Ind. J. Pharm. Edu. Res., 2024; 58(1s):s113-s125.
https://www.ijper.org

Original Article

Floating Drug Delivery of Sustained Release Anti-depressant Mirtazapine Tablets by Box-Behnken Design: Formulation and Optimization

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ABSTRACT

Background: Mirtazapine widely prescribed Antidepressant drug that belongs to BCS Class II drug with low solubility and high permeability characteristics. **Aim:** The Box Behnken design was used to statistically optimize the formulation on the efficacy of gastroretentive floating tablets of mirtazapine. **Materials and Methods:** The 3 components of 3 levels of the design were used to examine the replies and create a polynomial model using design expert software. Three different independent factors were compared. The concentration of Methocel K100 M premium (X1) Concentrations of ethyl cellulose(X2), cetyl alcohol (hexadecanol) (X3). To find properties of prepared tablets, swelling-erosion index, floating properties, *in vitro* dissolution, Comparison of marketed with F9 and Optimized formulation, drug release kinetics, and counter and 3D surface plots. **Results and Conclusion:** The formulations F1, F2, F3, F4, F6, F8, F9, and F12 release zero orders release and F5, F7, F10, F11, F13, F14, and F15, the high R^2 first order is seen. The release exponent formulations F1, F2, F3, F4, F5, F7, F9, F10, F11, F12, F13, and F14 are proven to be Fickain diffusion, while the release exponent formulations F6, F8, and F15 are noticed to be non-Fickain diffusion. In the marketed (Mirtafresh 15-MD) tablet, 100% of the medicine is released in 20 min, 100% in the F9 formulation in 6.5 hr, and 100% in the optimized formulation in 12 hr. The obtained optimized formulation underwent statistical optimization to ensure that it satisfied all of the dissolution criteria to validate the theoretical prediction.

Keywords: Floating, Sustained release, Drug release, Mirtazapine, Mirtafresh 15-MD.

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Received: 10-01-2023;
Revised: 30-03-2023;
Accepted: 14-08-2023.

INTRODUCTION

The regularly used antidepressant drug mirtazapine has low solubility and high permeability traits of a BCS Class II drug. Recent studies on mirtazapine focused on developing Solid Lipid Nanoparticles (SLNs) that were loaded with mirtazapine and assessing their potential as a topical drug delivery system for the treatment of pruritus. These SLNs were prepared by direct compression method using carbapol 934P and HPMC K4M as mucoadhesive controlled release agents.[1] Specifically created to prospectively compare the onset of antidepressant efficacy of sertraline at dosages frequently used in clinical practice and mirtazapine orally disintegrating tablets at the same dosage in individuals with serious depression, especially the elderly, the treatment with mirtazapine 15–45mg/day results in quick and durable improvements in depressive symptoms. It has a similar level of effectiveness to other anti-depressants and may act faster than Selective Serotonin Reuptake Inhibitors (SSRIs). Furthermore, compared to amitriptyline, it might potentially have a better probability of prolonged. The oral conventional drug delivery systems have some drawbacks, such as the potential for gastrointestinal destruction of labile molecules, low absorption of macromolecules, a slow onset of action, and an unavoidable fluctuation in drug concentration that can result in under- or overmedication with concurrent negative effects, especially for drugs with small therapeutic indices. The coating ratio of the drug was increased to 8% (w/w) for *in vitro* taste masking study, patients in the pediatric, geriatric, and psychiatric populations can benefit from the Orally Disintegrating Tablets (ODTs). The PLGA microparticles were prepared for prolonged release of mirtazapine by using the solvent anti-solvent technology, and to improve the solubility of practically insoluble mirtazapine by preparing nanosuspension, prepared by using solvent anti-solvent technology.[2-10] The statistically optimize the formulation parameter and assess the main effect, interaction effects, and quadratic of the formulation ingredient on performance, the Box Behnken design (BBD) was used. The mirtazapine-loaded SLNs were successfully developed and optimized using the BBD.[11-14] The purpose of the floating research is to effectively administer

DOI: 10.5530/ijper.58.1s.11

the medications while remaining in the stomach for a longer period. The method offers enhanced absorption at a pace that allows for the quick onset and long-term maintenance of effective plasma levels. An effervescent agent and a swellable polymer are both components of the medicinal composition in the form of tablets. They have a lower bulk density than gastric fluids, Hydrodynamically Balanced Systems (HBS), or Floating Drug Delivery Systems (FDDS) float for a long time in the stomach, and increased stomach residence duration results from the drug being released from the floating system at a controlled rate without causing changes in plasma drug concentration. The remaining medicine is evacuated from the stomach after being fully released from the delivery system. It is a low-density method whose bulk density is lower than gastric fluids and, as a result, it floats in the stomach, slowly releasing the medication without slowing down the rate at which the stomach empties for a protracted length of time.[15-27] The statistical comparison parameters provided by design expert software, including the Coefficient of Variation (CV), coefficient of determination (R^2), adjusted coefficient of determination (adjusted R^2), predicted coefficient of determination (Pred. R^2), adequate precision, optimisation, and desirability, were used to identify the best-fitting model. The Analysis of Variance (ANOVA) technique was also used to discover significant influences on the coefficients of the response regression. The software was also used to determine the *p*-values and *F* test.[28-33] To statistically optimize the formulation parameter and assess the main effect, interaction effects, and quadratic of the formulation ingredient on the efficacy of gastroretentive floating tablets of mirtazapine, the BBD was employed. Utilizing design expert software (Stat – Ease Inc., Minneapolis, MN, USA) the 3 factors 3 levels design was used to investigate the responses and build a polynomial model. Because it required applying a design that exhibited 15 trial runs and center points replicated (n=3), the BBD was chosen. A comparison was made between three independent variables. Concentration of Methocel K100 M premium (X1,) Concentrations of ethyl cellulose(X2), cetyl alcohol (hexadecanol) (X3). The floating lag time (seconds) (Y1), swelling index (%) (Y2), percentage of drug release after an hour (Y3), percentage of drug release after 2 hr (Y4), and T100 (Time necessary to 100% drug release (hr) (Y5) were chosen as the independent variables. Table 1 displays both the independent (low, medium, and high level) and dependent variables.

MATERIALS AND METHODS

Mirtazapine a sample had given as a gift by New Land Private Company, Hyderabad's, Methocel K100M a gift sample from Colorcon Asia Pvt. Ltd., Verna, Industrial Estate. Cetyl Alcohol is bought as a sample from Mumbai's Loba Chemie Pvt. Ltd., Ethyl cellulose is bought as a sample from Mumbai's Loba Chemie Pvt. Ltd., Sodium hydrogen carbonate is a sample purchased from Merck Life Science Private Limited, Carbapol was a sample purchased from Balaji Drugs, and Super tab 11sd was a sample gifted from IMCD Pvt. Ltd., Mumbai, Samples of talc were purchased from Loba Chemie Private Limited in Mumbai. Magnesium stearate was purchased as a sample from Loba Chemie Pvt. Ltd., Mumbai. Hydrochloric acid was purchased From Merck Life Science Private Limited, Mumbai.

