NKg/Cm ²	148 NKg/Cm ²	149 NKg/Cm ²	146 NKg/Cm ²
3	Thickness mm	4mm ± 0.2 mm	4 mm ± 0.2 mm	4 mm ± 0.2 mm	4 mm ± 0.2 mm
4	Weight	292 mg ± 2%	292 mg ± 2 %	292 mg ± 2 %	292 mg ± 2 %
5	Assay	99 %	98.8 %	98.65 %	98 %

Figure 1: FTIR Graph of Paroxetine HCl

Figure 2: FTIR Graph of Formulation

Figure 3: *In-vitro* drug release profile of trial batches F3 to F6

Figure 4: *In-vitro* drug release profile of factorial batches F7 to F10

Figure 5: *In-vitro* drug release profile of factorial batches F11 to F14

Figure 6: Half normal plot of residuals at Q2 h

Figure 7: Pareto chart showing factors significantly affecting the response Q2

Figure 8: Predicted vs Actual results of formulation variables on percentage release Q2

Figure 9: contour plot showing the effect of formulation variables on percentage release Q2

Figure 10: 3D Graph showing the effect of formulation variables on percentage release Q2

Figure 11: cube data showing actual response of particular factorial trial Q2

Figure 12: Half normal plot of residuals at Q9 h

Figure 13: Pareto chart showing factors significantly affecting the response Q9

Figure 14: Predicted vs Actual results of formulation variables on % Release Q9

Figure 15: Contour plot showing the effect of formulation variables on % Release Q9

Figure 16: 3D Graph showing the effect of formulation variables on percentage release Q9

Figure 17: Cube data showing actual response of particular factorial trial Q9

The *In-vitro* release studies

The *In-vitro* release studies were carried out using – XXIII dissolution assembly. Cumulative % drug release found to be 97.35 % and 98.01 % for formulation F3, F4 respectively. The results clearly indicate that, release profile was not desirable. So further study was planned by using some combination of polymers in different concentration and done coating with different %. Cumulative % drug release found to be 96.09 % and 98.73 % for formulation F5, F6 respectively. The results clearly indicate that, release profile was show satisfactory result. Coating of tablets with Instacoat EN II showed the release about of nearly 7.8 % in 2 h and use of different ratio of methocel and compritol showed release after 9 h was 98.73 %. From the result, concluded that Coating of tablets with Instacoat EN II, use of different ratio of methocel and compritol can be successfully utilized to create desire release profile at 2 h and 9 h similar to the targeted release profile in future study. On the basis of the preliminary trials in the present investigation a 2^3 full factorial design was applied to study the effect of independent variables, i.e. ratio of Methocel K100M and K4M (X_1) and concentration of compritol (X_2) and % of coating of Instacoat ENII on dependent variables like, % drug release at Q2 and Q9. The results obtained in the *in-vitro* drug release study are tabulated in Table 5. The cumulative percentage release of Paroxetine hydrochloride as a function of time for all the formulations are shown in Figure 3. Factorial batches of Paroxetine hydrochloride release were evaluated for the *In-vitro* drug release and by its regression analysis. The results obtained in the *in-vitro*

drug release study are tabulated in Table 6. The cumulative percentage of Paroxetine hydrochloride released for all the formulations (F7 to F14) are shown in Figure 4 and 5. The effect of the Ratio of Methocel K4M and K100M (X_1), Concentration of compritol (X_2) and % coating of Instacoat EN II was studied. The result of regression analysis showed that all the co-efficient bear a different sign, which indicate that both the Independent variables shows significant effect on dependent variables.

Effect of Independent Variables on Dependent Variables

Drug release at 2th h (Q2) gives correlation co-efficient 0.9803831. The P value for variable X_1 , X_2 and X_3 were 0.0012, 0.0082 and 0.0005 respectively ($P < 0.05$), it indicate that both variables shows significant effect on drug release. Result of ANOVA at Q2 h for selected factorial model Analysis of variance table are shown in Table 7 and Result of ANOVA Q2 h for selected factorial model Classical sum of squares - Type II are shown in Table 8. Combination co-efficient was negative but the P value was not less than 0.05, which indicates that combination of independent variable does show significant effect at 2nd h. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 23.516 indicates an adequate signal. This model can be used to navigate the design space. The "Pred R-Squared" of 0.92153 is in reasonable agreement with the "Adj R-Squared" of 0.98038. The Model F-value of 66.64 implies the model is significant. It shows that there is only a 0.07 % chance that a "Model F-Value" this large could occur due to noise. The response data was analyzed by using stat ease design expert software.

