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FORMULATION AND *IN VITRO* RELEASE KINETIC STUDY OF AN ENTERIC COATED PAROXETINE CONTROLLED RELEASE TABLETS

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ABSTRACT

The objective of the present study was to formulate the paroxetine controlled release enteric coated tablet and its *in-vitro* release kinetics and stability studies. Paroxetine core tablets were prepared by wet granulation process using HPMC K4M and K100M as matrix forming hydrophilic polymers. Instacoat En II (10%) in Isopropyl alcohol (90%) was used as an enteric coating solution. *In vitro* dissolution study was performed for all the formulations by using Tris buffer as dissolution medium. Different dissolution models were applied to evaluate release mechanisms and its kinetics. The result suggests that F11 formulation showed uniform (zero order) release of drug from the matrix tablet with good correlation value for 12 hours. The effect of paddle RPM in kinetic study was also done for F11 formulation. The stability studies were conducted for F11 at 40°C ± 2°C / 75% RH ± 5% for a period of 3 months. No significant differences were observed in the release profile of different batches of each enteric coated paroxetine CR tablet. The similarity and dissimilarity factors for F11 were 0.68 and 95.62 respectively. The best fit with higher correlation was found in the linear regression graph with the Hixon-crowel cube root law for selected formulation F11 and innovator brand. The present study concluded that the formulation F11 was stable and exhibited appreciable controlled release of an enteric coated paroxetine matrix tablet for reproducible and commercial manufacturing.

KEYWORDS

Paroxetine, Controlled release, Enteric coated, *In vitro* dissolution study and Release kinetic study.

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INTRODUCTION

Paroxetine hydrochloride is an orally administered psychotropic drug and act as a selective serotonin reuptake inhibitor (SSRI)[1,2]. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4R-(4'-fluorophenyl)-35'-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3$•HCl•1/2H_2O. The molecular

weight is 374.8 (329.4 as free base). Due to its stability issues, it is generally used as pharmaceutically acceptable salt form like paroxetine hydrochloride hemihydrate.

Conventional Immediate-release tablet dosage form of paroxetine is known to cause adverse gastrointestinal reactions such as nausea, vomiting, etc[3]. Such adverse reactions are mainly caused by abrupt increases in the blood level time profile of the drug and differences in the highest and lowest blood levels. Paroxetine is also known that -HT3 and 5-HT receptor subtypes, which are mainly present in the upper GI tract that cause the adverse reactions like nausea and vomiting[4]. Being an antidepressant drug, paroxetine has to be taken for a long period of time. Hence, it is important to improve patient compliance by making it convenient to take and reduces adverse GI reactions such as nausea and vomiting. To do so, the drug should be released only in the small intestine in controlled fashion and not in the stomach.

Hydroxypropyl Methyl Cellulose (HPMC) is the polymer most widely used as the gel forming agent in the formulation of controlled release dosage form. The predicted drug release rate can be obtained by modifying the polymer concentration, viscosity grade and the addition of different type of excipients[5,6]. HPMC was chosen as controlled release carrier of this formulation because it offers additional advantages like easily predictable kinetic release, high reproducibility and universal acceptability[7,8].

The present study relates to controlled release tablet comprising of paroxetine and HPMC using wet granulation method. The prepared tablets were coated with enteric polymer to enable the constant release of the drug without regard to the residence time of the tablet in the stomach. The purpose of enteric-coated formulation comprising a matrix layer is for preventing excessive release of drug at early stage. *In vitro* release kinetic study and stability studies were performed for the prepared enteric coated Paroxetine CR matrix tablet. The enteric coated paroxetine was to develop a generic tablet which was robust, stable, and of an acceptable formulation when compared to reference original product thereby fulfilling the requirement of essential similarity to the marketed product.

EXPERIMENTAL

MATERIALS

Paroxetine hydrochloride hemihydrate was obtained as gift sample from Alkem Labs, Mumbai. HPMC K4M, HPMC K100 M, Lactose Mono hydrate, PVP $K_{30,}$ Isopropyl alcohol, Compritol 888 ATO (glycerol dibehenate), Sodium starch glycollate, Aerosil 200, Magnesium Stearate and Talc were obtained from Alkem Labs, Mumbai.

METHODS

HPLC analysis method

An in-house developed and validated HPLC analysis method (Model – Aglient series 1100; C/18 column, 25 x 5.5 cm), wavelength of 295nm using UV-Visible detector was used for the estimation of drug in bulk, formulations and in dissolution samples. Sodium phosphate buffer and methanol (95:5) at pH 4.4 was used as mobile phase. (Injectable volume of 20µl; particle size of 5 µm and flow rate of 2ml/min).

