TITLE

OPTIMIZATION OF HPMC LOADED PAROXETINE HCL CONTROLLED RELEASE MATRIX TABLET BY CENTRAL COMPOSITE DESIGN

INTRODUCTION

A crucial challenge for the pharmaceutical industry in drug development is to produce efficient and safe drugs, therefore properties of drugs and how they are delivered must be optimized. A perfect controlled drug delivery system is one that delivers a drug at a defined rate systemically or locally for a set amount of time with minimal fluctuations in plasma drug concentration, minimal toxicity, and maximum efficiency. 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. In the current surroundings, new and innovative drug delivery methods are quickly replacing conventional drug dosage forms. In modern therapeutics, the sustained release/ controlled release dosage forms have become very popular. When compared to conventional forms that may need to be taken three or four times daily to achieve the same therapeutic effect, sustained-release tablets and capsules are typically taken only once or twice daily. The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period, an amount of the drug equivalent to the eliminated by the body. In the pharmaceutical field, 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.

Paroxetine hydrochloride is a Selective Serotonin Reuptake Inhibitor. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'-fluorophenyl)-3S-[(3',4'methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate [1]. As a reuptake inhibitor, paroxetine reduces the amount of serotonin taken up by the serotonin uptake carrier, increasing the quantity of serotonin that is available at the synapses. The dysfunction of the serotonin neurons brought on by excessive absorption is believed to be the cause of depression and other central nervous system disorders. In addition to treating depression, paroxetine helps in treating a wide range of disorders. The research paper describes paroxetine, which is used to treat depression, as an inhibitor of 5-hydroxytryptamine absorption. Even though paroxetine's primary effect is to stop serotonin from being reabsorbed, serotonin is linked to both norepinephrine and dopamine through the cascade of monoamine activities in the brain. Therefore, it is believed that greater serotonin availability is linked to higher availability of norepinephrine and dopamine.

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. 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. An alternative is to granulate the drug retardant mix and other additives prior to compression. The drug dissolution-controlled and diffusion-controlled mechanisms are constantly released by these systems. 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). 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.

OBJECTIVES

- To formulate the controlled release tablet of paroxetine by various HPMC grades using the wet granulation method.
- To perform the evaluation parameters:
  - Pre–compression parameters
  - Post–compression parameters
- In vitro dissolution study for the prepared Paroxetine CR matrix tablet.
- The main goal of our project is to meet the requirements of dissolution profile of paroxetine HCl as per USP.

Time point (i)	**Time (h)**	**Amount dissolved (tablets labeled to contain 25mg of paroxetine)**
1	2	10-30%
2	4	40-70%
3	12	NLT 80%

MATERIALS AND METHODS

Materials

Paroxetine hydrochloride were 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.

Methods

Estimation of Paroxetine Hydrochloride by UV method

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. The stock (primary) solution of 1000 µg/mL was subsequently prepared by adding distilled water to the volumetric flask until it reached the desired level. 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 above solution's absorbances were measured using a double-beam UV-Visible spectrophotometer at its maximum wavelength of 293 nm.

Compatibility studies of paroxetine HCl

A FTIR analysis carried out to confirm any potential physical or chemical interactions between the drug and formulation excipients. By comparing the obtained spectra for the existence of functional groups, FTIR spectra of the pure drug Paroxetine hydrochloride, pure polymers, and a mixture of both drug and polymers were performed .
The process was carried out using pellets of potassium bromide (KBr). Infrared scanning was done on the samples, region between 500 and 3500 cm^{-1} with a resolution of 4 cm^{-1} using a mixture of approximately 5 mg of samples and 50 mg of spectroscopic grade KBr.

Preliminary trail batches for paroxetine hydrochloride

Tablets containing 29 mg of Paroxetine were prepared by the wet granulation method. Accurate quantities of all the ingredients (HPMC K100M, HPMC K4M, HPMC K100M LV, PVP K-30, and Lactose monohydrate) were weighed and mixed in a mortar pestle shown in Table 1. As a binding solution, isopropyl alcohol was used. By gradually incorporating the binder solution into the above-mentioned combined ingredients, the granulation process was carried out. The wet bulk was passed through sieve #20 and left to dry for an hour. Following drying, the granules were mixed for 2–3 minutes with magnesium stearate, Talc, and colloidal silicon dioxide (Aerosil 200). On a rotating tablet compression machine, the lubricated granules were compressed into tablets using a 8.0 mm round concave punches with a broken line on one side.