Table 1: Experimental Design by Box Behnken design.

Factors (Independent Variables)	Levels			
	Low	Medium	High	
	(- 1)	0	(+1)	
X1: Methocel K 100 M Premium(mg)	100	110	120	
X2: Cetyl Alcohol (or) Hexadechanol(mg)	20	25	30	
X3: Ethyl Cellulose(mg)	30	35	40	
Response (dependent variables)				
Constraints				
Optimization	**Lower limit**	**Upper limit**	**Predicted**	**Goal**
X1: Methocel K 100 M Premium (mg)	100	120	135.75	Range
X2: Cetylalchol (mg)	0	30	27.97	Range
X3: Ethyl cellulose (mg)	30	40	30	Range
Y_1: Floating lag time (sec)	8	19.9	13.95	Targeted
Y_2: Swelling index (%)	60.92	67.3	67.3	Range
Y_3: % drug release 1hr (%)	21.61	93.355	71.55	Minimize
Y_4: % drug release 2hr (%)	39.98	100	95.58	Minimize
Y_5: T_{100} (Time required to 100% drug release) (hr)	2	12	11.3479	Maximize

Preparation of Tablets

By utilizing different amounts of polymers Methocel K100, Ethylcellulose, Cetylalchol, Carbapol, and Super tab11sd along with sodium bicarbonate, floating tablets containing mirtazapine were created. Every powder was precisely weighed and put through an 80 screen. The remaining ingredients—aside from the magnesium stearate were then vigorously mixed for 15 min. Talc was added as a lubricant after the medication and other ingredients had been thoroughly combined, and the mixture was then stirred for a further 2-3 min. Using a tablet punch machine, the finished mixture was compacted into tablets with an average weight of 300 mg (Rotary Compression Machine).

Swelling index and Erosion studies

In terms of the percentage of weight the tablet acquired, the swelling was calculated. In a Petri dish with 50 mL of 0.1 N hydrochloric acid buffer, three tablets from each formulation were weighed and maintained there. The tablets were removed from the Petri dish after the designated amount of time, and any excess buffer was wiped with tissue paper before being weighed. Swelling index = $W_t - W_0/W_t \times 100$, where W_t = weight of time't' (swelling tablet), W_0 = Initial weight of tablet. For the sample used in swelling tests, matrix erosion investigations were conducted. The swelled tablets were dried at 60°C in a traditional oven until a steady weight was attained. An equation was used to compute the weight change caused by erosion in tablets. Erosion percentage = $W_i - W_d/W_i \times 100$, Where W_i and W_d are the initial weight and dried weight of the tablet respectively.

Evaluation of Tablets

In vitro buoyancy tests (floating lag time and total floating time), *in vitro* dissolution studies, hardness tests, friability test, drug content uniformity tests, and weight variation test were all performed on all produced tablets.

Weight variation test

Take 20 tablets, and then weigh each one separately. Make a weight comparison between the average and each tablet's weight. No more than two tablets may deviate from the % limit, and no tablet may diverge by more than twice the percentage limit.

Hardness test

The hardness of tablets is measured using a hardness tester made by Monsanto.

Test of Friability

10 tablets were chosen at random and put in the drum of a tablet friability test device (LAB INDIA FT1020) tablet friability tester following the IP standards.

Drug content uniformity

Each of the ten tablets was weighed and crushed separately. An amount of powder extracted in 100 mL of buffered 0.1N hydrochloric acid that weighs one tablet. A cellulose acetate membrane (0.45 m) was used to filter the fluid. After an appropriate dilution with a buffer containing 0.1N hydrochloric

Table 2: Physical Characteristics of Floating Mirtazapine Tablets.

Sl. No.	Formulation	Total Weight (mg)	Friability (%)	Hardness (Kg/cm²)	Drug content (%)
1	F1	298±0.2	0.42	5.2	99.96
2	F2	299± 1.5	0.46	5.6	99.98
3	F3	299± 1.5	0.46	5.6	99.98
4	F4	298± 1.9	0.45	5.7	99.95
5	F5	300± 1.9	0.52	6	99.98
6	F6	298± 1.5	0.57	5.9	99.97
7	F7	299± 1.9	0.58	6.3	99.98
8	F8	298± 1.5	0.60	6.8	99.99
9	F9	299± 1.8	0.62	6.4	99.96
10	F10	300± 1.6	0.65	5.4	99.97
11	F11	299± 2.3	0.69	6.6	99.98
12	F12	299± 1.5	0.46	5.6	99.98
13	F13	299± 1.9	0.67	6.1	99.98
14	F14	300± 2.7	0.61	5.9	99.97
15	F15	299± 2.2	0.56	5.2	99.98
16	Optimized	300± 2.1	0.68	6.2	99.99

acid, the drug content was assessed using UV spectroscopy on an ELICO double-beam SL 210 UV spectrophotometer.

In vitro Buoyancy studies (Floating lag time and Total floating time)

According to the approach provided, the *in vitro* buoyancy was calculated using the total floating time and the floating lag time. The tablets (n = 4) were dissolved in 900 mL of buffer containing 0.1 N hydrochloric acid at 37± 0.5°C and 50 rpm. The length of time needed for the tablets to float to the surface was calculated as floating lag time. The total floating time was calculated as the amount of time the tablet form stayed on the surface continuously.

In vitro dissolution studies

Using the USP dissolution testing device type II (paddle method) LAB INDIA DS 8000, the release of mirtazapine from floating tablets (n = 4) was assessed. At 37± 0.5°C and 50 rpm, the dissolution was carried out using 900 mL of 0.1 N hydrochloric acid buffers. At predefined intervals (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, up to 12 hr), a sample (5 mL) of the solution was collected from the dissolution system and replaced with fresh dissolution medium. Using a UV Spectrophotometer (ELICO Double Beam SL), the samples were examined for drug release using 0.1 N Hydrochloric acid buffers as a blank at a wavelength of 232 nm.

Data Analysis

To establish the individual and combined effects of the three elements involved, the data examined by the zero order, first order, Higuchi, and Peppas kinetic models and released parameters were subjected to Analysis of Variance (ANOVA) using Design Expert software.

RESULTS AND DISCUSSION

The standard calibration curve created to determine the drug concentration in samples was linear, with Y=0.012x+0.005 and R^2=0.9927 in the concentration range of 10 to 70 µg/mL.