Compatibility studies of paroxetine HCl

The bulk drug was characterized by various tests of identification according to the manufacturer's certificate of analysis. The Fourier transformer Infrared (FT-IR) (IR Prestige-21, Shimadzu, Kyoto, Japan) spectrum obtained was compared with that of the standard. The compatibility study of Paroxetine with various formulation excipients was done by mixing the Paroxetine HCl with each formulation excipient in the ratio of 1:1. The compatibility studies were carried out up to six months.

Evaluation of paroxetine granules

Prior to compression, granules were evaluated for their characteristic parameters[9-11] like bulk density, tapped density and Hausner's ratio of the granules were assessed in accordance with the USP monograph using a tapped volumeter apparatus (Erweka, SVM101, Heusenstamm, Germany). Carr's compressibility index of the granules was determined. Loss on drying also was calculated for the granules in the different formulations.

Formulation Design

Core tablet preparation

Tablets containing 12.5 mg of Paroxetine were prepared by wet granulation method and the composition are given in Table No.1. The drug passed through sieve #20, diluent (Lactose mono hydrate) and controlled release polymers (HPMC K4M, HPMC K100M) were passed through sieve # 24. All the above ingredients were mixed together in planetary mixer (Kenwood CHEF) for 10 min at slow speed. 2 % PVP K30 in Isopropyl Alcohol was used as binder solution. Granulation process was done by slow addition of binder solution in to the above mentioned mixed ingredients using Rapid Mixing Granulator for 30 min. The wet mass was passed through sieve #8 and allowed to dry for 1 hour and rasping through sieve #20. Lipophilic matrix forming agent (Compritol 888 ATO), talc, magnesium stearate, colloidal silicon dioxide (Aerosil 200) and disintegrant (Sodium starch glycolate) were passed through sieve # 60. Lubricants were added in to the granules for 5 min and mixed for 20 min. The lubricated granules were compressed in to tablets on rotary tablet compression machine (16 stations) using 11.3 x 7.3 mm capsule shaped standard concave punch sets having break line on one side. Ensure that all in process checks of the tablets such as hardness, friability, disintegration time, average weight, weight variation, thickness and content uniformity were well kept within the limit.

Quality control tests for paroxetine compressed tablets

Physical properties[12] of paroxetine enteric coated tablets were evaluated for hardness, weight variation, friability and thickness as per Pharmacopoeia. The variation of weight of individual tablet is a valid indication of the corresponding variation in the drug content. Twenty tablets were selected at random and their average weight was determined using an electronic balance (Shimadzu Aux200, Japan). The tablets were weighed individually and compared with average weight. The hardness of three tablets from each batch was measured by using hardness tester (Monsanto hardness tester). Friability was determined by using Roche friabilator with 20 tablets for 4 minutes (100 revolutions). Ten tablets were used to measure the thickness using dial caliper (Mitutoyo, Japan).

Enteric coating of paroxetine core tablets

10% w/w of Instacoat EN II was slowly mixed with 90% w/w of Isopropyl alcohol under magnetic stirrer. Coating solution was allowed for two and half hour and then was passed with mesh #100 to remove solid material. Enteric coating was done by using standard 24 inch Accela-cota make with spray nozzle of 0.040 inch fluid orifice. The speed is of 25-27 rpm and tablet bed temperature is $25\text{-}30^0$ C. Coating solution was applied when exhaust temperature reaches 40^0C to 50^0 C. After spraying the total volume of solution stop the compressed air and roll the tablets for another 10 minutes for complete drying. Average weight of the coated tablets was calculated.

***In vitro* dissolution study**

In vitro release studies were carried out using dissolution test apparatus USP type II (n=6). For each sample, 1000 ml of Tris buffer pH 7.5 were stirred at 150 rpm and maintained at 37°C ± 0.5°C. Aliquot samples were withdrawn for a period of 12 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 as described under HPLC analysis.

Dissolution curves from the various formulations of enteric coated paroxetine CR tablets and commercial tablet (Paxil CR) were compared mathematically and provide an opportunity to test the similarity between two dissolution profiles. Fit factors ($f_1$and f_2) were used for comparing dissolution profiles[13]. An f_2 value $\geq$ 50 indicates similarity between two dissolution curves, whereas f_1 is used as an additional parameter to confirm the similarity when the value is $\leq$ 15.

