Research Article

Hacettepe University Journal of the Faculty of Pharmacy
Volume 44 / Number 4 / December 2024 / pp. 289- 305

Optimization of HPMC Loaded Paroxetine HCl Controlled Release Matrix Tablet by Central Composite Design

Komal B. PARMAR[1]*
ORCID: 0009-0009-9678-5044
Mehul N. PATEL[1]
ORCID: 0000-0002-5823-9706
Punitkumar BHATT[1]
ORCID: 0000-0001-6324-051X
Tejal G. SONI[1]
ORCID: 0000-0002-9159-4400
Bhanubhai N. SUHAGIA[1]
ORCID: 0000-0002-2527-9963

[1]Dharmsinh Desai University, Faculty of Pharmacy, Nadiad (Gujarat) India

Corresponding author:
Komal PARMAR
Dharmsinh Desai University, Faculty of Pharmacy, Nadiad (Gujarat), India
E-mail: komalparmar1509@gmail.com
Tel: 9558871415

Received date : 06.02.2024
Accepted date : 14.11.2024

DOI: 10.52794/hujpharm.1460738

ABSTRACT

The main aim of the present study was to improve the release profile of Paroxetine (PXT) using Novel Drug Delivery System (NDDS). Therefore, Controlled Release Matrix tablet of PXT was prepared to extend the release of the drug from 8 hours to 12 hours. In the present research work, controlled release matrix tablet of paroxetine (PXT) was prepared by wet granulation method using various polymer grades of Hydroxypropyl methylcellulose (HPMC) and Polyvinylpyrrolidone (PVP) like HPMC K100M, HPMC K4M, HPMC K100M LV, and PVP K-30. Central Composite Design was applied to optimize the amount of polymers in the tablet. Infrared Spectroscopic analysis was done to check the interaction between drug and polymers. Results showed that all pre-compression and post-compression parameters were as per standard limits and not deviated when compared with the marketed formulation. The release profile of the tablet formulated using optimized batch was also improved significantly. Specifically, PXT matrix tablet released approximately 29.382%, 41.29%, and 93.47% of the drug at the second, fourth, and twelfth hours, respectively. In conclusion, the dissolution profile of the optimized batch aligns closely with the established USP guidelines for PXT extended-release formulations.

Keywords: Paroxetine HCl, HPMC K4M, HPMC K100M, Dissolution, Kinetics

1. Introduction

Controlled release matrix tablets are getting popularity due to number of advantages like improved release profile, less side effects, better therapeutic monitoring and cost effectiveness [1]. The use of various polymers like Hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC), hydroxyl ethyl cellulose (HEC), natural polymers like xanthan gum, biodegradable polymers like Polylactic acid (PLA), Polyglycolic acid (PGA), etc. enables the control release of drug through matrices [2].

Such systems are designed to offer ideal delivery profiles that can result in therapeutic plasma levels. Because polymer characteristics affect drug release, they can be used to develop well-characterized and predictable dosage forms [3]. Due to this, sustained-release oral medication delivery methods are gaining popularity. A dosage product that provides for high drug loading is also of great interest, especially for medications with high water solubility [4].

PXT is white crystalline hygroscopic odourless powder having molecular weight 365.8 g/mole. The melting point is 120–134°C. It is slightly soluble in water, freely soluble in methanol, and sparingly soluble in methylene chloride and ethanol (96%). The pKa value of the drug is 9.9. As per United States Pharmacopoeia (USP), the PXT showed the release pattern as follow; Q2 (2-hour release): 10 to 30% CDR (Cumulative Drug Release). Q4 (4-hour release): 40–70% CDR. Q12 (12-hour release): Not less than (NLT) 80% CDR. (USP 42-NF 37, Monograph on Paroxetine Hydrochloride Controlled-Release Tablets). PXT is an Selective Serotonin Reuptake Inhibitor (SSRI), is widely used to treat major depressive disorder, generalized anxiety disorder, post-traumatic stress disorder (PTSD), panic disorder, and obsessive-compulsive disorder (OCD). It works by inhibiting the serotonin transporter (SERT), increasing serotonin levels in the synaptic cleft to correct mood disorders and reduce anxiety. Due to its short half-life (~21 hours), controlled-release (CR) formulations are essential for maintaining steady plasma concentrations, reducing peak-to-trough variations, and minimizing side effects like nausea, insomnia, dizziness, headache, and sexual dysfunction. CR tablets enable once-daily dosing, improving patient compliance and reducing the risk of therapeutic failure or adverse effects by maintaining drug levels within the therapeutic window [5].

The oral solid dosage forms known as matrix tablets are those in which the drug is uniformly dissolved or distributed within hydrophilic or hydrophobic polymeric matrices [6]. In order to manufacture sustained-release matrix tablets, a powder mixture of the drug, a retardant, and other additives is directly compressed to produce a tablet in which the drug is spread throughout a retardant matrix [7,8]. An alternative is to granulate the drug retardant mix and other additives prior to compression [9]. The drug dissolution-controlled and diffusion-controlled mechanisms are constantly released by these systems [10]. A major advance for a novel drug delivery system (NDDS) in the area of pharmaceutical technology has been made with the matrix tablet's sustained release (SR) [11,12]. The type and proportion of polymer used in the preparations mainly control the drug release rate from the dosage form, excluding more complex manufacturing processes like coating and pelletization. Matrix systems are commonly utilised to provide continuous release [13,14]. As per Bang and Keating (2004), paroxetine controlled release tablet is indicated for 3 times a day as 80% of the dose is released within 4 to 5 hours. To reduce the dosing frequency, the present work was designed and attempts have been made to extend the release of the drug up to 12 hours so patient would have to take only 2 tablets instead of 3 tablets per day [15].

2. Material and Methods

2.1. Materials

Paroxetine hydrochloride was obtained as a gift sample from Rhombus Pharma Private Limited, Gandhinagar. HPMC K4M, HPMC K100M, PVP K30, Lactose, Talc, Silicon dioxide and magnesium stearate were also obtained from Rhombus Pharma Private Limited, Gandhinagar.

2.2. Calibration curve of PXT

Paroxetine was precisely weighed at 100 mg, and 100 mL of distilled water and a sonicated well were used to dissolve and transfer the drug. From the above stock solution, a diluted standard solution was prepared with a concentration of 100 µg/mL. Aliquots of 1.0 to 6.0 mL portions of standard solutions were transferred to a series of 10 mL volumetric flasks and the volume in each flask was adjusted to 10 ml with distilled water to get the standard solutions. Aliquots

of the standard drug (1.0 mL to 6.0 mL) solution in distilled water were transferred into a series of 10 mL volumetric flasks and the solution was marked up to 10 mL with water to prepare a concentration of 10, 20, 30, 40, 50, 60 µg/ml.

The absorbance was measured using a double-beam UV-Visible spectrophotometer (ThermoFisher Scientific, Evolution 201) at its maximum wavelength of 293 nm as shown in Figure 1, illustrates the plot of the standard graph between concentration (on the X-axis) and absorbance (on the Y-axis).