Tablet properties

The greatest hardness was determined to be 6.9 and the hardness of all tablet formulas were found to be between 5.2 and 6.9 kg/cm^2. The tablets of mirtazapine have increased binding strength. To determine a tablet's physical strength, the friability test is helpful. All of the developed formulations adhere to the pharmacopeial criteria for a maximum weight loss of 1%. All manufactured tablets contain between 99.93 and 99.99% of the active ingredient shown in Table 2. The produced tablets meet all of the above-approved quality control criteria. The range of the floating lag time (sec) for the produced tablets, as shown in Table 3 was determined to be 8 to 19.9, and the total floating time (hr) was greater than 24. The tablets were studied for swelling behavior in a buffer of 0.1 N hydrochloric acid, and results showed that the swelling behavior had changed significantly in the sets F1 to F15.

In vitro Dissolution

In Figures 1 and 2, the produced gastroretentive tablets' *in vitro* dissolution profiles are shown. The Composition Maximum medication release times for F1 and F2 are 6 hr and 4.5 hr,

Table 3: Dissolution parameters of Floating Mirtazapine tablets formulations F1- Optimized.

Formulation	Floating lag time (sec)	Total floating time (hr)	Swelling index (%)	% Drug release 1 hr	% Drug release 2 hr	T_{50} (hr)	T_{100} (hr)
F1	11.24	>24	66.13	32.954	56.481	3	6
F2	8.0	>24	62.67	42.0044	50.2075	2.25	4.5
F3	8.0	>24	62.67	42.0044	50.2075	2.25	4.5
F4	14.9	>24	57.3	50.0481	65.1793	1.75	3.5
F5	14.5	>24	62.92	66.3016	83.1505	2	4
F6	17.2	>24	62.625	21.6177	39.9828	2.25	4.5
F7	11.0	>24	63.8	77.3366	90.9955	1.5	3
F8	10.23	>24	63.01	42.2612	59.9205	3	6
F9	9.9	>24	66.36	41.5391	52.4171	3.25	6.5
F10	9.0	>24	65.81	80.1356	92.4235	1.75	3.5
F11	11.0	>24	60.92	77.071	85.1453	2.5	5
F12	8.0	>24	62.67	42.0044	50.2075	2.25	4.5
F13	14.0	>24	62.87	76.6589	88.33	1.5	3
F14	15.0	>24	62.02	84.1861	92.6697	2	4
F15	19.9	>24	62.87	93.3559	100	1	2
Optimized	10.48	>24	65.17	31.856	34.372	6	12

respectively. Formulation F3 has a 4.5 hr maximum (100%) drug release, Formulation F4 has a 3.5 hr maximum (100%) drug release, Formulation F5 has a 4 hr maximum (100%) drug release, and Formulation F6 has a 4.5 hr maximum (100%) drug release. Formulation F7 maximum (100%) drug release is 3 hr, Formulation F8 maximum (100%) drug release is 6 hr, Formulation F9 maximum (100%) drug release is 6.5 hr, Formulation F10 maximum (100%) drug release is 3.5 hr, Formulation F11 maximum (100%) drug release is 5 hr, Formulation F12 maximum (100%) drug release is 4.5 hr, Formulation F13 maximum (100%) drug release is 3 hr, Formulation F14 maximum (100%) drug release is 4 hr and F15 maximum (100%) drug release 2 hr. The list below illustrates the

Table 4: Correlation Co-efficient (r) of Formulation F1 to Optimized Formulation.

	Correlation Co-efficient (r)				
Formulation	**Zero-order**	**First order**	**Higuchi**	**Peppas**	**'n' (diffusion exponent)**
F1	0.9698	0.9327	0.9919	0.6346	0.3741
F2	0.7589	0.5479	0.8306	0.6095	0.4747
F3	0.7589	0.5479	0.8306	0.6095	0.4747
F4	0.8274	0.5847	0.951	0.4151	0.0461
F5	0.8714	0.9849	0.9746	0.4768	0.023
F6	0.9091	0.6653	0.8755	0.5875	0.7591
F7	0.8553	0.9586	0.9694	0.5876	0.223
F8	0.5529	0.2797	0.6534	0.3282	0.588
F9	0.8716	0.7854	0.9077	0.5042	0.196
F10	0.796	0.9707	0.9383	0.5789	0.24
F11	0.753	0.9368	0.9028	0.5627	0.065
F12	0.7589	0.5479	0.8306	0.6095	0.4747
F13	0.8619	0.9664	0.9568	0.3699	0.189
F14	0.7508	0.9735	0.9088	0.5632	0.1692
F15	0.8716	0.9146	0.3945	0.5016	0.924
Optimized	0.912	0.705	0.905	0.576	0.864

Table 5: Release Rate constant values of F1 to Optimized.

Formulation	Zero order (K_0)	First order (K_1)	Higuchi (K_H)	Peppas (K_P)
F1	12.345	0.265	22.362	0.275
F2	9.064	0.274	12.841	0.481
F3	9.064	0.274	12.841	0.481
F4	5.237	0.141	6.429	0.772
F5	5.139	0.585	15.389	0.177
F6	9.416	0.075	20.862	0.683
F7	8.850	0.799	26.497	0.278
F8	3.505	0.232	21.108	0.265
F9	2.925	0.161	25.811	0.898
F10	4.824	0.492	19.1	0.291
F11	8.596	0.345	14.442	0.607
F12	9.064	0.274	12.841	0.481
F13	15.507	0.801	43.343	0.227
F14	6.874	0.384	17.594	0.316
F15	21.803	0.519	10.423	0.379
Optimized	7.634	0.161	36.449	0.431

Table 6: Statistical Parameters of various dependent variables.

Parameter	Y_1 Floating lag time (sec)	Y_2 Swelling index (%)	Y_3 % drug release 1 hr (%)	Y_4 % drug release 2 hr (%)	Y_5 (T_{100}) Time required for 100% drug release (hr)
Std.DEV	0.15	0.95	11.08	9.21	0.68
Mean	2.46	63.52	57.93	70.47	4.33
C.V%	6.19	1.49	19.12	13.07	15.71
PRESS	1.84	43.57	9815.95	6781.57	19.40
-2 Loglikelihood	30.46	24.43	98.24	93.69	21.61
R^2	0.9028	0.9170	0.9112	0.9269	0.8262
Adj R^2	0.7278	0.7677	0.7512	0.7952	0.6958
Pred R^2	0.5552	0.1927	0.4215	0.1701	0.0906
Adeq precision	6.031	7.107	7.461	7.742	8.869
BIC	-3.38	51.51	125.32	119.77	40.56
AICc	44.54	99.43	173.24	167.69	61.61

Table 7: Analyses of Variance (ANOVA) of Floating lag time (sec) (Y1).