Release kinetics and its mechanism

The order and mechanism of Paroxetine release from enteric coated matrix tablets were determined by fitting the release rate studies data into various kinetic models[14]. The zero order rate Eq. (1) describes the systems where the drug release rate is

independent of its concentration[15]. The first order Eq. (2) describes the release from system where release rate is concentration dependent[16, 17] described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of the particles or tablets[18].

The following plots were made: cumulative % drug release vs. time (zero order kinetic models); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model) log cumulative % drug release vs. log time (korsmeyer model) and cube root of drug % remaining in matrix vs. time (hixson-crowell cube root law) (Table No.4)[19].

Effect of RPM in kinetic study

To study the influence of agitation[20,21] on the dissolution rate kinetics for selected formulation F11, dissolution studies were conducted at paddle speeds of 50, 75, and 100 rpm with the USP apparatus 2 (paddle method). Dissolution procedure for this study was followed same as in an *in vitro* dissolution study with the paddle speeds of 150 rpm.

Stability studies of formulation F11

The purpose of stability testing[22] 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 condition. The formulation F11 under storage condition used for stability studies are 25^0C, 60%±2% RH, 30^0C, 65%±2% RH, 40^0C, 75%±2% RH for three months (Table No.5). The tablets were analyzed for the parameters such as physical characteristics, assay and dissolution profile.

RESULTS AND DISCUSSION

Compatibility studies of paroxetine HCl

FTIR spectra of paroxetine HCl and formulation components of paroxetine with various excipients used in the preparation of CR tablets were studied. The characteristic peak of N-H stretching group between 3500 - 3300, C-F stretching group between 1400 - 1000, aromatic group between 850 - 710 and Phenoxy C-O stretching group at 1200 and 1400 - 1300 present in the entire spectrum indicates the stability nature of Paroxetine HCl in the blend. Compatibility study result reveals that there is no interaction between the drug and other excipients used in all the formulation.

Formulation Design

In formulation F1 and F2, 7% of Methocel K100 LV and 7% of Methocel K15M was used respectively. In both formulations, low viscous polymers were used instead of Methocel K100M that causes the floating of tablets in the dissolution medium and rapid disintegration was observed in these formulations because of the absence of hydrophobic retarding agent like compritol 888 ATO. From the above reasons, the *in vitro* dissolution study of F1 and F2 formulations was withdrawn from the study and the release data was not included. In formulation F3, 13% of Methocel K4M was used which gives only 87.7% of drug release from the formulation. In order to enhance the drug release from the matrix tablet, the concentration of Methocel K4M was reduced to 7% in formulation F4. It flavors the initial burst release and gives the maximum of drug release to 99%. In formulation F5 contains 7% of compritol 888 ATO was added which results very minimal initial burst release of 11% and maximum drug release of 95%. Further modification was done in other formulations by reducing the compritol 888 ATO concentrations to 5.50% which gives 99% of total drug release but it suffers from low initial drug release of 12% only. Using 3% of sodium starch glycolate in the formulations F7, F9, F10 and F11 provide increases in the initial drug release. Formulation F8 did not show any significant release characteristics even after addition of 1%. The release of paroxetine enteric coated from controlled release matrix tablets varied according to the types and proportion of matrix forming polymers.

Evaluation of paroxetine granules

The results of compressibility index (Table No.2) indicate a slightly decreases in flowability with increases the Methocel K100M; however, all

formulations showed good flow properties. In general, hausner's ratio values up to 1.25% results in good to excellent flow properties. Loss on drying of the prepared granules was around 2% but formulation F1, F4 and F10 showed a slightly higher range. Density analysis results showed that material has good compressibility index. This confirms the prepared granules has good flow property and compressibility index.

Quality Control tests for paroxetine tablets

Hardness of the prepared tablets was lies between 150N to 161N. Friability values of uncoated tablets showed that 0.063% to 0.0853 ± 0.013%. Thus, the tablets were mechanically stable and ready for enteric coating. Thickness of the tablets was founded between 4.08± 0.045 mm and 4.87±0.050 mm. The percentage weight variation and drug content uniformity in all the formulations were found to be within the pharmacopoeial limits (Table No.3).