Table 1:
Preliminary screening trails

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

Experimental design and optimization of the formula

Utilizing Design Expert Version 13 programs, experimental design and formulation optimization were carried out. The optimization used the central composite design. There was a total of 13 trials needed for this experimental design, including five centre points. Based on preliminary experiments, the high and low values of each variable were established.

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
F10	0	0	24	18
F11	0	0	24	18
F12	0	0	24	18
F13	0	0	24	18

RESULTS AND DISCUSSION

Estimation of Paroxetine HCl using Uv spectroscopy and Compatibility study

The standard graph of Paroxetine HCl has shown good linearity R^2 value 0.9994 in 1000 ml 0.05 M tris buffer pH 7.5 under λmax of 293nm. The physical mixture's and the drug's FTIR spectra were recorded in the 4000-400 cm-1 region. Paroxetine HCl displayed some notable and recognizable peaks. The peak at 2924cm-1 and 2817 cm-1were due to stretching vibrations of the C-H and N-H bond respectively. Peaks at 1620cm-1, 1512 cm-1, and 1222 cm-1 could be assigned to sp2 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.

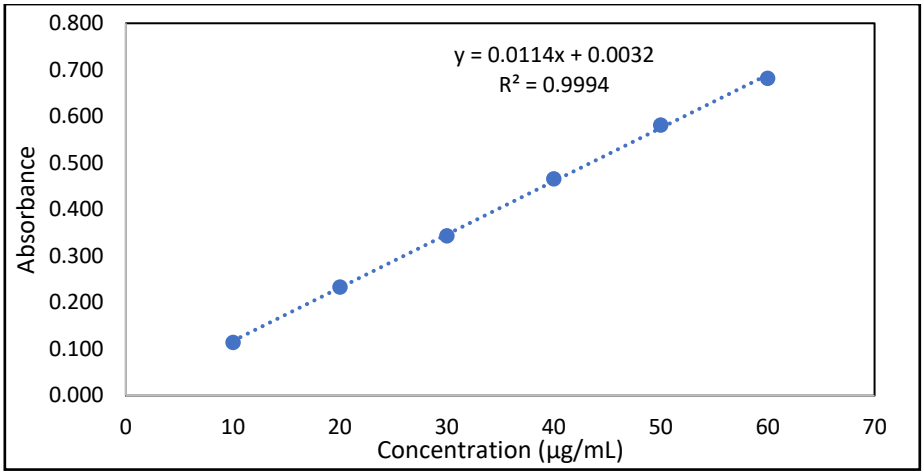


Fig 1: Estimation of Paroxetine HCl

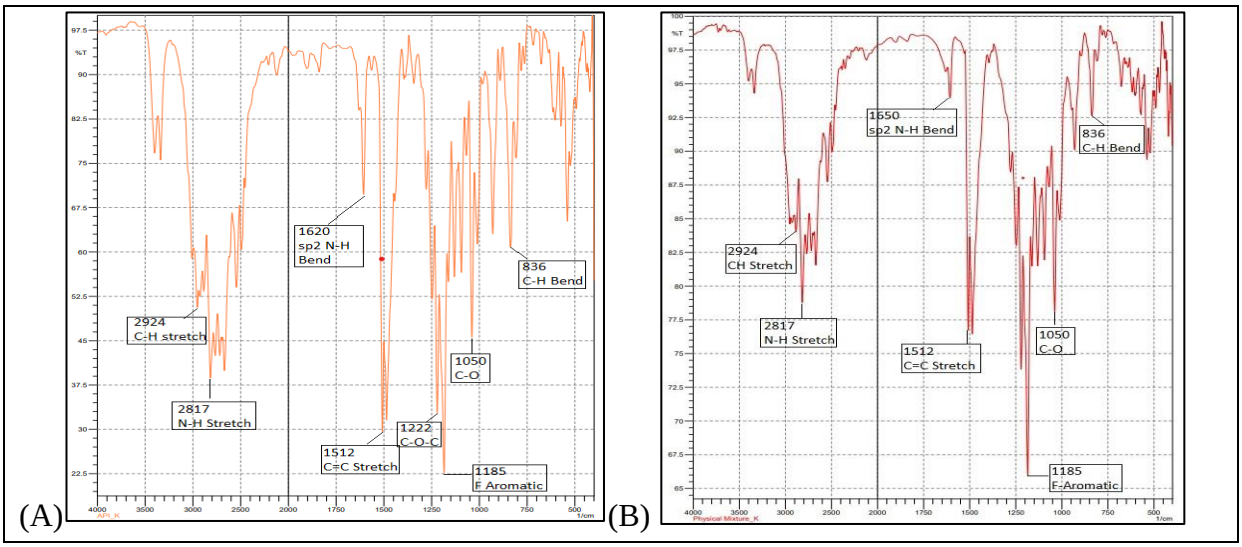


Fig 2: FTIR spectra of (a) Pure Drug and (b)Physical Mixture

Preliminary screening

Formulation P6 shows drug release extended for 12 hrs as per USP requirements. Batch P6 contains 24 mg of HPMC K4M and 18 mg of HPMC K100M. So, these two grades of HPMC have been selected for DOE trails.

Table 3:
Composition of Central Composite design batches