The software gives statistical analysis of data. The interaction effect of these formulation factors on the drug release can be studied using the results of statistical analysis. Responses were shown in Figure 6 to Figure 11:

Final equation in terms of coded factors

$$Q5 = 23.29 + 8.5366 - 2.663333 + 3.7266 - 1.18333$$

Drug release at 9th h (Q2) gives correlation co-efficient 0.9997. The P value for variable X₁, X₂ and X₃ were 0.0013, 0.0002 and 0.0439 respectively (P < 0.05), it indicates that both variables show significant effect on drug release. Result of ANOVA at Q9 h for selected factorial model Analysis of variance table are shown in Table 9 and Result of ANOVA Q9 h for selected factorial model Classical sum of squares - Type II are shown in Table 10. Combination co-efficient was negative but the P value was not less than 0.05, which indicates that combination of independent variable does show significant effect at 9th h. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 98.501 indicates an adequate signal. This model can be used to navigate the design space. The "Pred R-Squared" of 0.9952 is in reasonable agreement with the "Adj R-Squared" of 0.9990. The Model F-value of 1346.69 implies the model is significant. It shows that there is only a 0.07 % chance that a "Model F-Value" this large could occur due to noise. Precision" measures the signal to noise ratio. The Model F-value of 19.96 implies that the model is significant. It shows that there is only a 0.07 % chance that a "Model F-Value" this large could occur due to noise.

Final equation in terms of coded factors

$$Q9 = 97.31625 - 0.60125 - 1.54125 + 0.09875 - 0.37875 - 0.43875$$

The response data was analyzed by using stat ease design expert software. The software gives statistical analysis of data. The interaction effects of these formulation factors on the drug release can be studied using the results of statistical analysis. Responses were shown in Figure 12 to Figure 17. The Q2 and Q9 for all the batches F7 to F14 varied from 3.52 % to 6.96 % and 94.45 % to 99.66 % with correlation coefficient as 0.962596 and 0.95228 respectively. Formulation F10 showed the least drug release at Q2 with only 3.52 % drug release but it failed to release the drug at Q9 with only 94.45% drug release. Formulation F12 showed 4.21 % drug release at Q2 but it showed maximum release at Q9 with 99.13 % drug release and hence on this basis it was considered as best formulation.

Stability study of Paroxetine hydrochloride controlled release tablets

The stability study was carried out at 40°C / 75 % RH for formulation F12 up to 30 days. At every 10 days time interval, the devices were analyzed for Physical Properties and *In-vitro* drug release. The results of accelerated stability study are tabulated in Table 11. The results of accelerated stability study showed that there was no change in the formulation after one month. *In-vitro* drug release study showed that after 10, 20 and 30 days; values obtained were 4.56 %, 4.4 % and 4.60 % respectively. The drug release throughout 2 h obtained within range of targeted release profile. Values obtained were 97.75 %, 98.02 % and 97.12 % respectively. The drug release throughout 9 h obtained within range of targeted release profile. Assay result after 10, 20 and 30 days; values obtained were 98.8 %, 98.65 % and 98 % respectively. After 30 days accelerated stability study the assay result was stable.

98.02 % and 97.12 % respectively. The drug release throughout 9 h obtained within range of targeted release profile. Assay result after 10, 20 and 30 days; values obtained were 98.8 %, 98.65 % and 98 % respectively. After 30 days accelerated stability study the assay result was stable.

CONCLUSION

The study was undertaken with an aim of Formulation Development and Evaluation of Paroxetine controlled release tablets using different polymers as release retarding agent. Preformulation study was done initially and results directed for the further course of formulation. Based on preformulation studies different a batch of Paroxetine was prepared using selected excipients. Granules were evaluated for Bulk density, Tapped density, Compressibility index, and Hausner's ratio. Tablets were tested for weight variation, thickness, hardness and friability as per official procedure. After compression tablets are subjected for enteric coating to mask the release of drug in stomach. Dissolution was carried out in pH 7.5 Tris buffer Medias. Based on dissolution tests, it was concluded that F12 satisfactorily release drug through 9 h. Optimization enabled formulation of Paroxetine hydrochloride CR tablets shown that formulation with Methocel K100M and Methocel K4m (1:2 ratio), Compritol 888 ATO (12 mg) and (10 %) coating of Instacoat EN II within the desired release profile. The optimized formulation showed release profiles and responses which were close to predicted responses. From the above results and discussion it is concluded that formulation of controlled release tablet of Paroxetine hydrochloride of formulation F12 can be taken as an ideal or optimized formulation of controlled release tablets for 9 h release as it fulfills all the requirements for controlled release tablet and our study encourages for *In-vivo* studies, Clinical trials on this formulation. Stability study was carried out after one month of time. Stability study report confirmed that formulation was not shown any color change and no significant release profile, Assay from initial period. Thus confirms that prepared formulation was stable.