2.3. Drug-excipient compatibility studies of PXT

A Fourier Transform Infrared Spectroscopy (FTIR, Shimadzu Corp., Japan) analysis carried out using KBr pellet for PXT alone and a mixture of drug and polymers was performed to check the interactions (Figure 2).

2.4. Preliminary trial batches for paroxetine hydrochloride

Tablets containing 29 mg of Paroxetine were prepared by the wet granulation method. Accurate quantities of all the polymers (HPMC K100M, HPMC K4M, and HPMC K100M LV, PVP K-30, and Lactose monohydrate) were weighed and mixed in a mortar pestle shown in Table 1. Isopropyl alcohol was used as binder solution. By gradually incorporating the binder solution into the above-mentioned combined ingredients, the granules were prepared. The wet bulk was passed through sieve #20 and left to dry for an hour in oven below 40°C. Following drying, the granules were mixed with magnesium stearate, Talc, and colloidal silicon dioxide (Aerosil 200). On a rotating tablet compression machine (Cronimach, India) the lubricated granules were compressed into tablets using a 8.0 mm round concave punches with a broken line on one side.

The polymers of HPMC K4M and HPMC K100M were selected based on difference in viscosity classes and effect on drug release rate. These are both used in sustained-release matrix systems since they are hydrophilic, biologically inert and permit control of release of drug through gel formation and erosion. (HPMC K4M)Viscosity Grade (~4000 mPa·s) it Provides moderate gel strength thereby, permitting initial regulation of the substance invention in the first four hours. This contributes to uniform diffusion of the drug through the hydrated gel layer thus maintaining and controlling both the initial burst and sustained phases. (HPMC K100M) Viscosity Grade (~100,000 mPa·s) it Offers a higher gel matrix with enhanced cohesiveness required for immediate drug release in addition to the delayed release 8–12 hours beyond. Reduces matrix degradation rate, thus no dose dumping and the rate of release is zero order.

Here, K4M physical entrapment releases the drug and maintains constant drug release. On the other hand, this K100M regulates the rate of drug release in the body. This is important in order to achieve the targeted 12-hour release profile as the release kinetic data shown in the study (Figure 9) indicates [1,3].

2.5. Experimental design and optimization of PXT

The formulation was optimized by using central composite design using Design Expert software version 13. A total of 13 trials were designed including five centre points. The high and low values of each variable were determined based on preliminary trials (Table 2).

2.6. Evaluation of PXT formulation

All the evaluation parameters were performed as per the procedure given by Lachman et al. (1991) and Aulton (2008) [16,17].

2.6.1. Angle of repose

The angle of repose of the granules was determined by the funnel technique. A funnel was filled with perfectly weighted granules. The funnel's height was adjusted so that the tip of the funnel slightly touched the top of the granules' heap. The funnel was left open, allowing the granules to easily discharge onto the surface. The following equation was used to determine the angle of repose and estimate the diameter of the powder cone:

$$tan\theta = \frac{h}{r}$$

Where, h= height of powder heap; r = radius of the powder heap; Θ = angle of repose

ISSN: 2458 - 8806

Table 1. Preliminary screening trials

Ingredients (mg)	P1	P2	P3	P4	P5	P6
Paroxetine hydrochloride	29	29	29	29	29	29
HPMC K4M	9	15	30	26	24	24
HPMC K100M	9	14	28	26	18	18
HPMC K100M LV	11	-	-	13	8	-
PVP K30	4	4	4	4	4	4
Lactose Monohydrate	140	140	111	104	119	127
IPA	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Magnesium stearate	2	2	2	2	2	2
Talc	4	4	4	4	4	4
Silicon dioxide	2	2	2	2	2	2
Total	210	210	210	210	210	210

Table 2. Central composite design

STD	CODED		ACTUAL	
	HPMC K4M	HPMC K100M	HPMC K4M	HPMC K100M
F1	-1	-1	1	12
F2	1	-1	30	12
F3	-1	1	18	24
F4	1	1	30	24
F5	-1.414	0	15.5147	18
F6	1.414	0	32.4853	18
F7	0	-1.414	24	9.5147
F8	0	1.414	24	26.4853
F9	0	0	24	18

2.6.2. Bulk density and tapped density

After precisely pouring the powder or granules into the graduated glass cylinder according to an exact weight (W), the volume (V_0) was calculated. The graduated cylinder was then fitted into the tap density tester USP after being sealed with a lid. The density apparatus was set for 100 tabs and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal. Using the accompanying formulas, the bulk density (BD) and the tapped density (TD) were determined.

$$bulk\ density = \frac{w}{v_0}$$

$$tapped\ density = \frac{w}{v_f}$$

Where, W= Weight of the powder; V_0 = Initial volume; V_f = final volume

2.6.3. Carr's index (CI)

This index was derived from the bulk and tapped densities to determine flowablity using the equation as follow:

$$\text{CARR'S INDEX (CI)} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

2.6.4. Hausner's ratio

It is a ratio of tapped density to bulk density. According to Hausner's, this ratio correlates with interparticle friction and can be used to forecast the characteristics of powder movement. A value less than 1.25, and 20% of Carr's index, generally denotes favourable flow properties.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.6.5. Thickness

Twenty tablets were chosen at random from the standard sample, and each tablet's thickness was measured using a digital vernier calliper (Mitutoyo, Japan). Values for the average thickness and standard deviation were calculated.

2.6.6. Hardness

A hardness tester (Monsanto, USA) was used to determine the hardness of tablets. Six tablets from each sample were tested for hardness, and an average of the six results was recorded along with standard deviations.

2.6.7. Friability test

Ten tablets from each batch were carefully weighted and put in the friability test device (Roche friability tester, Electrolab, India). Tablets were monitored as the device rotated for 4 minutes at a speed of 25 rpm. After 100 revolutions, the tablets were removed, dusted, and weighed. The percentage of weight loss was used to determine the friability.

% Friability was calculated as follows:

$$\%\ \text{Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where W1 = Initial weight of the 20 tablets; W2 = Final weight of the 20 tablets after testing.

Friability values below 1.0 are generally acceptable.

2.6.8. Weight variation test

Twenty tablets were used to determine weight variation using electronic balance. The following formula was used to determine the parameter.

$$\%\ \text{weight variation} = \frac{W_A - W_I}{W_A} \times 100$$

2.6.9. In Vitro drug release characteristics

The drug release was carried out in 1000 ml of Tris (hydroxymethyl) aminomethane acetate buffer, kept at 37°C 0.5°C, n = 3 USP type II paddle technique dissolution apparatus (Electrolab, India) at 100 rpm. At certain intervals, an aliquot (10 mL) was withdrawn and replaced with the same volume of newly prepared dissolving medium that has been preheated to 37±0.5°C. The withdrawn samples were analyzed using a UV-visible spectrophotometer at a wavelength of 293 nm. *In vitro* drug release study of formulated controlled release tablet was carried out as per the USP monograph. Dissolution study was carried for the duration of 12 hrs.