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Paroxetine HCl*	29	29	29	29	29	29	29	29	29	29	29	29	29
HPMC K4M	18	30	18	30	15.5	32.4	24	24	24	24	24	24	24
HPMC K100M	12	12	24	24	18	18	9.5	26.4	18	18	18	18	18
PVP K-30	4	4	4	4	4	4	4	4	4	4	4	4	4
Lactose Monohydrate	139	127	127	115	118.6	135.5	118.6	127	127	127	127	127	127
IPA	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	Qs	Qs
Mg. Stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4
Silicon dioxide	2	2	2	2	2	2	2	2	2	2	2	2	2
Total:	210	210	210	210	210	210	210	210	210	210	210	210	210

Precompression 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. 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 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.

Table 4:

Flow Properties of Precompression 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
F10	32.0±0.070	0.411±0.030	0.515±0.050	20.20±1.98	1.23±0.67
F11	32.8±0.037	0.420±0.089	0.523±0.010	19.60±1.00	1.24±0.83
F12	30.9±0.089	0.391±0.010	0.488±0.045	20.00±2.74	1.25±0.87
F13	31.8±0.084	0.410±0.038	0.512±0.045	20.00±4.23	1.25±1.95

Table5:

Physical Evaluation of Matrix Tablets

Formulation	Weight Variation⁎(mg)	Thickness (mm)†	Hardness (N/mm^2) ‡	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
F10	208±0.013	4.40±0.20	5.10±0.30	0.49±0.39
F11	212±0.012	4.40±0.40	5.70±0.10	0.48±0.30
F12	211±0.010	4.30±0.20	5.35±0.15	0.48±0.50
F13	212±0.010	4.10±0.10	5.20±0.20	0.50±0.09

⁎All values represent mean ± Standard Deviation (SD), n=20

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

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

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. 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 to F13 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.