Source	Sum of Squares	d_f	Mean Square	F Value	*p*-value Prob > F	Remark
Model	1.07	9	0.12	5.16	0.0427	Significant
A- Methocel K 100 M	0.058	1	0.058	2.52	0.1735	
B- Hexadechanol	7.002E-004	1	7.002E-004	0.030	8.69E-01	
C- Et. Cellulose	0.30	1	0.30	13.10	0.0152	
AB	0.32	1	0.32	14.09	0.0132	
AC	0.067	1	0.067	2.93	0.1478	
BC	0.017	1	0.017	0.74	0.4288	
A^2	0.092	1	0.092	4.00	0.1019	
B^2	0.32	1	0.32	13.68	0.0140	
C^2	0.24	1	0.24	10.33	0.0236	
Residual	0.12	5	0.023			
Lack of Fit	0.12	3	0.038			
Pure Error	0.000	2	0.000			
Cor Total	1.19	14				

increasing order of medication dissolution for various floating formulations.

F9>F8=F1>F11>F12=F6=F3=F2>F14=F5>F10=F4>F13=F7>F15

Drug release kinetics

To elucidate the mechanism of drug release from the floating tablets, the drug release kinetics was applied to the data obtained from *in vitro* drug release investigations. Models like the zero order, first order, Higuchi, and Korsmeyer Peppas models are shown in Tables 4, 5 and Figures 3-6. It was noticed that the formulation's R^2 was higher when it was fitted to a zero-order equation, indicating that the formulations F1, F2, F3, F4, F6, F8, F9, and F12 release zero orders. In F5, F7, F10, F11, F13, F14, and F15, the high R^2 first order is seen. The release exponent formulations F1, F2, F3, F4, F5, F7, F9, F10, F11, F12, F13, and F14 are proven to be Fickain diffusion, while the release exponent formulations F6, F8, and F15 are noticed to be non-Fickain diffusion.

Comparative studies

The comparative investigations using market tablets, (Mirtafresh 15MD) F9 and Optimized. The commercial tablets discharge their entire contents in 20 min. The F9 provides 100% drug release in 6.5 hr and 100% drug release at 100% in 12 hr as optimized. So that the dissolution profile data given in Figure 7 for market tablets with F9 and optimized were not identical.

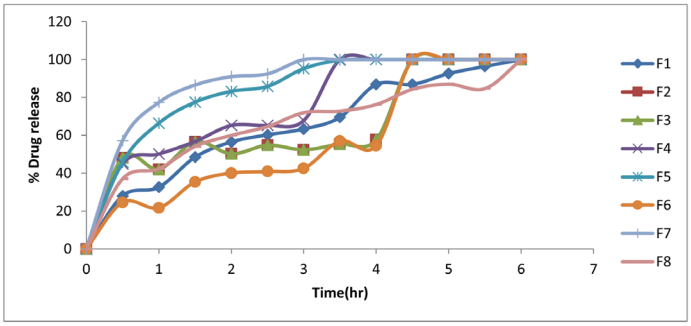

Figure 1: Mean dissolution profile of Mirtazapine Formulation F1 to F8.

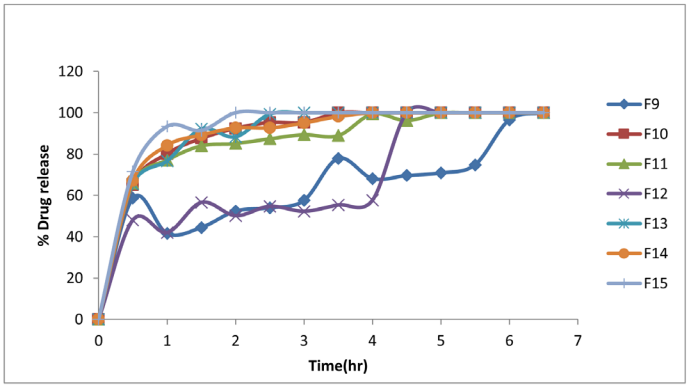

Figure 2: Mean dissolution profile of Mirtazapine Formulation F9 to F15.

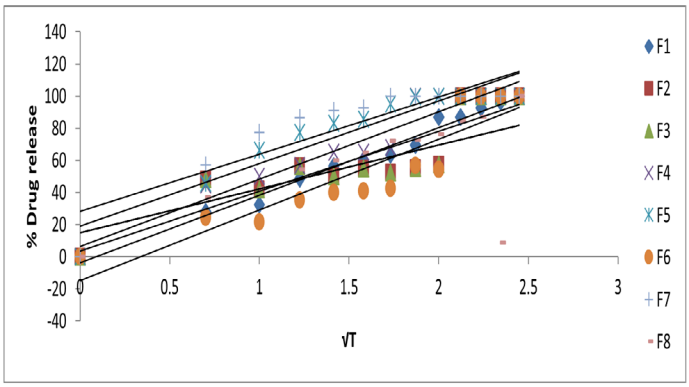

Figure 3: Higuchi dissolution profile of Mirtazapine Formulation F1 to F8.

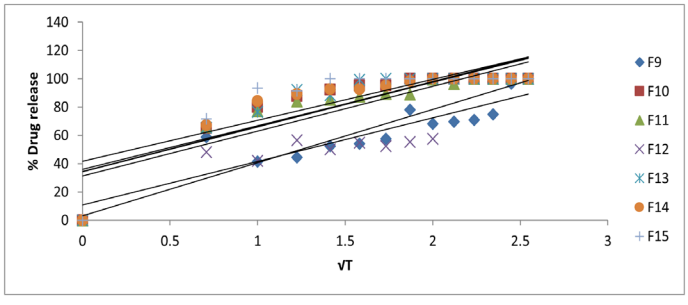

Figure 4: Higuchi dissolution profile of Mirtazapine Formulation F9 to F15.

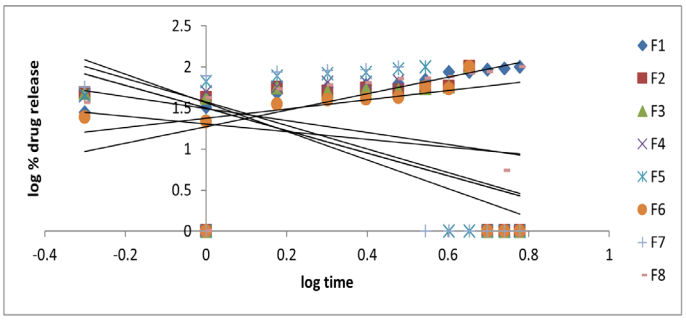

Figure 5: Peppas dissolution profile of Mirtazapine Formulation F1 to F8.

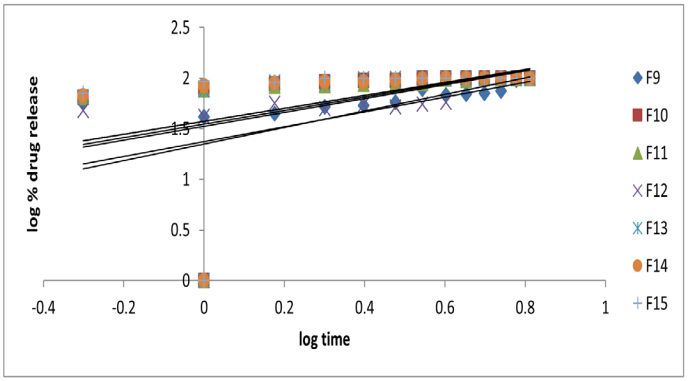

Figure 6: Peppas dissolution profile of Mirtazapine Formulation F9 to F15.