2.6.10. Kinetic analysis of dissolution data

Several kinetic models that explain the release kinetics were used to analyse the *in vitro* release data. The zero-order rate (Equation 1) describes the systems where the drug release rate is independent of its concentration. The first order (Equation 2) describes the release from a system where the release rate is depending on concentration. Higuchi (1963) described the release of drugs from the insoluble matrix as a dependent square root of a time-dependent process based on Fickian diffusion (Equation 3) [18].

$$C = K_0 t \quad (1)$$

ISSN: 2458 - 8806

Where, K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC_0 - \frac{K_1 t}{2.303} \quad (2)$$

Where C_0 is the initial concentration of the drug and K1 is the first-order constant

$$Q = K_H t^{1/2}. \quad (3)$$

Where K_H is the constant reflecting the design variables of the system.

Using the *in vitro* drug release data, the following plots were created.

1. Cumulative % drug release vs. time (Zero order kinetic model);
2. Log cumulative of % drug remaining vs. time (First order kinetic model);
3. Cumulative % drug release vs. square root of time (Higuchi model);

In order to characterise drug release from a polymeric system, a simple relationship was derived (Equation 4). The Korsmeyer-Peppas model was fit to the first 60% of the drug release data to determine the process of drug release [19].

$$\frac{M_t}{M_\infty} = Kt^n \quad (4)$$

Where M_t / M_∞ is a fraction of the drug released at time 't'; K is the release rate constant incorporating structural and geometric characteristics of the tablet, and 'n' is the release exponent. Different release methods are characterised using the n value. Log cumulative % drug release was plotted against log time. The line's inclination was 'n' [20].

2.6.11. Statistical analysis

The statistical optimization in the study was carried out with Design-Expert® Software, Version 13 (Stat-Ease Inc., Minneapolis, USA). This software can help in optimizing process variables by using for instance Central Composite Design (CCD). Two variables and three responses (according to USP 25 tolerances for dissolution profile for Paroxetine Hydrochloride Controlled-Release Tablets) were involved in the experimental design [3,19]. The two variables are F1=HPMC K4M and F2= HPMC K100M and the three response were Q2=10-30%CDR (Cumulative Drug Release), Q4=40-70% and Q12= NLT 80%.

2.6.12. Statistical optimization

Numerical optimization has been carried out using design expert software. Constraints were applied to all factors and responses and results of optimization with desirability are shown in Table 11. Optimized formulation is prepared as suggest by the software. Previously determined method is followed to prepare the optimized controlled release matrix tablet of paroxetine HCl [21]. The composition of the optimized batch is shown in Table 12.

3. Result and Discussion

3.1. Estimation of Paroxetine HCl using UV spectroscopy and compatibility study

The standard graph of PXT has shown a good linearity R^2 value 0.9994 at λ_{max} of 293 nm. In case of compatibility study using FTIR, the peak at 2924 cm^{-1} and 2817 cm^{-1} were due to stretching vibrations of the C-H and N-H bond respectively. Peaks at 1620 cm^{-1}, 1512 cm^{-1}, and 1222 cm^{-1} could be assigned to sp^2 N-H bend, C=C stretching, and C-O-C bond, respectively. There was no interaction between the drug and the excipients in Figure 2 as indicated by the availability of all the Paroxetine HCl characteristic peaks in the formulation that was optimized.

3.2. Preliminary screening

Drug release from formulation P6 was extended up to 12 hrs as per USP requirements. Batch P6 contained 24 mg of HPMC K4M and 18 mg of HPMC K100M. So, these two grades of HPMC have been selected for design of experiment trials.

3.3. Pre-compression and post-compression parameters

Regarding the bulk density, angle of repose, tapped density, Hausner's ratio, and Carr's index the granules for matrix tablets were characterised in Table 4. All the batches' granules had angles of repose that were less than 35 degrees and Carr's index values that were under 21, indicating good to fair flowability and compressibility [23]. For all the batches, Hausner's ratio was less than 1.25, suggesting good flow characteristics. Table 5 lists the findings regarding the tablets' hardness, consistency of weight, thickness, and friability. Given that their weights ranged