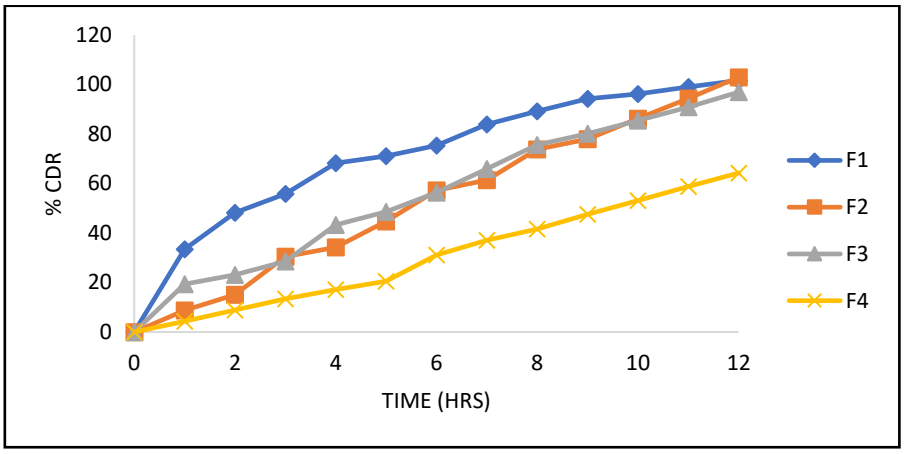


Fig 3: Release profile of F1-F4

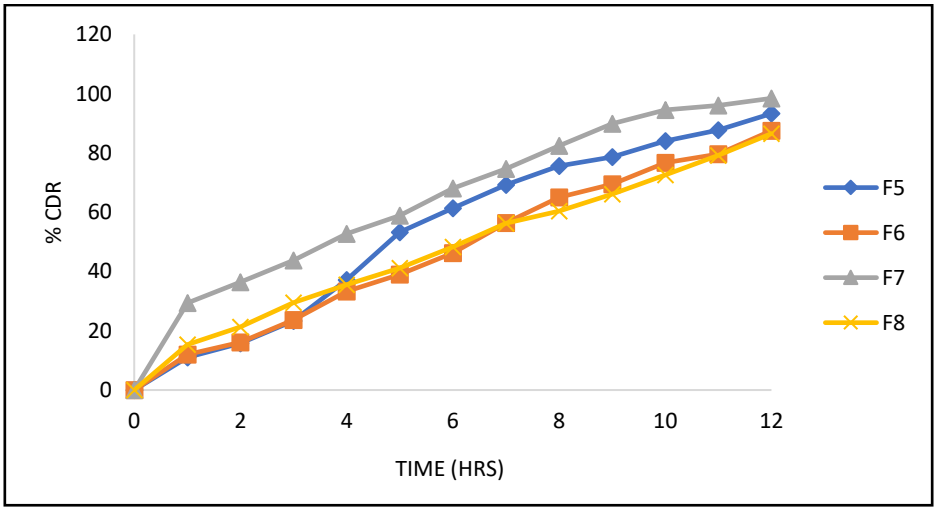


Fig 4: Release Profile of F5-F12

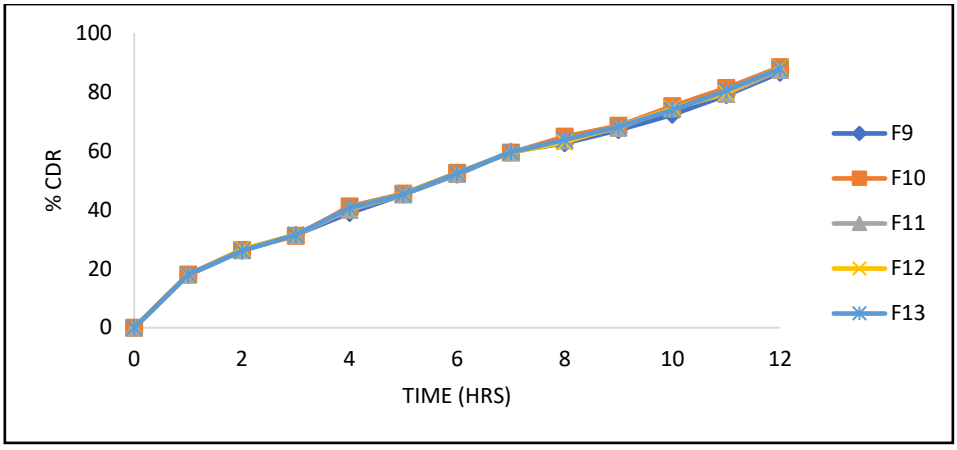


Fig 5: Release Profile of F9-F13

Kinetics analysis

The drug release kinetics parameters like zero order, first order, Higuchi model and korsmeyer – peppas is shown Table 6. All formulation shows good linearity in the zero order.

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
F10	0.9801	0.9309	0.9857	0.9924	0.6456
F11	0.9789	0.9308	0.9865	0.9933	0.6404
F12	0.9789	0.9298	0.9856	0.9936	0.6392
F13	0.9793	0.9303	0.9863	0.9934	0.6423

R^2= Correlation coefficient; n= Diffusional exponent

STATISTICAL ANALYSIS

Effect on response Q2

Model significance is suggested by F-value of 4.24. A high F-value cannot be explained by noise except with a 4.00% probability. There is only a 4.00% chance that an F-value this large could occur due to noise.