***In vitro* dissolution study**

In a matrix-tablet comprising drug and hydrophilic polymer, the release may follow three steps. Firstly, hydration of the tablet matrix takes place and then swelling with subsequent dissolution or erosion of the matrix. Finally the transport of dissolved drug passed through the hydrated matrix to the medium[23]. *In vitro* dissolution study of paroxetine from all the formulation was performed for 12 hours in pH 7.5 Tris Buffer (Figure No.1). The release of paroxetine from controlled release matrix tablets varied according to the types and proportion of matrix forming polymers. Ideally, a controlled release tablet releases the required quantity of drug in a controlled fashion in order to maintain an effective drug plasma concentration. From *In vitro* drug dissolution profile of Paroxetine CR tablet, was found that 87.7±7.10 of drug release till 12 h from F3 formulation. In marked formulation the percentage release was found to be 99.8±1.39% at 12 h time period. The formulations F4, F5, F6, F10 and F11 exhibited more than 95% of drug release, but formulation F4 showed a higher drug release of 42% at 2nd hour due to high concentration of Compritol 888 ATO. Formulation F6 which contains 4.50% of Methocel K100M and 5.5% of Compritol 888 gives only 39% of release at 4th hour which is lower than that of the reference listed drug (RLD) release. Formulation F8 which contains 1% of Sodium Lauryl Sulphate (SLS) showed a release of only 93.00±4.17% at 12 h time period and does not support the complete release from the matrix tablets. Further modification was done in F10 by changing the concentration of Methocel K100M to 3% and addition of 3% Sodium Starch Glycolate gives the drug release which is closer to the RLD release. Hence, further fine tuning was done in formulation F11 by increasing the Methocel K100M to 5.5% and reduces Methocel K4M and Sodium Starch Glycolate to 11% and 1% respectively which gives similar release profile of RLD product.

Release kinetics and its mechanism

The kinetic treatment reflected that release data of selected formulation F11 and F10 showed R^2 value of 0.9907 and 0.9906 respectively which is very closer to 1, indicating that release of drug follows Hixon-crowel cube root law (Table No.4). This showed that the change in surface area, diameter of the dissolved particles or tablets and the change in diffusion path length during the dissolution process follow the cube root law (Hixson and Crowell, 1931). The *In vitro* drug release of F9 was best explained by Higuchi's equation, as the plots showed the highest linearity (R^2 =0.9871). The drug release significantly followed a first order kinetic model for formulation F7, as the plot showed the highest linearity (R^2 = 0.9775). The *In vitro* drug release of F6 was best explained by zero order kinetic, as the plots showed the highest linearity (R^2 =0.9724). The slope values of selected formulations (F11) for Korsemeyer and Peppa's diffusion model was (0.6332) ($0.45 < n < 0.89$) and exhibited as release mechanism of drug through polymeric membrane was found anomalous (non-Fickian) diffusion. The best fit with higher correlation was found in the linear regression graph with the Hixon-crowel cube root law for selected formulation F11 and Innovator brand (Figure No.2).

The dissolution rate gradually increased with increases in the agitation rate from 50, 75, 100 and 150 rpm. The data support the position that the

higher agitation rate of 150 rpm is necessary for a quality control procedure or a compendial standard for the products tested. At paddle speed of 50 RPM, the drug release from dosage form follows first order kinetic and at paddle speed of 75, 100 and 150 RPM drug release follows Hixon-crowel cube root law. The n values of selected formulations (F11) at different rotational speed of paddle such as 50, 75, 100 and 150 RPM for Korsemeyer and Peppa's diffusion model was between $0.45 < n < 0.89$ and exhibited as release mechanism of drug through polymeric membrane was found anomalous (non-Fickian) diffusion. The effect of RPM in selected formulation F11 showed, the release mechanism from dosage form follows diffusion cum erosion as per peppas equation at all the rotational speed (Figure No.3).

Stability studies of formulation F11

The obtained results from three months stability study of formulation F11 at 25^0C, 60%±2% RH, 30^0C, 65%±2% RH, 40^0C, 75%±2% RH revealed that there were no significant changes in the physical properties of the tablets. The manufacturing process for enteric coated Paroxetine CR tablets was reliable and reproducible because no significant differences were observed in the release profile of different batches of each enteric coated Paroxetine CR tablet (Figure No.4). Hence, suggesting that enteric coated paroxetine was stable in HPMC matrices.

Table No.1: Compositions of paroxetine core tablet preparation

S.No	Ingredients	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)	F10 (%)	F11 (%)
1	Paroxetine	16.34	16.34	16.34	16.34	16.34	16.34	16.34	16.34	16.34	16.34	16.34
2	Methocel K4M	13	13	13	7	13	13	13	13	13	13	11
3	Methocel K100M	0	0	7	7	5.50	4.50	4.50	4.50	2.25	3	5.50
4	Methocel K100 LV	7	0	0	0	0	0	0	0	0	0	0
5	Methocel K15M	0	7	0	0	0	0	0	0	0	0	0
6	Compritol 888 ATO	0	0	7	7	7	5.50	5.50	5.50	5.50	5.50	5.50
7	Sodium Starch Glycolate	0	0	0	0	0	0	3	0	3	3	1
8	Lactose Mono hydrate	57.65	57.65	51.00	56.65	52.15	54.65	51.65	53.65	53.65	53.10	54.65
9	PVP K30	2	2	2	2	2	2	2	2	2	2	2
10	IPA	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
11	Talc	2	2	2	2	2	2	2	2	2	2	2
12	Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1
13	Aerosil 200	1	1	1	1	1	1	1	1	1	1	1
14	SLS	0	0	0	0	0	0	0	1	0	0	0
15	Total	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.99	99.74	99.94	99.99