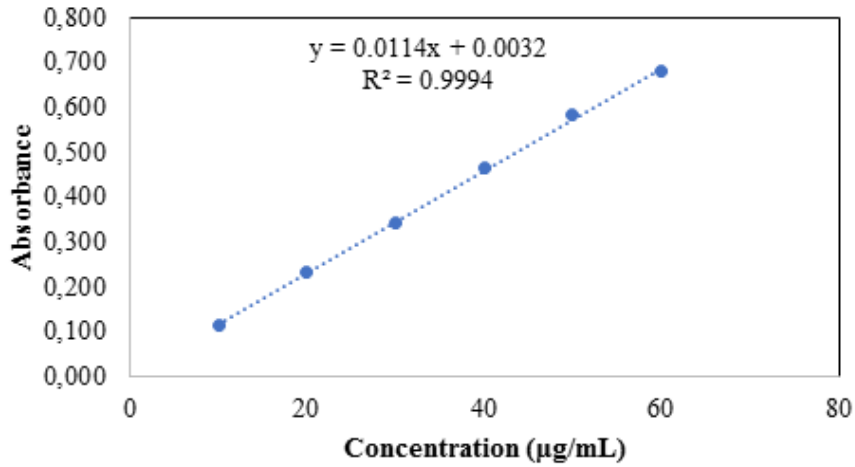

Figure 1. Estimation of Paroxetine HCl

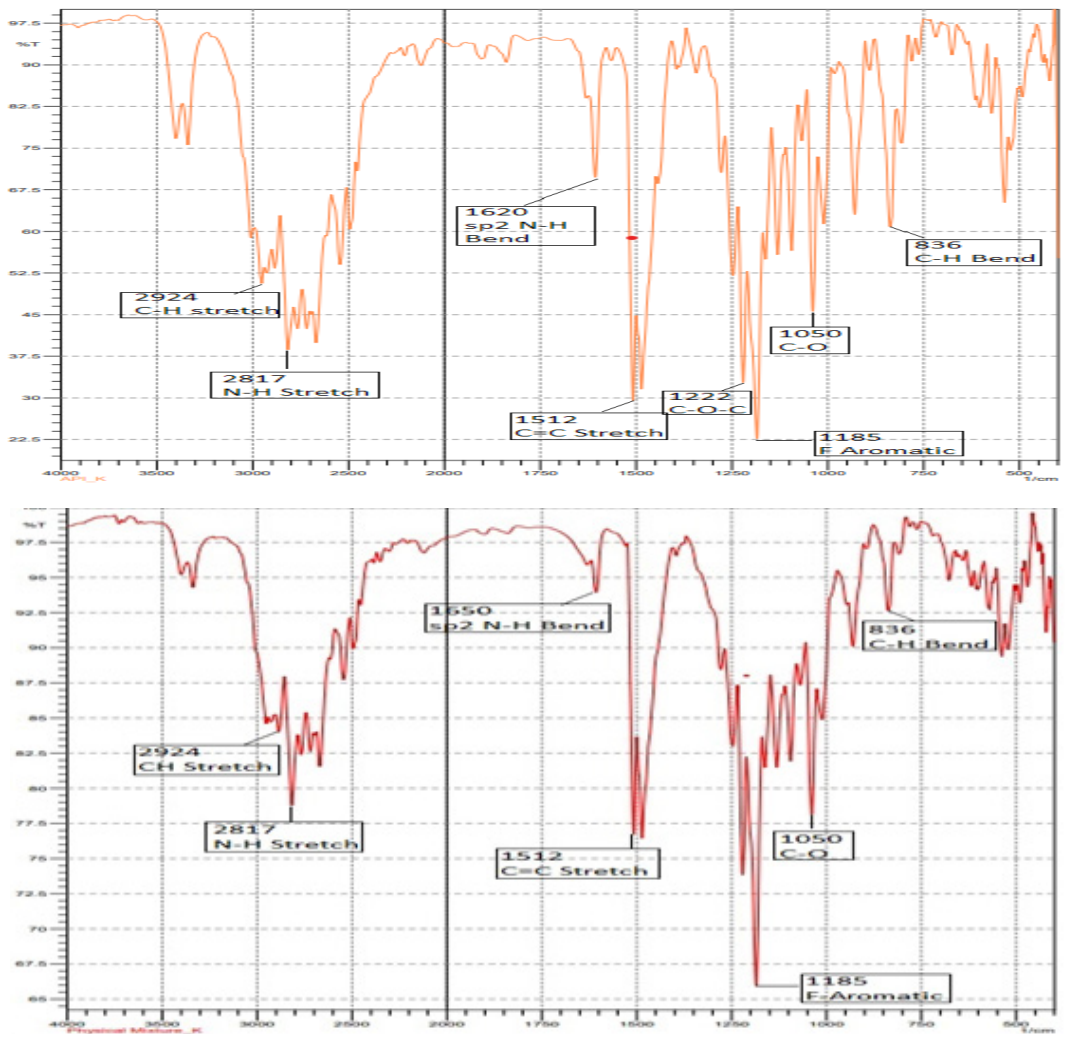

Figure 2. FTIR spectra of (A) Pure drug and (B) Physical mixture

ISSN: 2458 - 8806

Table 3. Composition of central composite design batches

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Paroxetine HCl*	29	29	29	29	29	29	29	29	29
HPMC K4M	18	30	18	30	15.5	32.4	24	24	24
HPMC K100M	12	12	24	24	18	18	9.5	26.4	18
PVP K-30	4	4	4	4	4	4	4	4	4
Lactose Monohydrate	139	127	127	115	118.6	135.5	118.6	127	127
IPA	QS	QS	QS	QS	QS	QS	QS	QS	QS
Mg. Stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Silicon dioxide	2	2	2	2	2	2	2	2	2
Total	210	210	210	210	210	210	210	210	210

between 203 and 212 mg, all the tablets from various samples were within the range of weight uniformity. The matrix tablets were compact and rigid, with hardness values ranging from 4.05 to 5.7 N/mm2 and friability values less than 0.56%. The tablets had a thickness that varied from 4.1 to 4.55 millimetres. As a result, it was discovered that virtually all the prepared tablets' physical characteristics were within control.

3.4. In vitro drug release study

Drug release profile plot of %CDR vs Time were plotted for all the formulation. Figure 3 shows drug release profile of batch F1 to F4. Formulation F1 shows higher drug release due to less amount of the both the polymers whereas Formulation F4 shows lesser drug release because of the higher amount of both the polymer. These results indicated that increasing polymer concentration may retard the drug release. Drug release profile plot of %CDR vs Time were plotted for all the formulation [24]. Figure 4 shows drug release profile of batch F5 to F8. All the Formulation shows higher drug release due to less amount of the both the polymers. Figure 5 shows drug release profile of batch F9 which is centre point and the drug release profile all this batch shows similar drug release because all these batch has similar concentration of the polymer.

As per As per Bang and Keating (2004), the clinical study included four doses 12.5 mg, 25 mg, 37.5 and 50 mg to assess the pharmacokinetics of the drug. In the present work, the dose was decided on the basis of trial and error prior to the main experiment in which various doses were incorporated in the formulations and release pattern was evaluated. On the basis of results of the trials, the dose of 29 mg was decided. The dose of 29 mg Paroxetine HCl was chosen with reference to the therapeutic dose familiar with the treatment of Major Depressive Disorder and related symptoms. This is in concordance with the daily range of dose Paroxetine that is prescribed, which is about 20-40 mg/day; given in both the immediate and controlled release types of the drug. In controlled release matrix tablets, it is therefore desirable to obtain planned and sustained therapeutic plasma concentrations over an elongated time. The 29 mg dosage is perfect since it covers safety to the formulation and efficacy as well as patient compliance. Further, this dose has a role of reducing side effects than those associated with higher onset plasma concentrate that is characteristic of the immediate-release products [4].

3.5. Kinetics analysis

The drug release kinetics parameters like zero order, first order, Higuchi model and Korsmeyer- Peppas is

Table 4. Flow properties of pre-compression blend

Formulation	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio
F1	31.0±0.070	0.426±0.043	0.538±0.057	20.80±4.37	1.26±0.70
F2	31.6±0.094	0.435±0.067	0.542±0.033	19.70±3.78	1.24±0.94
F3	30.8±0.131	0.378±0.012	0.463±0.078	18.35±1.34	1.22±1.04
F4	31.3±0.094	0.433±0.045	0.541±0.098	20.00±4.38	1.25±0.29
F5	31.2±0.089	0.352±0.040	0.435±0.056	19.00±3.57	1.23±0.57
F6	32.7±0.122	0.430±0.020	0.520±0.094	17.30±2.67	1.20±1.56
F7	33.8±0.131	0.410±0.038	0.512±0.022	20.00±2.56	1.25±0.39
F8	33.5±0.098	0.391±0.056	0.488±0.034	20.00±1.67	1.25±0.34
F9	33.1±0.080	0.398±0.050	0.499±0.067	20.00±4.67	1.25±0.89

All values represent mean ± Standard Deviation (SD), n=3

Table 5. Physical evaluation of matrix tablets

Formulation	Weight Variation*(mg)	Thickness (mm)†	Hardness (N/mm2) †	Friability (%w/w) †
F1	203±0.010	4.15±0.05	4.95±0.05	0.49±0.30
F2	200±0.004	4.40±0.10	4.90±0.10	0.56±0.45
F3	208±0.014	4.05±0.05	5.30±0.20	0.51±0.98
F4	206±0.010	4.05±0.05	5.40±0.40	0.48±0.45
F5	206±0.010	4.55±0.05	5.00±0.10	0.54±0.60
F6	212±0.009	4.60±0.30	4.95±0.15	0.50±0.45
F7	212±0.012	4.35±0.15	5.65±0.25	0.48±0.67
F8	207±0.008	4.25±0.25	5.40±0.40	0.48±0.20
F9	212±0.010	4.30±0.00	5.35±0.45	0.48±0.18

*All values represent mean ± Standard Deviation (SD), n=20
†All values represent mean ± Standard Deviation (SD), n=3

shown Table 6. All formulation shows good linearity in the zero order.