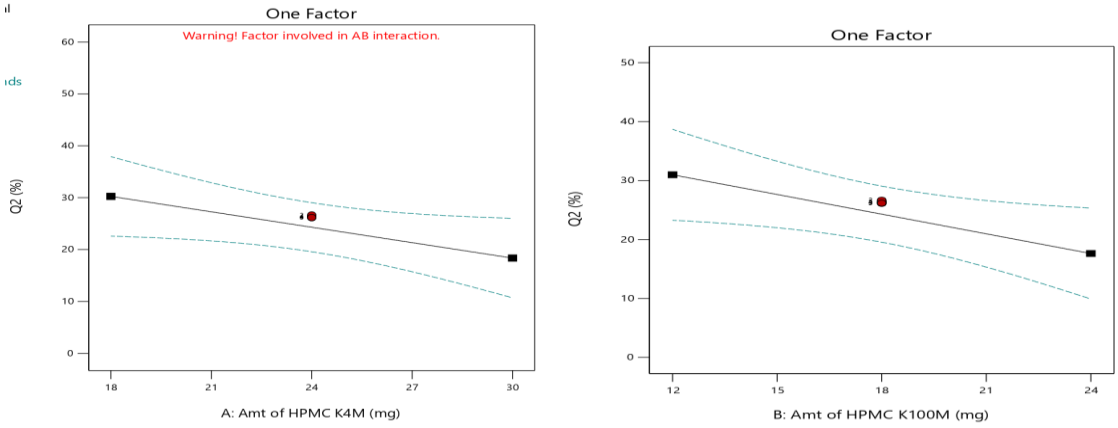
Coded Value: Q2=+24.30-5.95A-6.68B+4.54AB

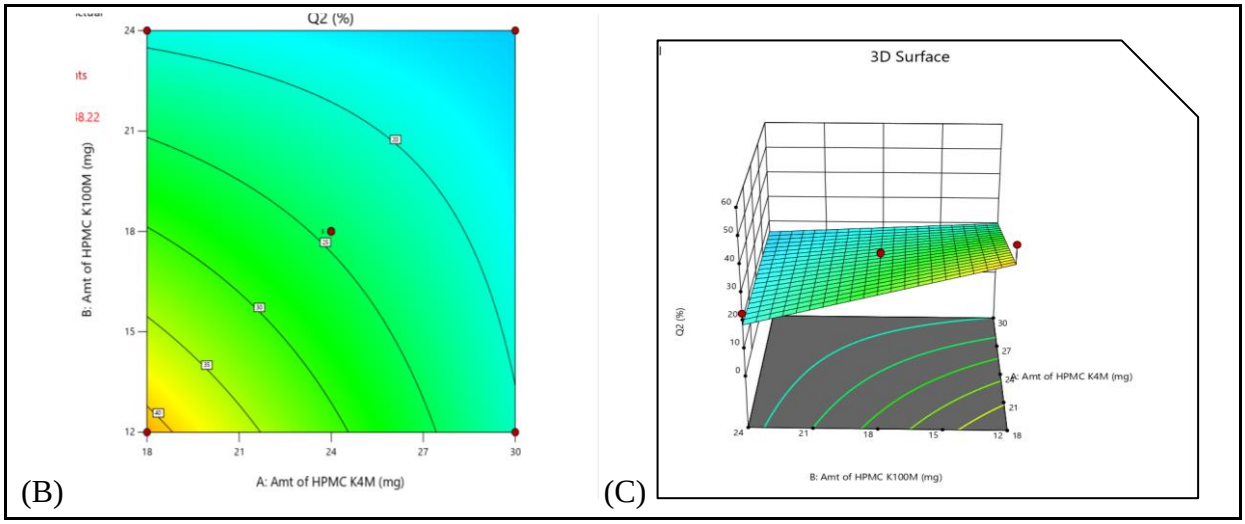
Model terms are considered significant when the P-value is less than 0.0500. B is a significant model term in this case. Model terms are not significant if the value is higher than 0. 1000.If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Table 7: ANOVA Response data of Q2(2 hours)

Source	**Sum of squares**	**df**	**Mean square**	**F-value**	**p-value**	
Model	721.86	3	240.62	4.24	0.0400	Significant
A-Amt of HPMC K4M	282.76	1	282.76	4.98	0.0526	
B-Amt of HPMC K100M	356.83	1	356.83	6.28	0.0335	
AB	82.26	1	82.26	1.45	0.2595	
Residual	511.30	9	56.81			
Lack of fit	511.11	5	102.22	2137.65	<0.0001	Significant
Pure error	0.1913	4	0.0478			
Cor total	1233.16	12				

(A)





(B) (C)

Fig 6:(A) one factor plot (B)contour plot (C) Response surface plot of Q2%

Effect on response Q4

The Model F-value of 10.62 implies the model is significant. There is only a 0.34% chance that an F-value this large could occur due to noise.

Coded Equation: Q4=+40.26-8.22A-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.