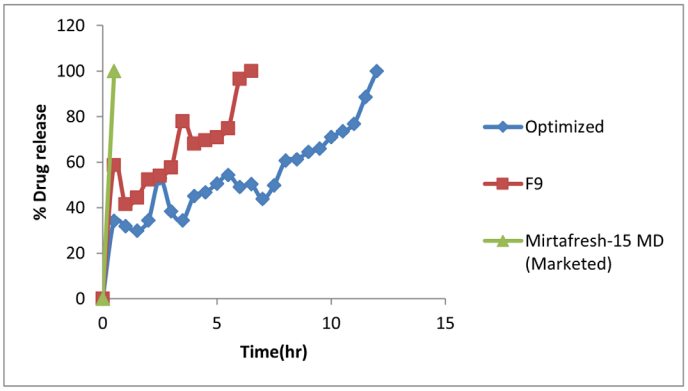

Figure 7: Comparison of Marketed with F9 and Optimized Formulation.

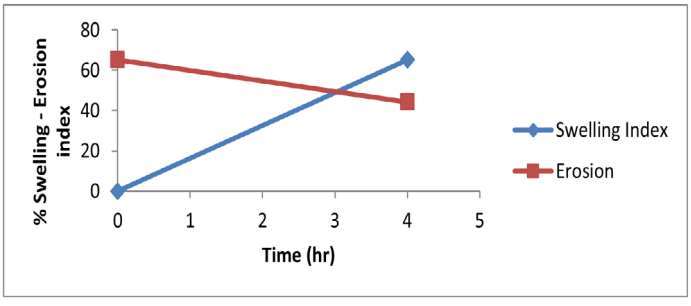

Figure 8: Swelling index and Erosion of Optimized Formulation.

Table 8: Analysis of Variance (ANOVA) Swelling index (%) (Y2).

Source	Sum of Squares	d_f	Mean Square	F Value	*p*-value Prob > F	Remark
Model	49.49	9	5.5	6.14	0.0299	Significant
A- Methocel K 100 M	0.27	1	0.27	0.30	0.6079	
B- Hexadechanol	0.29	1	0.29	0.32	0.5947	
C- Et. Cellulose	1.12	1	1.12	1.25	0.3141	
AB	10.34	1	10.34	11.54	0.0193	
AC	1.56	1	1.56	1.74	0.2447	
BC	18.02	1	18.02	20.12	0.0065	
A^2	0.14	1	0.14	0.15	0.7103	
B^2	17.82	1	17.82	19.91	0.0066	
C^2	0.35	1	0.35	0.39	0.5583	
Residual	4.48	5	0.90			
Lack of Fit	2.44	3	0.81	0.8	0.5988	Not Significant
Pure Error	2.04	2	1.02			
Cor Total	53.96	14				

Table 9: Analysis of Variance (ANOVA) % drug release 1hr (Y3).

Source	Sum of Squares	d_f	Mean square	F Value	p-value Prob > F	Remark
Model	629.91	9	699.10	5.70	0.0349	Significant
A- Methocel K 100 M	2659.39	1	2659.39	21.67	0.0056	
B- Hexadechanol	58.16	1	58.16	0.47	0.5218	
C- Et. Cellulose	26.43	1	26.43	0.22	0.6621	
AB	584.19	1	584.19	4.76	0.0809	
AC	104.14	1	104.14	0.85	0.3992	
BC	1154.30	1	1154.30	9.41	0.0279	
A^2	684.81	1	684.81	5.58	0.0646	
B^2	1104.91	1	1104.91	9.01	0.0301	
C^2	4.04	1	4.04	0.033	0.8631	
Residual	613.50	5	122.70			
Lack of Fit	613.50	3	204.50			
pure Error	0.000	2	0.000			
Cor Total	6905.41	14				

Swelling and erosion

For the produced tablets shown in Figures 8 and 9, the gravimetric swelling and erosion patterns were dissimilar from one another. Only until 2 hr after taking the tablet does it swell gravimetrically, and then the optimized formula-driven erosion begins. Only the lower and lateral portions of the floating tablets constricted the dissolving media during the test. Due to the HPMC's strong propensity to expand axially, the tablet was able to maintain its enlarged thickness even as erosion occurred.

Optimization

After fitting these data, the design expert utilized it to calculate an appropriate model equation.[34,35] Five variables were chosen for statistical optimization and model fitting, including Y1 (floating lag time (sec)), Y2 (swelling index (%)), Y3 (% drug release in 1 hr (%), Y4 (% drug release in 2 hr (%)), and Y5 (T100 Time required to 100% drug release (hr's)). The statistical parameter summary is shown in Table 6, including R^2, PRESS, and Std. Dev, Mean, C.V% Adj. R-squared, Pred. R-squared, Adeq. Precision, BIC, AIC c, -2 log-likelihood, F values, and P values were calculated using Design Expert software.