A kinetics analysis of your formulation revealed that your formulation mainly conforms to zero order that is appropriate in sustaining drug concentration. Furthermore, the Korsmeyer-Peppas model with an exponent 'n' of 0.6388 implies that the drug release mechanism follows an anomalous diffusion regime that is non Fickian, a combination of diffusion and polymer erosion mechanisms. This is typical for matrix controlled tablets intended for sustained release and is in contrast with commercial products for which the release profiles plateau earlier and are mostly governed by diffusion control mechanisms.

ISSN: 2458 - 8806

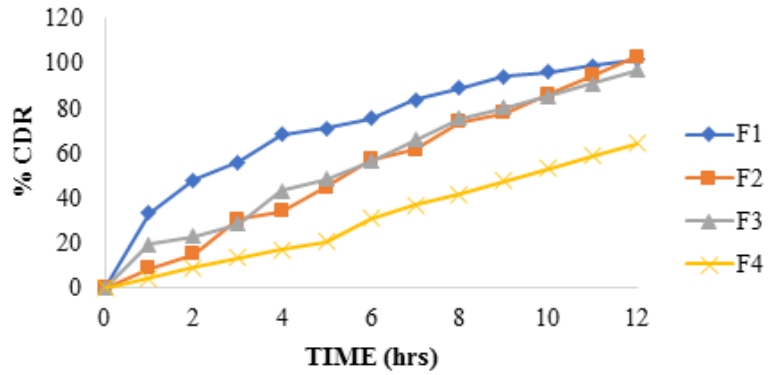

Figure 3. Release profile of F1-F4

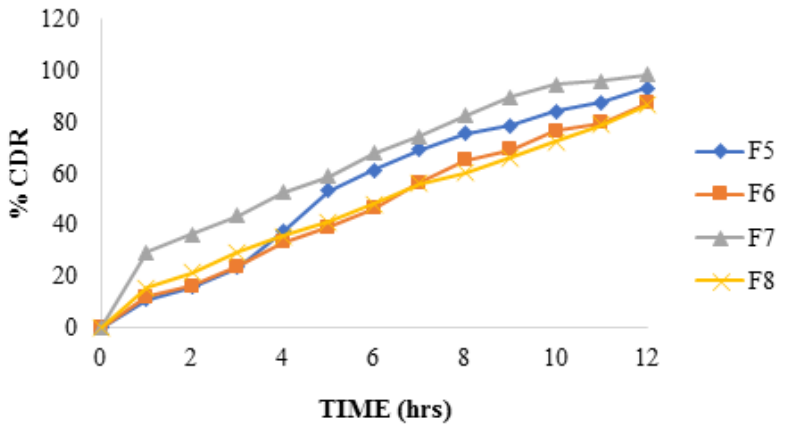

Figure 4. Release profile of F5-F8

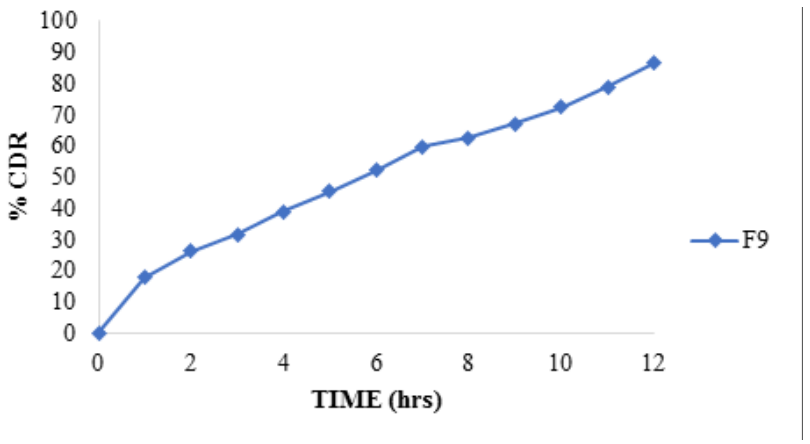

Figure 5. Release profile of F9

3.6. Statistical analysis

Nine formulations employed in the Central Composite Design give a stable model in the development process. The use of centre points enhances predictive capacity and the authenticity of the model particularly when considering polyelectrolyte interaction

Table 6. Drug release kinetics of central composite design batches

Formulation	Zero-order (R^2)	First Order (R^2)	Higuchi model (R^2)	Korsmeyer -Peppas (R^2)	n
F1	0.8739	0.8601	0.9898	0.9935	0.4464
F2	0.9951	0.8685	0.9830	0.9917	1.0093
F3	0.9845	0.9284	0.9778	0.9688	0.7213
F4	0.9935	0.9133	0.9571	0.9937	1.1089
F5	0.9655	0.8462	0.9782	0.9726	0.9454
F6	0.9939	0.9210	0.9776	0.9855	0.8602
F7	0.9461	0.9335	0.9862	0.9821	0.5350
F8	0.9909	0.9367	0.9800	0.9915	0.7130
F9	0.9774	0.9282	0.9864	0.9938	0.6388

R^2= Correlation coefficient; n= Diffusional exponent

effects between some polymers such as HPMC K4M and HPMC K100M. Using a P-values test (<0.05) on variables such as Q4 and Q12 it can be demonstrated that HPMC grades have a highly significant impact. The close to unity R^2 values (>) 0.98 suggest good fit in the model. Used to achieve the required extent of dissolution control as was defined by USP within the specified range (e.g., 40 – 70% at 4hrs).

3.6.1. Effect on response Q2

Model non-significance is suggested by F-value of 3.31. There is only a 10.77% chance that an F-value this large could occur due to noise.

Coded Value: Q2=+23.47-5.91A-6.62B

Model terms are considered significant when the P-value is less than 0.0500. A and B is a no significant model term in this case. Model terms are not significant if the value is higher than 0. 1000. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model (Figure 6) [25].

3.6.2. Effect on response Q4

The Model F-value of 6.41 implies the model is significant. There is only a 3.25% chance that an F-value this large could occur due to noise.

Coded Equation: Q4=+40.09-8.20A-8.30B

Model terms are considered significant when the P-value is less than 0.0500. A and B serve as significant component elements in this instance. Model terms are not significant if the value is higher than 0.1000. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model (Figure 7).

3.6.3. Effect on response Q12

The Model F-value of 8.70 implies the model is significant. There is only a 1.99% chance that an F-value this large could occur due to noise.

Coded Value: Q12=+90.90-4.93A-7.53B-8.50AB

Significant model variables are those with P-values less than 0.0500. In this instance, A, B, and AB constitute significant model terms. If the value is higher than 0.1000, the model terms are not considered significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model (Figure 8).

3.7. Evaluation optimized batch

Pre-compression blend of optimized composition were evaluated for flow property. Various parameters have been determined like angle of repose, Bulk density, tapped density, carr's index and Hausner's ratio and was reported within the range. The result of the Angle of repose and Carr's index, and Hausner's ratio indicates that it has good flow property and good compressibility index.