Table 8: ANOVA Response data of Q4(4 hours)

Source	**Sum of squares**	**df**	**Mean square**	**F-value**	**p-value**	
Model	1092.60	2	546.30	10.62	0.0034	Significant
A-Amt of HPMC K4M	540.94	1	540.94	10.52	0.0088	
B-Amt of HPMC K100M	551.66	1	551.66	10.73	0.0084	
Residual	514.33	10	51.43			
Lack of fit	510.65	6	85.11	92.61	0.0003	Significant
Pure error	3.68	4	0.9190			
Cor total	1606.93	12				

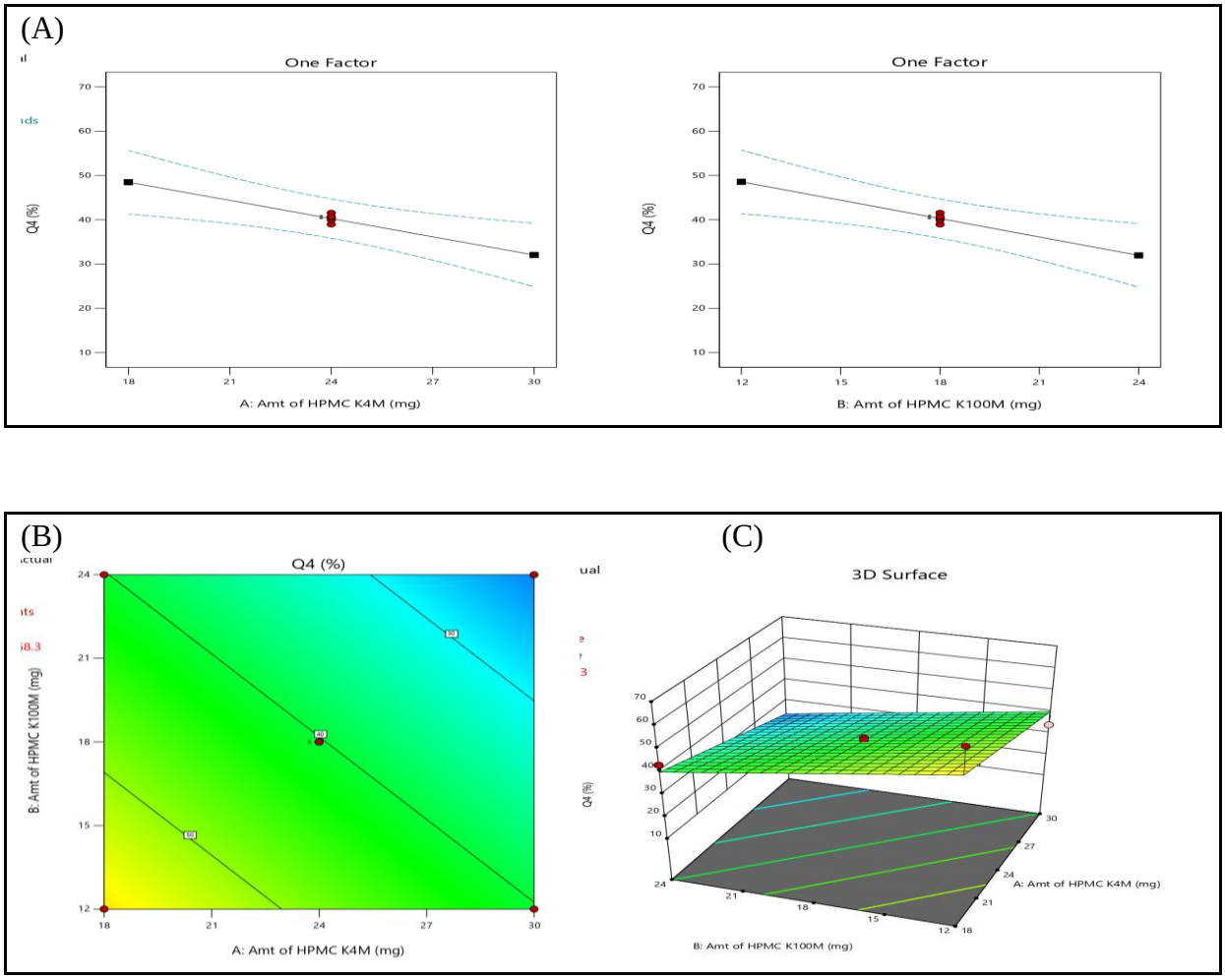


Fig 7: (A) one factor plot (B)contour plot (C) Response surface plot of Q4%

Effect on response Q12

The Model F-value of 13.83 implies the model is significant. There is only a 0.10% chance that an F-value this large could occur due to noise.