Table No.2: Physical evaluations of prepared paroxetine granules

S.No	Formulation	Bulk density	Tapped density	Compressibility Index	Hausner's ratio	Loss on drying
1	F1	0.6586±0.034	0.7976±0.014	17.81±4.29	1.20±0.064	2.00
2	F2	0.6576±0.017	0.7970±0.014	17.50±2.51	1.20±0.038	1.98
3	F3	0.6690±0.010	0.8066±0.026	18.98±3.60	1.20±0.044	1.76
4	F4	0.6753±0.018	0.8150±0.016	17.24±2.90	1.20±0.038	2.02
5	F5	0.6690±0.010	0.8156±0.030	18.90±1.74	1.21±0.029	1.98
6	F6	0.6663±0.015	0.7890±0.021	15.50±3.54	1.18±0.051	1.96
7	F7	0.6713±0.017	0.7960±0.012	15.62±3.36	1.18±0.015	1.83
8	F8	0.6766±0.023	0.7960±0.012	14.94±4.16	1.17±0.059	1.88
9	F9	0.6763±0.017	0.8100±0.022	16.49±4.48	1.20±0.061	1.96
10	F10	0.6766±0.001	0.8113±0.039	15.29±4.65	1.18±0.064	2.12
11	F11	0.6730±0.012	0.8190±0.014	17.80±2.47	1.21±0.040	1.88

Table No.3: Quality control test for prepared paroxetine tablets

S.No	Formulation	Thickness‡ (mm)	Weight of tablets† (mg)	Friability†	Hardness‡ (N)	Assay (%)
1	F1	4.08±0.045	299.30±1.52	0.077±0.014	156.30±8.08	99.50
2	F2	4.87±0.050	301.00±2.64	0.078±0.008	155.00±8.88	99.80
3	F3	4.12±0.045	298.33±4.16	0.085±0.016	157.30±2.51	101.20
4	F4	4.10±0.072	299.33±2.51	0.082±0.001	157.66±0.51	102.20
5	F5	4.86±0.071	298.33±3.21	0.074±0.004	161.00±5.29	98.80
6	F6	4.10±0.091	297.00±3.21	0.079±0.013	155.16±5.86	97.90
7	F7	4.13±0.061	300.00±3.45	0.082±0.005	152.00±3.46	101.10
8	F8	4.09±0.030	298.33±3.21	0.079±0.001	152.63±7.23	100.10
9	F9	4.14±0.066	304.00±2.00	0.066±0.005	152.66±4.93	100.20
10	F10	4.09±0.041	298.00±2.51	0.074±0.001	153.63±2.08	99.50
11	F11	4.13±0.042	304.00±1.00	0.066±0.006	150.66±0.39	99.30

†All values are expressed as mean ± SD, n = 20, ‡All values are expressed as mean ± SD, n = 6.

Table No.4: Release kinetics studies of enteric coated paroxetine CR tablets

S.No	Formulation	Release Characterization of Paroxetine CR Tablet						
		First order (R^2)	Zero order (R^2)	Higuchi model (R^2)	Hixon-crowel cube root law (R^2)	Korsmeyer-Peppas (n)	F1	F2
1	F3	0.9572	0.9837	0.9702	0.9873	0.7780	22.32	38.24
2	F4	0.9749	0.8913	0.9754	0.9877	0.6507	8.46	55.87
3	F5	0.9508	0.9654	0.9464	0.9768	0.8864	10.34	53.83
4	F6	0.8982	0.9724	0.9524	0.9689	0.8582	8.29	56.79
5	F7	0.9775	0.9241	0.9677	0.9798	0.6277	6.05	65.11
6	F8	0.9231	0.9676	0.9772	0.9883	0.7170	8.56	59.68
7	F9	0.8309	0.9238	0.9871	0.9810	0.5959	6.34	61.38
8	F10	0.9111	0.9340	0.9825	0.9906	0.6704	5.35	64.99
9	F11	0.8955	0.9359	0.9841	0.9907	0.6332	0.68	95.62
10	Innovator Brand	0.8956	0.9375	0.9612	0.9918	0.8320	-	-