ISSN: 2458 - 8806

Table 7. ANOVA response data of Q2 (2 hours)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	630.39	2	315.19	3.31	0.1077	not significant
A-HPMC K4M	279.86	1	279.86	2.94	0.1375	
B-HPMC K100M	350.52	1	350.52	3.68	0.1036	
Residual	572.03	6	95.34			
Core Total	1202.42	8				

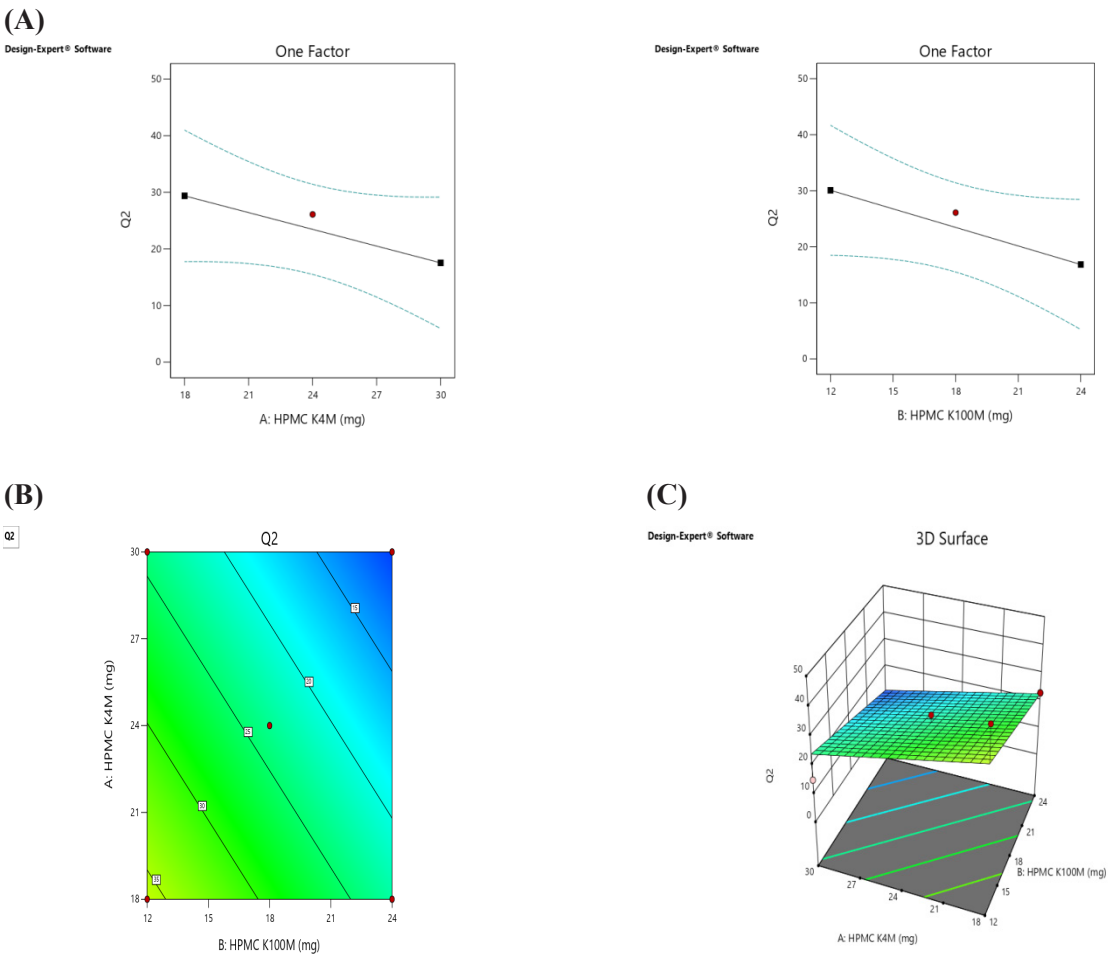

Figure 6. (A) One factor plot (B) Contour plot (C) Response surface plot of Q2%

Tablets were prepared using rotary compression machine of optimized batch of paroxetine HCl was evaluated for various post compression parameters like weight variation, thickness, hardness, and friability result indicates that post compression parameters are within the pharmacopeial limits.

3.8. Comparison of optimized batch with marketed product

When comparing the optimized batch with the marketed product, the marketed product releases the drug up to 8 hours whereas the optimized batch

Table 8. ANOVA response data of Q4 (4 hours)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1088.73	2	544.36	6.41	0.0325	significant
A-HPMC K4M	538.17	1	538.17	6.33	0.0455	
B-HPMC K100M	550.55	1	550.55	6.48	0.0438	
Residual	509.94	6	84.99			
Core Total	1598.67	8				

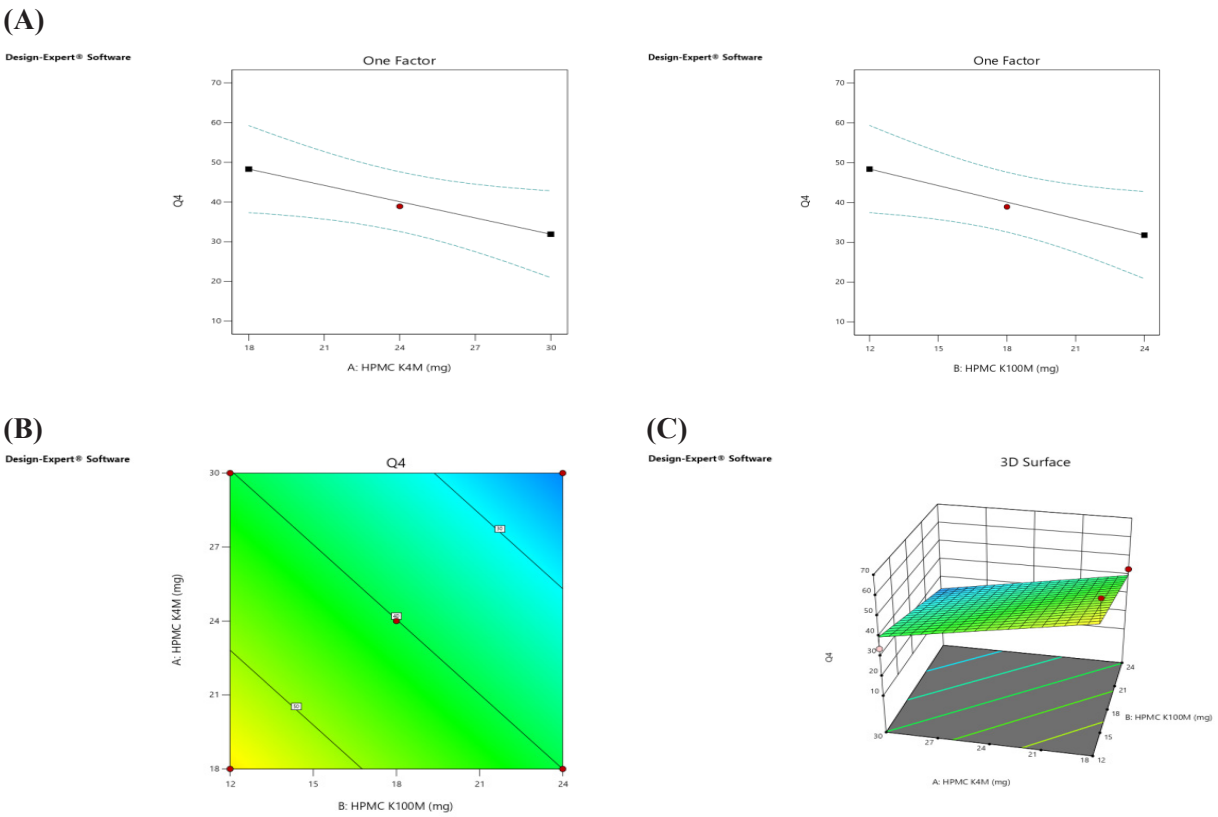

Figure 7. (A) One factor plot (B) Contour plot (C) Response surface plot of Q4%

extended the release up to 12 hours. The results of dissolution studies shows that optimized formulation, exhibited a drug release pattern is near to the theoretical release profile. The designed matrix tablets of optimized formulation of paroxetine HCl released 29.382%, 41.29%, and 93.47% of the drug in the second, fourth, and twelfth hours, respectively (Figure 9).