ACKNOWLEDGEMENT

Authors are thankful to Principal and Head of Department of Pharmaceutics, Karavali College of Pharmacy, Mangalore, Karnataka, India, for providing necessary facilities during the course of this study.

REFERENCES

- Lachman L, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy, 3rd ed, Varghese Publishing House; 1990. p. 430-453.
- Debjit B, Harish G, Kumar BP, Duraivel S, Kumar KPS. Controlled Release Drug Delivery Systems. *pharm innovation J* 2012; 1(10): 24-32.
- Notari R. Bio pharmaceutics and Clinical Pharmacokinetics an Introduction, 3rded, Marcel Dekker Inc; 1971. p. 152-154.
- Martin Alford N, Sinko Patrick J. Martin's Physical Pharmacy and Pharmaceutical Sciences. 5thed, Lippincott Williams and Wilkins; 2006. p. 667-672.
- Brahmankar DM, Jaiswal SB. Bio pharmaceutics and pharmacokinetics a treatise, 2nd ed, Vallabh prakashan; 2010. p. 397-515.
- Chungh I, Seth N, Rana AC, Gupta S. Oral sustained release drug delivery system: an overview. *International Research Journal of pharmacy* 2012; 3(5): 57-62.
- Nokhodchi A, Raja S, Patel P, Asare Addo K. Role of oral controlled release matrix tablets in drug delivery system. *BiolImpacts* 2012; 2(4): 175-187. PMID:23678458 PMCID:PMC3648939
- Kamboj S, Gupta GD, Oberoy J. Matrix tablets: an important tool for oral controlled-release dosage forms. Online available at www.pharmainfo.net
- Prescribing Information of Paxil
- Prescribing Information of Paxil CR
- www.rxlist.com Pae CU, Patkar AA. Paroxetine: current status in psychiatry. Department of Psychiatry and Behavioural Sciences. Expert

- Rev Neurother 2007; 7(3): 313-314. <http://dx.doi.org/10.1586/14737175.7.3.313>
12. Golden RN, Nemeroff CB, Mc Sorley P, Pitts CD and Dube EM. Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. *J Clin Psychiatry* 2002; 63: 577-584. <http://dx.doi.org/10.4088/JCP.v63n0707> PMID:12143913
13. Eaddy M, Bramley T, Regan T. Time to antidepressant discontinuation: a comparison of controlled-release Paroxetine and immediate-release selective serotonin-reuptake inhibitors. *Manag Care Interface* 2003; 16(12): 22-27. PMID:14750459
14. Barnes RD, Wood Kaczmar MW, Curzons AD, Lynch IR, Richardson JE, Harlow, Buxton PC. Anti-depressant crystalline paroxetine hydrochloride hemihydrate. US 4721723; 1988.
15. Leonard, Gramham S, David P. Paroxetine controlled release compositions. EP0839039 A1; 1998.
16. Raju DB, John KS, Verma MM. Formulation and evaluation of Losartan potassium matrix tablets for controlled oral release. *J Chem Pharm Res* 2010; 2(2): 130-135.
17. Saravanan M, Natrajan KS, Ganesh KS. Hydroxypropyl methylcellulose based Cephalexin extended release tablets: influence of tablet formulation, hardness and storage on *in-vitro* release kinetics. *Chem Pharm Bull* 2003; 51(8): 978-983. <http://dx.doi.org/10.1248/cpb.51.978> PMID:12913240
18. Shaikh AC, Nazim S, Shaikh S, Khan T, Patel MS, Zameeruddin M *et al.* Formulation and evaluation of sustained release tablets of Aceclofenac using hydrophilic matrix system. *Int J Pharm Pharm Sci* 2011; 3(2): 145-148.
19. ICH guidelines for stability studies.

Cite this article as:

Namrata Vaidya, Ravikumar Nayak, Raja Benhar, Narayanswamy VB. Design and evaluation of controlled release tablets of Paroxetine hydrochloride. *Int. Res. J. Pharm.* 2013; 4(9):84-92 <http://dx.doi.org/10.7897/2230-8407.04917>

Source of support: Nil, Conflict of interest: None Declared