Table No.5: Effect on physical properties of tablet at various storage conditions

S.No	Properties	Initial	After three months		
			25^0C/60% RH	30^0C/65% RH	40^0C/75% RH
1	Appearance	White coloured, capsular shaped tablets	White coloured, capsular shaped tablets	White coloured, capsular shaped tablets	White coloured, capsular shaped tablets
2	Hardness	150 N	148 N	149 N	146 N
3	Thickness (mm)	4±0.2	4±0.2	4±0.2	4±0.2
4	Weight (mg)	292 ± 2%	292 ± 2%	292 ± 2%	292 ± 2%
5	Assay	99.00%	98.80%	98.65%	98.00%

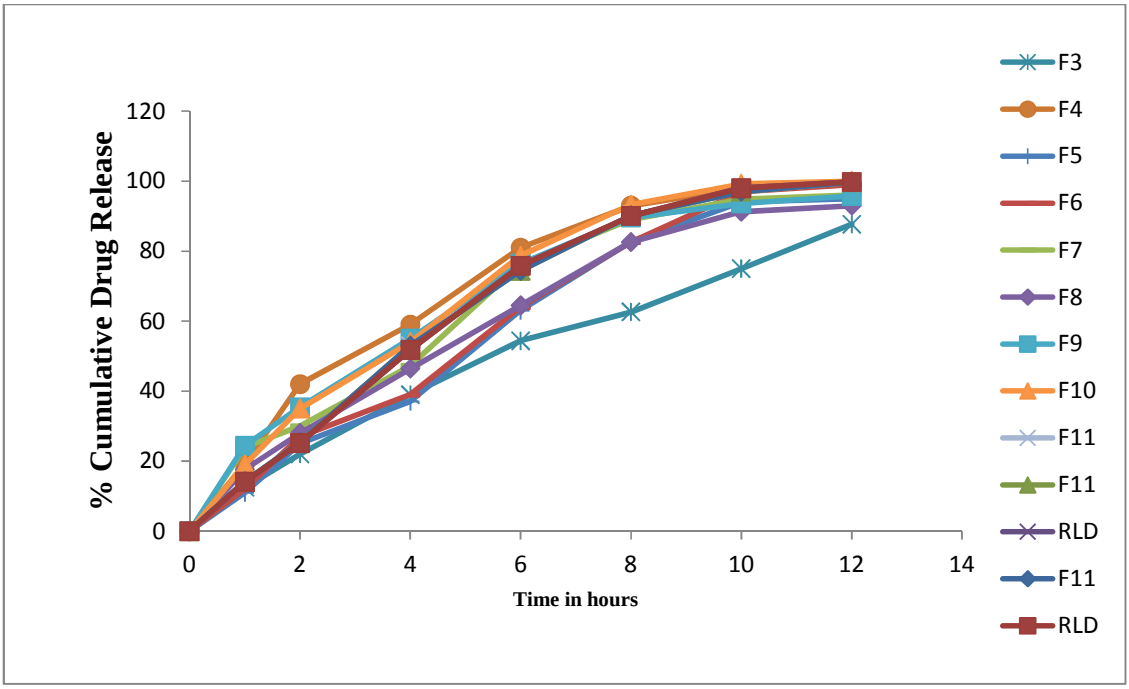

Figure No.1: *In vitro* dissolution profile of enteric coated paroxetine CR tabletsin pH 7.5 Tris Buffer