The plots displayed the greatest linearity (R^2= 0.9820), the zero-order equation provided the best explanation for drug release data.

The corresponding plot for the Korsmeyer-Peppas equation (log cumulative percent drug release vs. time) demonstrated acceptable linearity (R^2= 0.9898). The diffusion exponent n was 0.6344, which appears to indicate a coupling of the diffusion and erosion processes and could indicate that more than one mechanism was controlling the drug release. (Anomalous diffusion).

ISSN: 2458 - 8806

Table 9. ANOVA response data of Q12 (12 hours)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	936.51	3	312.17	8.70	0.0199	significant
A-HPMC K4M	194.07	1	194.07	5.41	0.0676	
B-HPMC K100M	453.44	1	453.44	12.64	0.0163	
AB	289.00	1	289.00	8.06	0.0363	
Residual	179.37	5	35.87			
Core Total	1115.88	8				

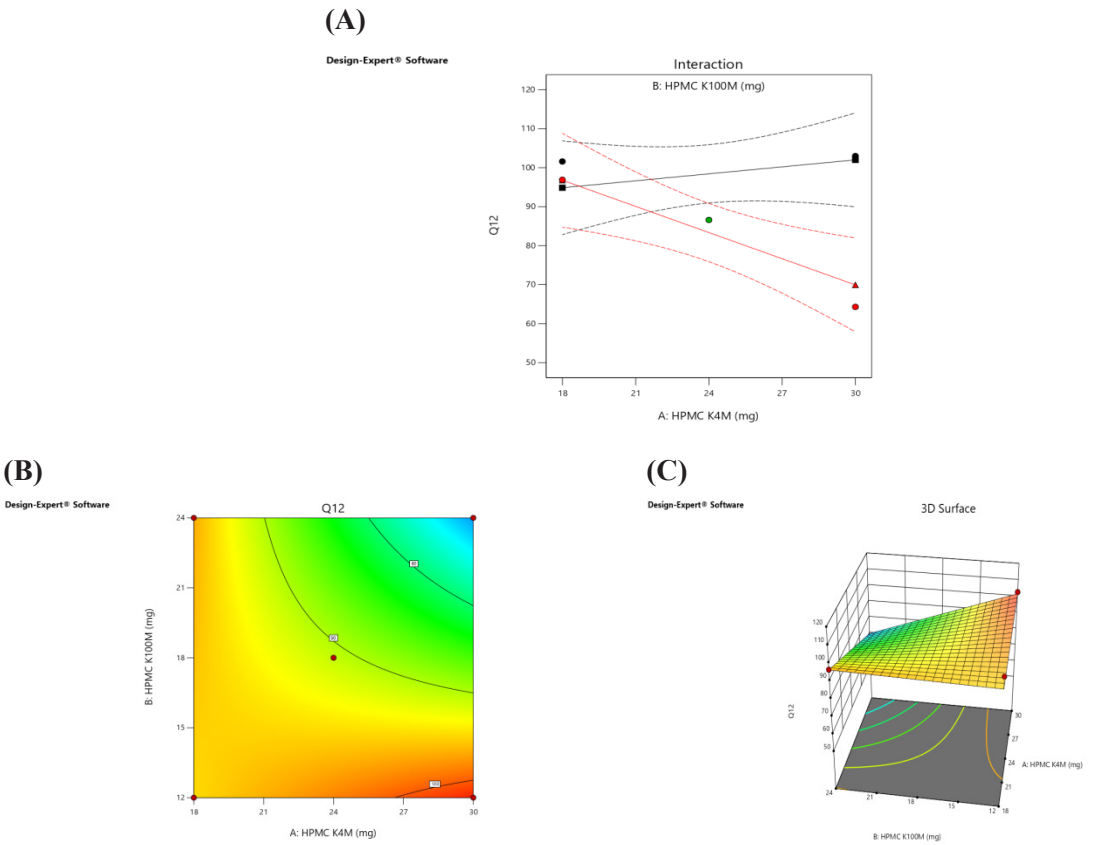

Figure 8. (A) One factor plot (B) Contour plot (C) Response surface plot of Q12%

4. Conclusions

The designed matrix tablet of optimized formulation of paroxetine HCl released up to 29.382%, 41.29%, and 93.47% of the drug in the second, fourth, and twelfth hours which was as per the United State Pharmacopoeia monograph. As comparing the optimized batch with the marketed product, the marketed product releases the drug for up to 8 hours whereas the optimized batch extended the release up to 12 hours.

Table 10. Composition of optimized batch

Ingredients	Quantity (mg)
Paroxetine HCl	29
HPMC K4M	20.8
HPMC K100M	16
PVP K-30	4
IPA	q.s
Lactose monohydrate	132.2
Talc	4
Mg. stearate	2
Silicon dioxide (Aerosol 200)	2
Total	210

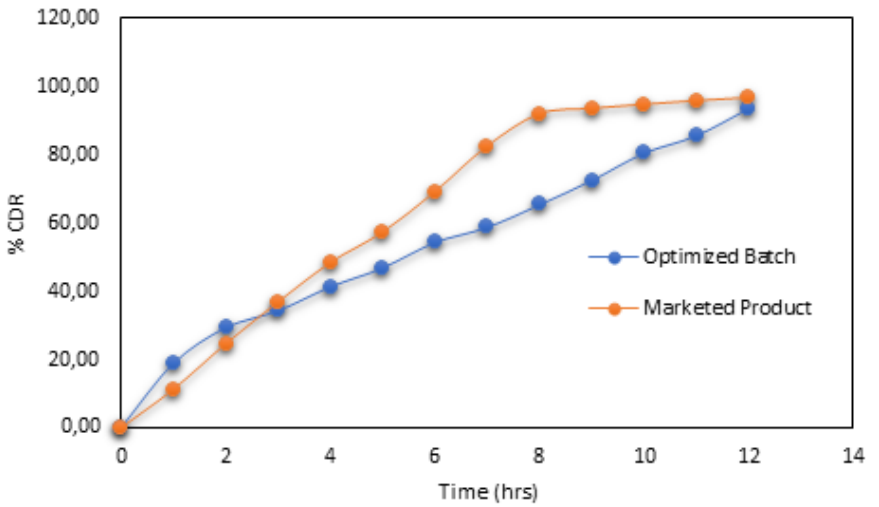

Figure 9. In Vitro Release profile of optimized batch and marketed product

Conflict of Interest

There are no competing interests.