Coded Value: Q12=+90.05-4.95A-7.54B-8.49AB

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.

Table 9: ANOVA Response data of Q12

Source	**Sum of squares**	**df**	**Mean square**	**F-value**	**p-value**	
Model	938.10	3	312.70	13.83	0.0010	Significant
A-Amt of HPMC K4M	195.09	1	195.09	8.63	0.0166	

B-Amt of HPMC K100M	454.35	1	454.35	20.09	0.0015	
AB	288.66	1	288.66	12.76	0.0060	
Residual	203.53	9	22.61			
Lack of fit	201.18	5	40.24	68.27	0.0006	Significant
Pure error	2.36	4	0.5893			
Cor total	1141.63	12				

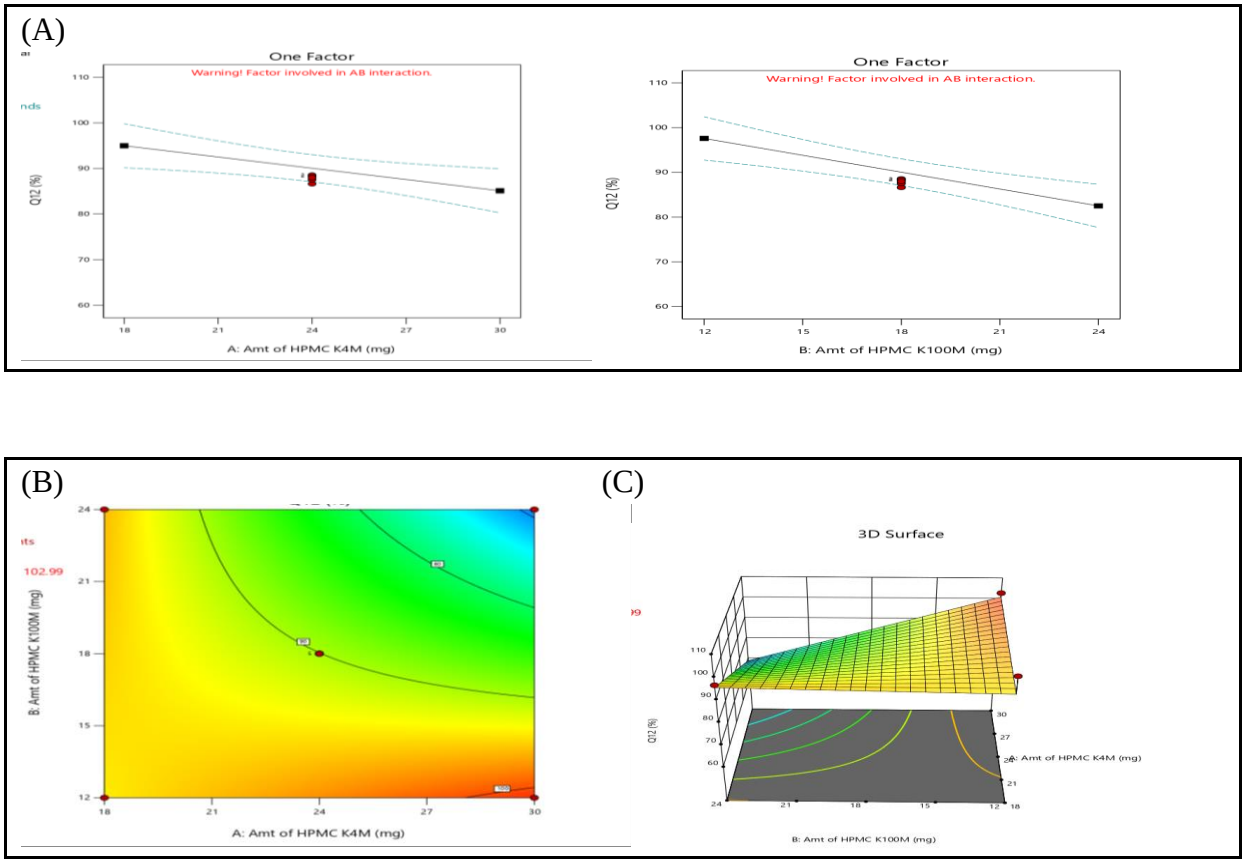


Fig 8:(A) one factor plot (B)contour plot (C) Response surface plot of Q12%

Table 10: Composition of optimized batch

Ingredients	**Qty (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

Evaluation Optimized batch

Precompression 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.

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 limit.