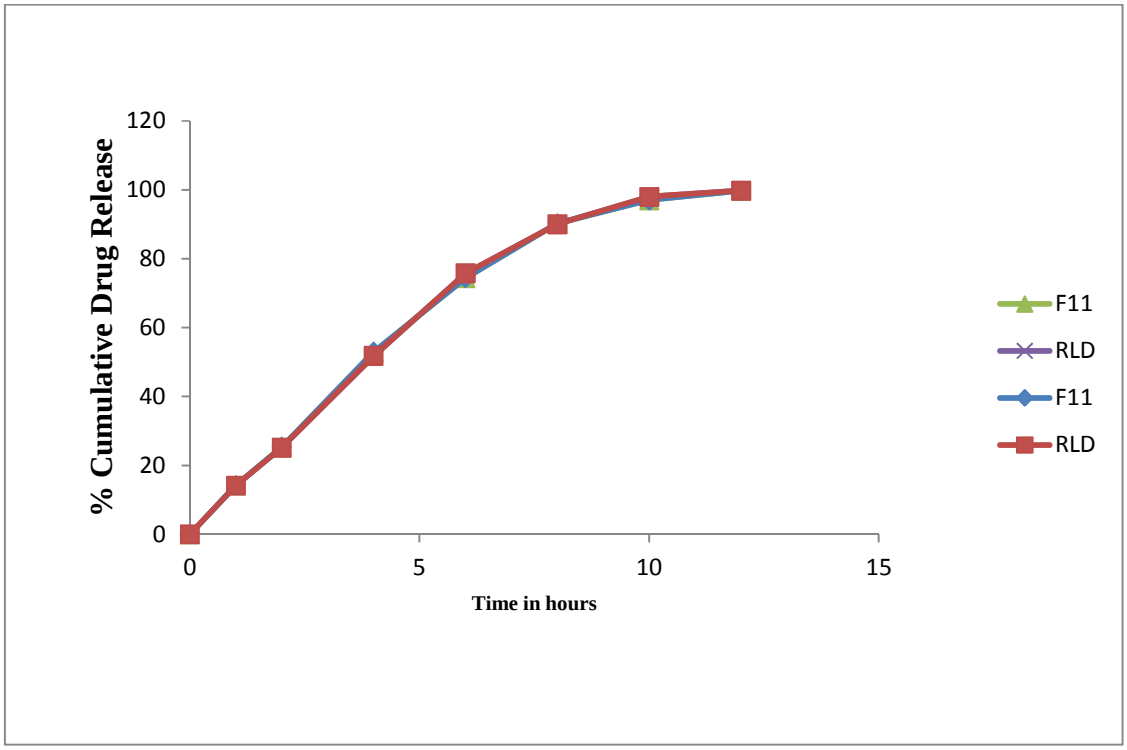

Figure No.2: Comparative dissolution profile of F11 Vs RLD

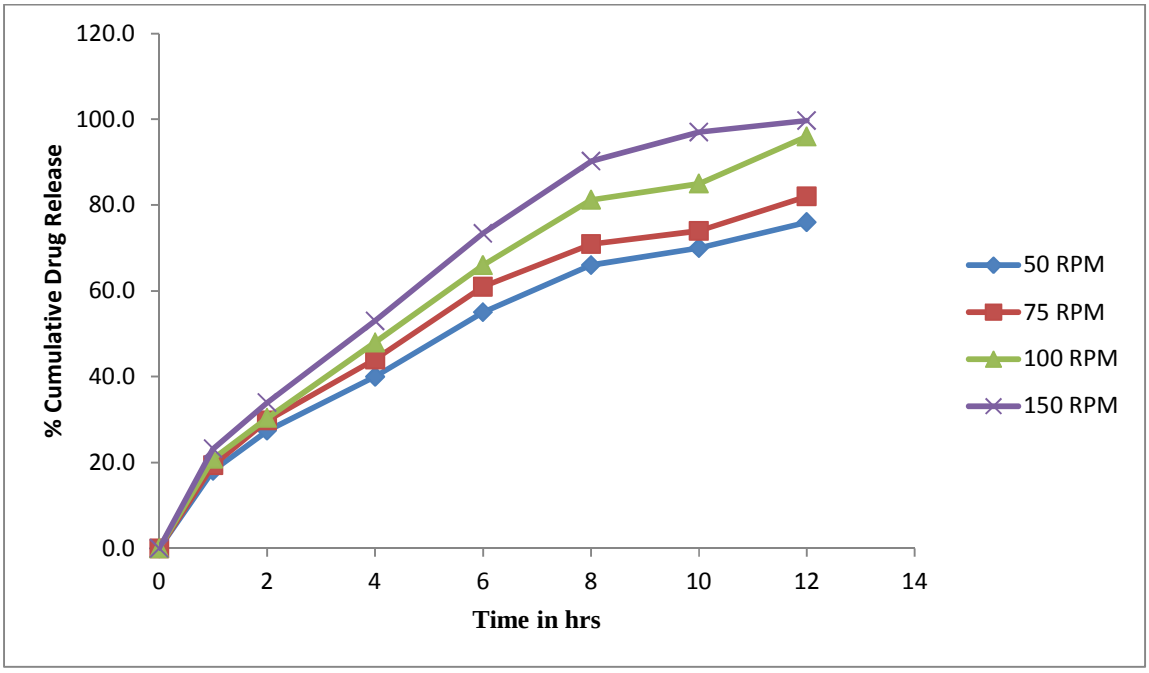

Figure No.3: Effect of RPM in release kinetic study of F11

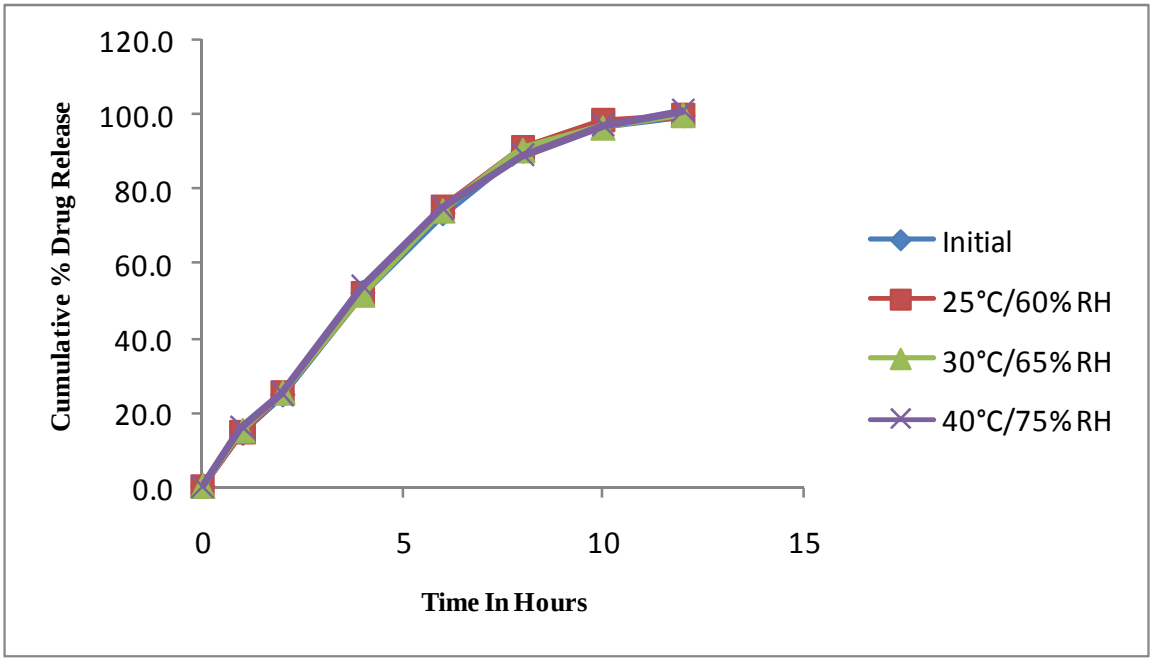

Figure No.4: Dissolution profile of F11 in stability study

CONCLUSION

Paroxetine controlled release tablets were prepared by wet granulation method using HPMC as retard releasing polymer. Density analysis results showed that material has good compressibility index. Post compression parameters like hardness and friability values showed that the tablets were mechanically stable. The percentage weight variation and drug content uniformity in all the formulations were found to be within pharmacopoeial limits. The

designed enteric coated Paroxetine CR tablets showed good and reproducible physical properties indicating that the methods of preparation of formulation are suitable and acceptable for preparing good quality matrix tablets. In order to prevent the release of drug at early stage, Paroxetine matrix tablets were coated with enteric polymers. The manufacturing method was relatively simple and can be easily adopted in conventional tablet manufacturing units in industries on a commercial scale. Rapid breakdown of the particles were found in the formulations F1 and F2. Hence, the dissolution study of those formulations was not considered for i*n vitro* kinetic study.

Formulations F4, F5, F6, F10 and F11 showed more than 95% of drug release at the end of 12 hours. The release behavior of these formulations was compared with the innovator brand by comparing the similarity and dissimilarity factors. From our study it was observed that the formulation F11 containing 11% Methocel K4M, 5.50% Methocel K100M and 5.50% Compritol 888 ATO found to be of good quality and achieve required dissolution profile. The similarity and dissimilarity factors for F11 formulations were 0.68 and 95.62 respectively. The best fit with higher correlation was found in the linear regression graph with the Hixon-crowel cube root law for selected formulation F11 and Innovator brand. Comparison of kinetic study at different RPM of F11 exhibited as release mechanism of drug through polymeric membrane was found anomalous (non-Fickian) diffusion and follows diffusion cum erosion as per peppas equation at all the rotational speed. Three months stability study revealed that there were no significant changes observed in the physical properties as well as release profile of different batches of each enteric coated Paroxetine CR tablet. Herewith, concluding that the prepared enteric coated Paroxetine CR tablet was stable in HPMC matrix polymer and can be reproduced for commercial manufacturing.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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