Statement of Contribution of Researchers

Concept – K.B.P., M.N.P; Design – K.B.P., M.N.P; Supervision– P.R.B., M.N.P, T.G.S, B.N.S; Resources – P.R.B., M.N.P., T.G.S., B.N.S.; Materials – K.B.P, P.R.B., T.G.S., M.N.P., B.N.S.; Data Collection and/or Processing – K.B.P., Literature Search – K.B.P., Writing – K.B.P., P.R.B.; Critical Reviews – P.R.B., M.N.P., T.G.S., B.N.S.

Acknowledgement:

The present work was financed by Dharmsinh Desai University, Nadiad (Gujarat) India.

ISSN: 2458 - 8806

Table 11. Theoretical value and optimized value of Paroxetine HCl

Time	Theoretical value (% CDR)	Optimized value (% CDR)
Q2	29.728	29.382
Q4	47.484	41.29
Q12	93.697	93.47

References

1. Nokhodchi A, Raja S, Patel P, Asare-Addo K. The role of oral controlled release matrix tablets in drug delivery systems. BioImpact. 2012; 2(4):175-187. https://doi.org/10.5681%2Fbi.2012.027
2. Agarwal P, Semimul A. A comprehensive review on sustained release matrix tablets: a promising dosage form. Universal J Pharm Res. 2018;3(6):49–54. https://doi.org/10.22270/ujpr.v3i6.222
3. Yang Y, Huang Z, Zhang X, Li J, Huang Y, Chen W, Pan X, Wu C. Development of Paroxetine Hydrochloride Single Layer Controlled-Release Tablets Based on 3^2 Factorial Design. Pharmaceutics. 2018;10(4): 243. https://doi.org/10.3390/pharmaceutics10040243
4. Davis BA, Nagarajan A, Forrest LR, Singh S K. Mechanism of Paroxetine (Paxil) Inhibition of the Serotonin Transporter. Sci Report. 2016;6:23789. https://doi.org/10.1038/srep23789
5. Rajesh HJ, Shashikiran YH, Anu PA, Priyanka RG. Review on Sustain Release Matrix Tablets. World J Pharm Pharm Sci. 2021;10(11):545-553
6. Khan R, Ashraf MS, Afzal M, Kazmi I, Jahangir MA, Singh R. Formulation and evaluation of sustained release matrix tablet of rabeprazole using wet granulation technique. J Pharm Bioal Sci. 2014;6(3):180-184. https://doi.org/10.4103%2F0975-7406.130961
7. Madgulkar AR, Bhalekar MR, Kolhe VJ, Kenjale YD. Formulation and optimization of sustained release tablets of venlafaxine resinates using response surface methodology. Indian J Pharm Sci. 2009;71(4):387-394. https://doi.org/10.4103%2F0250-474X.57287
8. Mortazavi SA, Jafariazar Z, Ghadjahani Y, Mahmoodi H, Mehtarpour F. Formulation and *In vitro* Characterization of Sustained Release Matrix Type Ocular Timolol Maleate Mini-Tablet. Iranian J Pharm Res. 2014;13(1), 19–27
9. Sheskey PJ, Robb RT, Moore RD, Boyce BM. Effects of lubricant level, method of mixing, and duration of mixing on a controlled-release matrix tablet containing hydroxypropyl methylcellulose. Drug Develop Ind Pharm. 1995;21(19):2151–2165. https://doi.org/10.3109/03639049509065898
10. Bravo SA, Lamas MC, Salomón CJ. *In vitro* studies of diclofenac sodium controlled-release from biopolymeric hydrophilic matrices. J Pharm Pharm Sci. (2002); 5(3):213–219.
11. Shah VP, Gurbarg M, Noory A, Dighe S, Skelly JP. Influence of higher rates of agitation on release patterns of immediate-release drug products. J Pharm Sci. 1992;81(6) 500–503. https://doi.org/10.1002/jps.2600810604
12. Nair A, Gupta R, Vasanti S. *In vitr*o controlled release of alfuzosin hydrochloride using HPMC-based matrix tablets and its comparison with marketed product. Pharm Develop Technol. 2007;12(6):621–625. https://doi.org/10.1080/10837450701563277
13. Ravi PR, Kotreka UK, Saha RN. Controlled release matrix tablets of zidovudine: effect of formulation variables on the *in vitro* drug release kinetics. AAPS Pharm SciTech. 2008;9(1):302–313. https://doi.org/10.1208/s12249-007-9030-8
14. Patel H, Panchal DR, Patel U, Brahmbhatt T, Suthar M. Matrix type drug delivery system: A review. J Pharm Sci Biosci Res. 2011; 1(3):143–151
15. Bang LM, Keating GM. Paroxetine Controlled Release. CNS Drugs. 2004; 18, 355–364. https://doi.org/10.2165/00023210-200418060-00003
16. Aulton ME. Aulton's Pharmaceutics: The design and manufacture of medicine. 3rd Edition. Churchil livingstone, Elsevier, UK, 2008
17. Lachman L, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd Edition. Varghese Publishing House, Bombay, India. 1991
18. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52(12):1145–1149. https://doi.org/10.1002/jps.2600521210
19. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15(1):25-35. https://doi.org/10.1016/0378-5173(83)90064-9
20. Lieberman HA, Lachman L. Pharmaceutical Dosage Forms. In: Dekker M (ed) Tablet 1980.75-128

21. Bushra R, Shoaib MH, Ali H, Zafar F, Naeem MI, Aslam N. Formulation design and optimization of aceclofenac tablets (100 mg) using central composite design with response surface methodology. Lat Am J Pharm. 2014;33(6):1009–1018
22. Barsagade P, Khetade R, Nirwan K, Agrawal T, Gotafode S, Lade U. Review Article of Dissolution Test Method Development and Validation of Dosage Form by Using RP-HPLC. Int J Pharm Sci Rev Res. 2021; 70(1):28-38 https://dx.doi.org/10.47583/ijpsrr.2021.v70i01.005
23. Kunamaneni P, Kovvasu SP, Janjanam KC. Formulation and optimization of controlled release paroxetine hydrochloride tablets using response surface methodology. J Global Trend Pharm Sci. 2016; 7(4):3520–3534
24. Thirumaran M, Balakumar K, Vijaya Raghavan C, Thuvaragan S. Formulation and *in vitro* release kinetic study of an enteric coated paroxetine-controlled release tablets. Asian J Res Chem Pharm Sci. 2014; 2(2):63-73
25. Avachat A, Kotwal V. Design and evaluation of matrix-based controlled release tablets of diclofenac sodium and chondroitin sulphate. AAPS Pharm SciTech. 2007; 8(4):51–56. https://doi.org/10.1208/pt0804088

ISSN: 2458 - 8806