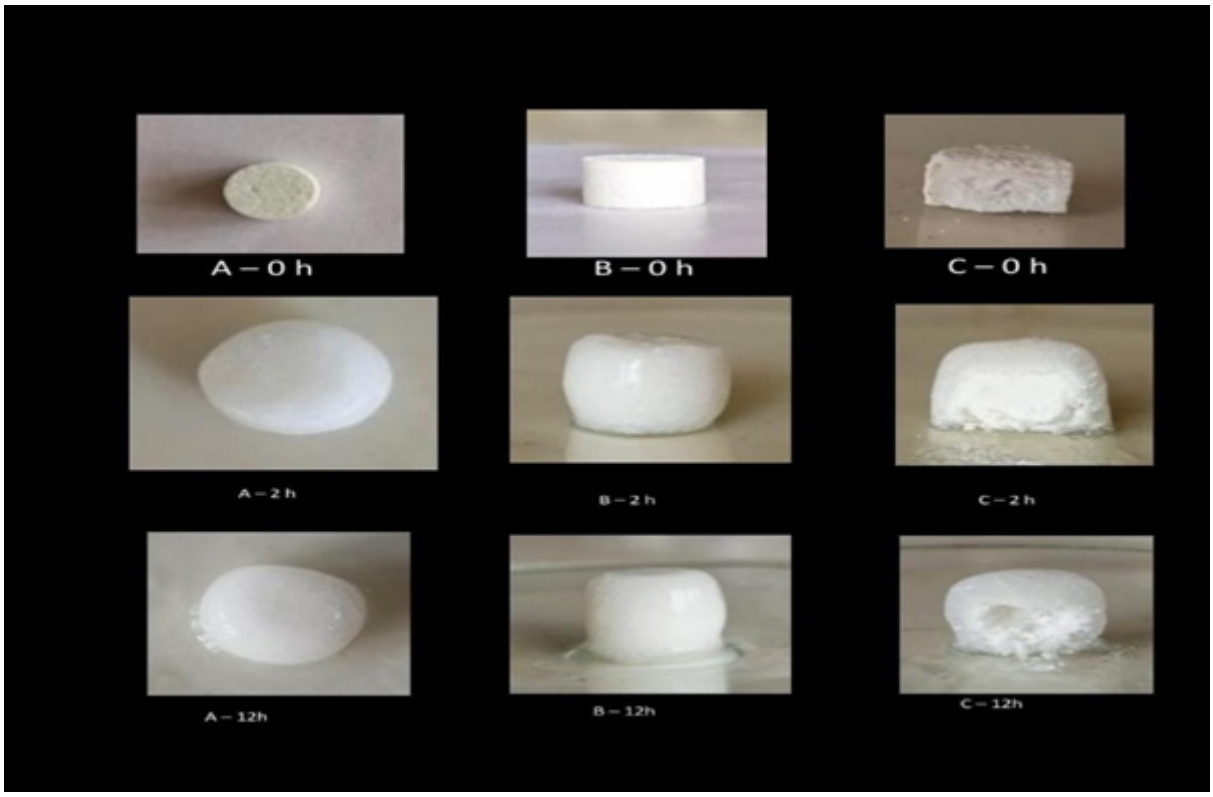

Figure 9: Swelling index – Erosion Studies of Optimized formulation A – 0 hr: (Top view), B – 0 hr: (Lateral view), C – 0 hr: (Cross section); A – 2 hr: (Top view), B – 2 hr: (Lateral view), C – 2 hr: (Cross section); A – 12 hr: (Top view), B – 12 hr: (Lateral view), C – 12 hr: (Cross section).

Table 10: Analysis of Variance (ANOVA) % drug release 2 hr (Y4).

Source	Sum of Squares	d_f	Mean square	F Value	*p*-value Prob > F	Remark
Model	5371.87	9	596.87	7.04	0.0224	Significant
A- Methocel K 100 M	2053.83	1	2053.83	24.23	0.0044	
B- Hexadechanol	96.55	1	96.55	1.14	0.3347	
C- Et. Cellulose	7.20	1	7.20	0.085	0.7824	
AB	478.87	1	478.87	5.65	0.0634	
AC	49.63	1	49.63	0.59	0.4787	
BC	733.33	1	733.33	8.65	0.0322	
A2	706.53	1	706.53	8.33	0.0343	
B2	1359.79	1	1359.79	16.04	0.0103	
C2	91.37	1	91.37	1.08	0.3468	
Residual	423.85	5	84.77			

$$Y1= b_0+ b_1 X_1+ b_2 X_2 + b_3 X_3 + b_{12} X_1 X_2 + b_{13} X_1 X_3 + b_{23} X_2 X_3 + b_{11} X^2_1 + b_{22} X^2_2 + b_{33} X^2_3$$

Where Y_1 is the measured response associated with each Factorial level combination, b_0 to b_{33} is the estimated regression coefficient computed from the observed experimental values of Y_1, and X_1, X_2, and X_3 are the coded levels of the independent variables. The interaction and quadratic terms denoted by the terms X_1, X_2, X_3, and X2i I = 1, 2, or 3), are shown separately. **a) Response of floating lag time (sec) (Y1)**; A model with p <0.0427 as the statistically significant result. Table 7 and Figure 10 display the analysis of variance for the floating lag time. The model equation explains floating lag time = + 36.55807 – 0.29476 X1 – 0.044187 X2 -1.04134 X3 – 5.70009 E – 003 X1 X2 + 2.59792 E – 003 X1 X3 + 2.61359 E –003 X2 X3 + 1.58094 E – 003 $X^2$1 + 0.011694 $X^2$2 + 0.010159 $X^2$3. The decreased level of X1, X2, and X3 decrease the

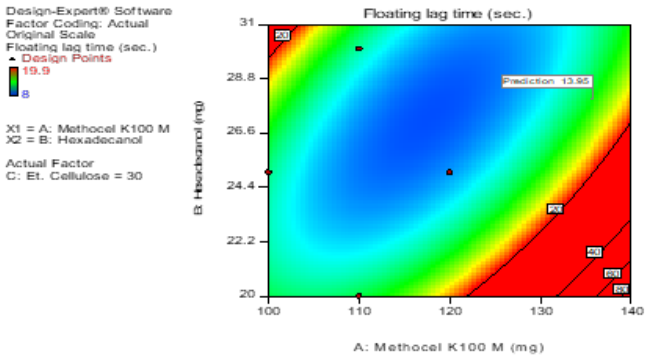

Figure 10: Contour plot of Floating lag time (sec).

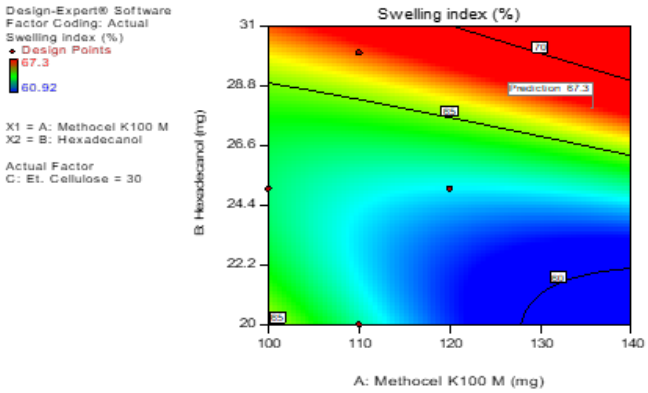

Figure 11: Contour plot of a swelling index (%).