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 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, release 29.382%,41.29%, and 9,3.47% of the drug in the second, fourth, and twelfth hours respectively is shown in 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).

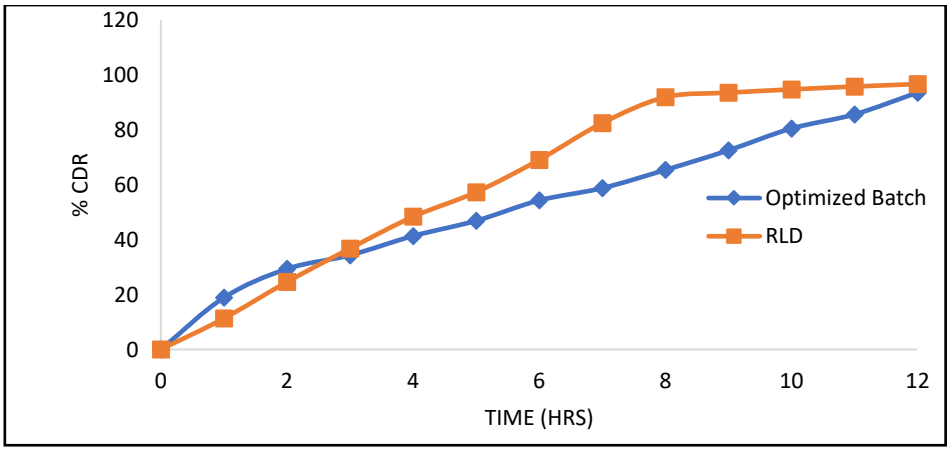


Fig 9: In-Vitro Release profile of optimized batch and marketed product

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
Q5	93.697	93.47

IMPACT OF THE RESEARCH IN THE ADVANCEMENT OF KNOWLEDGE OR BENEFIT TO MANKIND

The research work titled "Optimization of HPMC Loaded Paroxetine HCl Controlled Release Matrix Tablet by Central Composite Design" focuses on optimizing the formulation of a controlled-release matrix tablet containing Paroxetine HCl using a central composite design approach. This type of research has several potential impacts on the advancement of knowledge and benefits to mankind:

- Pharmaceutical Advancement: This research contributes to the field of pharmaceutical science by developing an optimized formulation for controlled-release medications. Controlled-release formulations are essential for ensuring prolonged and steady drug release, which can improve patient compliance and reduce side effects by maintaining therapeutic drug levels over an extended period.

- Drug Delivery Technology: The utilization of central composite design (CCD) showcases the application of advanced experimental design techniques in pharmaceutical research. This methodology not only helps in optimizing the formulation of a specific drug but also sets a precedent for other researchers to apply similar approaches in developing various drug delivery systems.

- Enhanced Patient Treatment: The optimized controlled-release matrix tablet has the potential to improve patient outcomes by providing a more consistent and sustained release of Paroxetine HCl. This could lead to better management of conditions that the drug treats, such as depression, anxiety disorders, and certain mood disorders.

- Reduced Side Effects: Controlled-release formulations can often lead to reduced side effects compared to immediate-release formulations, as they maintain drug concentrations within the therapeutic range and minimize peaks and troughs. This can enhance patient comfort and treatment adherence.

- Cost-Effectiveness: By optimizing the formulation, the research might lead to the development of more efficient production processes. This could potentially reduce manufacturing costs, making the medication more accessible and affordable to patients.

- Scientific Knowledge: The research contributes to the scientific community's understanding of how different factors and variables impact the release profile of drugs from controlled-release matrix tablets. This knowledge can be valuable not only for this specific drug but also for the broader field of drug formulation and delivery.

- Basis for Further Research: The research's findings and methodology can serve as a foundation for further studies in the optimization of other drugs and formulations. Researchers can build upon the central composite design approach to develop controlled-release formulations for various medications, expanding the applications of this research.

- Academic and Industrial Collaboration: This type of research often involves collaborations between academia and the pharmaceutical industry. Such collaborations can facilitate the translation of research findings into practical applications, leading to the development of new medical products that benefit patients.

In summary, the research work on optimizing the HPMC loaded Paroxetine HCl controlled-release matrix tablet using a central composite design has the potential to advance pharmaceutical knowledge, improve patient treatment outcomes, and contribute to the broader field of drug delivery systems. It showcases the application of advanced experimental techniques and has the capacity to positively impact both medical practice and scientific understanding.

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Sincerely,

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