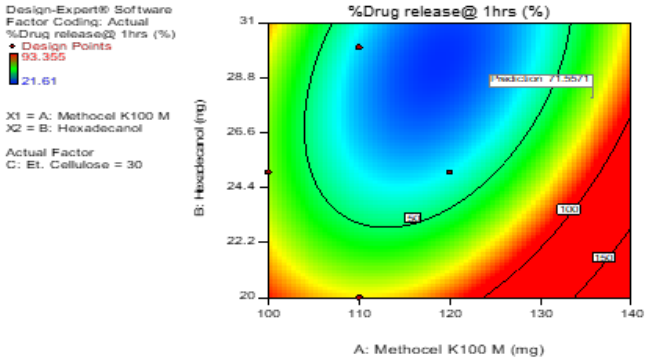

Figure 12: Contour plot of % Drug release 1 hr (%).

floating lag time, as indicated by the negative sign for X1, X2, and X3. The floating lag time R-square value of 0.9028 shows a strong correlation between the independent and dependent variables. The 'F' values for Floating lag time were found to be of model 5.16 and independent variable X1 =2.52 and other statistical parameters such as Adj. R2 0.9028 PRESS = 1.84, Adeq precision = 6.013, BIC = -3.38, AICC = 44.54, -2 log likelihood = 30.46, Mean = 2.46, Std. DEV= 0.15, C.V% = 6.19, pred. R square = 0.5552. **b) Response of swelling index (%) (Y2);** Swelling index analysis variance a model with a *p*-value of $p< 0.0299$ that is statistically

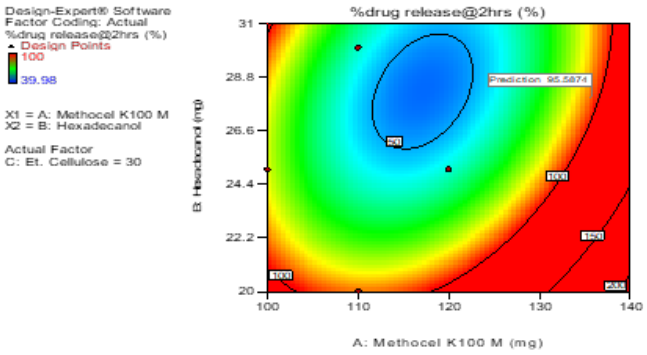

Figure 13: Contour plot of % drug release 2 hr (%).

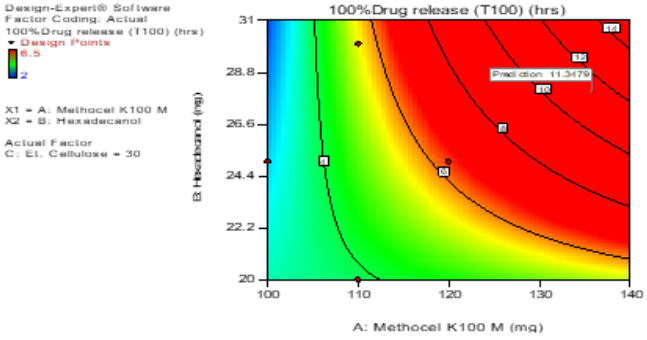

Figure 14: Contour plot of 100% drug release (hr).

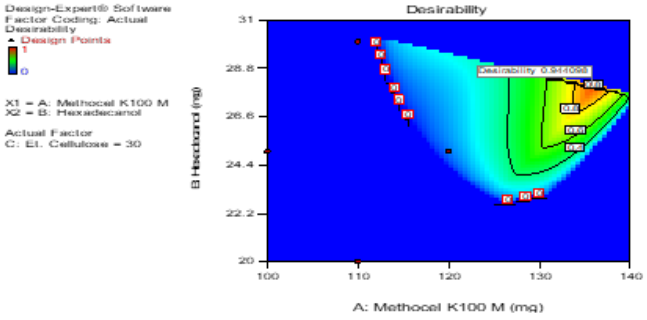

Figure 15: Counter plot of Desirability.

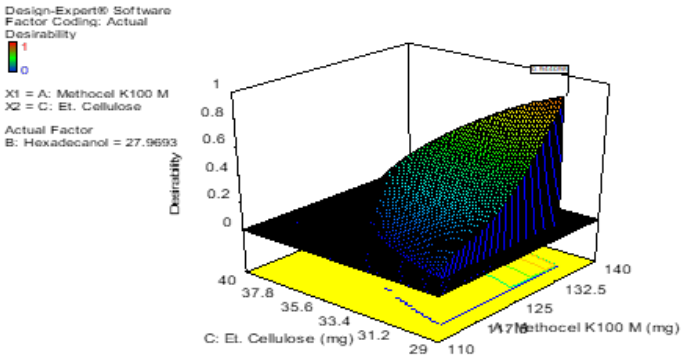

Figure 16: 3D Surface plot of Desirability.

Table 11: Analysis of Variance (ANOVA) 100% Drug release (T100) (Y5).

Source	Sum of Squares	d_f	Mean Square	F *p*-value Prob > F		Remark
Model	17.62	6	2.94	6.34	0.0102	Significant
A- Methocel K 100 M	5.28	1	5.28	11.39	0.0097	
B- Hexadechanol	2.00	1	2.00	3.31	0.0714	
C- Et. Cellulose	0.78	1	0.78	1.69	0.2304	
AB	6.25	1	6.25	13.48	0.0063	
AC	3.06	1	3.06	6.61	0.0331	
BC	0.25	1	0.25	0.54	0.4837	
Residual	3.71	8	0.46			
Lack of Fit	3.71	6	0.62			
Pure Error	0.000	2	0.000			
Cor Total	21.33	14				

Table 12: Optimized Formulation with Predicted and Experimental values.

Independent variable	X_1 (Methocel K100 M)	X_2 (Hexadechanol/or Cetyl alcohol)	X_3 (Ethyl cellulose)
Composition (mg)	135.75	27.96	30
Response	Floating lag time (sec)	Swelling index (%)	T_{100} (hr)
Predicted value	13.95	67.3	11.3479
Experimental value	10.48	65.171	12
Predicted error (%)	-33.110	-3.266	5.4341

significant shown in Table 8 and Figure 11. The parameter Swelling index can be explained using the model equation. The Swelling index = + 219.26542 – 1.64797 X1 – 4.99733 X2– 0.18832 X3 + 0.032150 X1X2 + 0.012470 X1X3 – 0.084900 X1X2 + 1.93667 E – 003 $X^2$1 +0.087887 $X^2$2 + 0.012347$X^2$3. The decreased level of X1, X2, and X3 decreases the swelling index, as indicated by the negative sign for X1, X2, and X3. Swelling index R square values of 0.9170 show the great correlation between independent and dependent variables. **c) Response of % drug release 1 hr (%) (Y3)**; A model with p< 0.0349 as the statistically significant result. In Table 9 and Figure 12, the analysis of variation % drug release throughout 1 hr is presented. The model equation can explain the parameter% drug release 1 hr. = +1809.38250– 22.17025 X1 – 32.33225 X2 – 2.46900 X3 + 0.24170 X1X2 – 0.10205 X1X3 + 0.67950 X2X3 + 0.13619 $X^2$1 + 0.69195 $X^2$2 – 0.041850 $X^2$3. The negative sign for X1, X2, and X3 indicates that the decreased level of X1, X2, and X3 decreases % the drug release by 1 hr. The R^2 values 0.9112 for % drug release 1 hr indicating a good correlation between independent and dependent variables. **d) Response of % drug release 2 hr (%) (Y4);** A model having a result that is statistically significant at p< 0.0224 is shown in Table 10 and Figure 13. The 2 hr drug release parameter% can be explained by the model equation. % drug release 2 hr= + 2000248. 65250 – 24.09838 X1 – 33.96050 X2 – 19.90885 X3 - 0.21883 X1 X2 - 0.070450 X1X3+ 0.54160 X2 X3 + 0.13833 $X^2$1 + 0.76762 $X^2$2 + 0.19898 $X^2$3. The negative sign for X1, X2, and X3 denotes a decreased level of X1, X2, and X3 and a decreased percentage of 2 hr drug release. The R-square for the percent medication release is 0.9269. 2 hr shows that the independent and dependent variables have a strong relation. **e) Response of T100 (Time required for 100% drug release) (Y5);** A model with *p* <0.0102 as the statistically significant result. The time needed for 100% drug release (in hours), as reported in Table 11 and Figure 14, was the subject of an analysis of variance. The model equation can be used to define the parameter T100, or "Time necessary for 100% drug release" (in hours) = - 12.29167 + 0.068750 X1 –2.30000 X2 +2.11250 X3 + 0.025000 X1 X2 - 0.017500 X1 X3 – 0.010000 X2 X3. The increase in X1, X3, and their respective levels results in an increase in T100 (Time required to 100% Drug Release), whereas the drop in X2 levels results in a decrease in T100 (Time required to 100% Drug Release). The R square values 0.8262 for indicating a good correlation between independent and dependent variables. The Optimize formulas can directly generate the desirability function response surface plots from the greater desirability value, which shows the more acceptability of the formulation. The optimum formula's desirability concern was found to be higher (0.94407), demonstrating the formulation's appropriateness. Every answer is optimized with the desired

aim and adjustment point. The following variables were set to be minimized: Y1 (Floating lag time (sec)), Y2 (Swelling index %), Y3 (% drug release1 hr), Y4 (% drug release 2 hr), and Y5 (T100 time necessary for 100% drug release) set to maximized. The improved formulation's three independent variables were optimized per the objectives of answers by using a desirability function, as shown in Figures 15 and 16 with a corresponding desirability function of 0.94407; the X1, X2, and X3 were Drug: Methocel K100 M (135.75 mg) (X1), Hexadecanol (or) Cetyl alcohol (27.969 mg), and Ethyl cellulose (30.0 mg), respectively. The prepared optimized formulation underwent statistical optimization to satisfy all the dissolution parameters to validate the theoretical prediction. The *in vitro* predicted as percentage drug release Y1 (Floating lag time (sec)) was found to be 13.95, Y2 (Swelling index %) was found to be 67.3, Y3 (% drug release1 hr) was found to be 71.55%, Y4 (% drug release 2 hr) was found to be 95.58%, and Y5 (T100 time required for 100% drug release) was found to be 11.3479 hr. Table 12 shows the observational data and model prediction. The calculated relative errors between the experimental and predicted values for each response were found to be 33.110, -3.266, -39.7011, -61.2124, and 5.4341, respectively. These values confirmed the model's predictability and validity because the experimental and predicted values agreed with one another. The most effective recipe produced It was discovered that Y_1 (Floating lag time (sec)) was 10.48, Y_2 (Swelling index (%)) was 65.171, Y_3 (% drug release 1 hr (%)) was 31.856, Y_4 (% drug release 2 hr (%)) was 34.372, and Y_5 (T100 time required for 100% drug release (hr's) was 12 accordingly. The drug release from the best formulation follows a zero-order kinetic model and non-fickain diffusion (n=0.86). The % prediction error was used to assess the predictability and accuracy of the value using a comparison between the expected value and experimental value. A gastroretentive floating continuous release of mirtazapine tablets was made possible by the enhanced formulation.

CONCLUSION

The current study improves Box Behnken Design's (BBD) successfully designed and created mirtazapine floating formulation. The manufactured tablets' quality control standards are compliant with IP's official tablet specifications. The F9 Formulation, which contains HPMC K100M 120 (mg), cetyl alcohol (30 mg), and ethyl cellulose (20 mg), has a noticeably higher dissolution performance and releases all of the medicine within 6.5 hr, with a Fickain diffusion mechanism, the F9 Formulation follows zero order. F9 and Market tablets have different dissolution properties when compared to the Optimize formulation. In the marketed (Mirtafresh 15-MD) tablet, 100% of the medicine is released in 20 min, 100% in the F9 formulation in 6.5 hr, and 100% in the optimized formulation in 12 hr. The obtained optimized formulation underwent statistical optimization to ensure that it satisfied all of the dissolution criteria to validate the theoretical prediction. It was discovered that the Optimized formula's 100% drug release time (in hr) was 12 in this case. The drug release from the improved formulation adheres to non-fickain diffusion and the zero-order kinetic model (n = 0.86). The appropriate release profile for the gastroretentive floating sustained release of mirtazapine tablets is demonstrated by the optimized formulation.

ACKNOWLEDGEMENT

The author appreciates Sri Venkateswara College of Pharmacy, Etcherla, Srikakulam for providing research facilities, my sincere thankful to my Guruji Late. Prof. Dr. KPR. Chowdary for giving me valuable advice regarding statistical designs and principles, P.V. Bhaskar-developed design software (design expert), and Methocel K100M, a free sample from Colorcon Asia Pvt. Ltd., Verna, Industrial Estate, and Super Tab SD were samples provided by IMCD Pvt. Ltd., in Mumbai.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BCS: Biopharmaceutical classification system; **SLN:** Solid lipid nanoparticles; **SSRI:** Serotonin reuptake inhibitors; **ODTs:** Orally disintegrating tablets; **PLGA:** Poly Lactic-co-Glycolic Acid; **HBS:** Hydro dynamically balanced systems; **FDDS:** Floating drug delivery systems; **CV:** Coefficient of variation; **R^2:** Coefficient of determination; **Adjusted R^2:** Adjusted coefficient of determination; **Pred. R^2:** Predicted coefficient of determination; **ANOVA:** Analysis of variance; **BBD:** Box Behnken Design's.

SUMMARY

The performance of gastro-responsive floating tablets of mirtazapine was assessed using the main effect, interaction effects, and quadratic of the formulation ingredient using the BBD. Because it required applying design that exhibited 15 trial runs and centre points duplicated (n=3), the BBD was chosen. The acquired improved formulation underwent statistical optimization to make sure it complied with all the dissolution requirements to support the theoretical prediction. In this instance, the 100% drug release time (measured in hr) for the Optimized recipe was found to be 12. Non-fickain diffusion and the zero-order kinetic model are both followed by the drug release from the optimized formulation. The improved formulation shows the suitable release profile for the gastroretentive floating continuous release of mirtazapine tablets.

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Cite this article: Ramarao CT, Laxmi SB. Floating Drug Delivery of Sustained Release Antidepressant Mirtazapine Tablets by Box-Behnken Design: Formulation and Optimization. Indian J of Pharmaceutical Education and Research. 2024;58(1s):s113-s125.