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Invitro Evaluation Of Fluvoxamine Maleate Fast Dissolving Oral Films By Design Of Experiment

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ABSTRACT

Fluvoxamine is an antidepressant drug belonging to the class serotonin re uptake inhibitor(SRI),exhibits maximum absorption through the oral route of administration. The objective of current research is to formulate mouth dissolving fluvoxamine films by employing super disintegrants. The central composite design employed to examine the effects of amount of hydroxyl propyl methylcellulose (HPMC) E15, eudragitRL100 and polyethyleneglycol (PEG4000) on response variables such as tensile strength, disintegration time and cumulative% drug release. Fluvoxamine mouth dissolving films are formulated by using solvent-casting method using HPMCE15, EudragitRL100, and PEG4000. CCD is employed to optimize the effective dosage of formulation super disintegrants. 27 formulations were prepared according to CCD and evaluated for physic-chemical parameters and invitro dissolution studies. The formulation FF15 were observed with a maximum tensile strength of 55.63±1.37mg, least disintegration time of 29±1.85 seconds, and highest drug release of 98.29±1.87% and is chosen as an optimal formulation with maximum content uniformity and folding endurance. It is evident from the above results that the developed formulation can be an innovative dosage form to improve the drug delivery, quick on set of action, as well as, improve patient compliance in the effective management of depression.

Keywords: Antidepressant, Central composite design, Design of Experiment, Fluvoxamine, Mouth dissolving films.

Introduction

Drug delivery systems aim to efficiently deliver the drug to desired parts of the body, during which the onset time, therapeutic efficiency, and patient compliance are neglected. Mouth dissolving films are one such alternative for oral administrative routes that pose convenient dosage, facilitate the rapid onset of drug action, bypass first-pass metabolism, and receive the highest patient compliance. These systems are particularly appropriate for pediatric and elderly patients[1] are novel drug delivery systems that rapidly disintegrate and dissolve in saliva within few seconds even in the absence of water, thus avoid facilitating rapid drug absorption. The oral cavity offers direct entry of the drug into the systemic distribution, thus the hepatic first-pass effect, and can terminate delivery whenever required. Most of the excipients used

in the design of mouth dissolving films are amorphous, enhancing the bioavailability of the drug entrapped[2.] Fluvoxamine is an antidepressant

that belongs to selective serotonin re uptake inhibitor (SSRI), mainly used to treat social phobia or obsessive-compulsive disorders. Fluvoxamine is absorbed to maximum post oral administration, which is quickly and evenly distributed throughout the body. The drug is eliminated with a mean half-life of 15hours, with arrange from 9to28 hours [3.] Design of experiment (DoE) is a structured tool for establishing the relationships amongst independent variables affecting one or more dependent variables through mathematical models. In this approach, the restricted input factors are methodically varied to establish their effects on the output responses that determine the most important input factors, leading to optimized output responses and the elucidation of interactions between input factors. The CCD is frequently used optimization designs that employ 5 levels of each input factor with a reduced experiment number compared to three-level full factorial design[4].

Materials and Methods

Fluvoxamine maleate is generously gifted by Hetero Drugs Ltd, Hyderabad, India. All the formulation excipients HPMCE5, eudragitRL100, polyethyleneglycol (PEG)4000, sucralose, aspartame purchased from Signet Chemicals Corporation Pvt. Ltd. Mumbai, India.

Preparation of Fluvoxamine Mouth Dissolving Film

Fluvoxamine mouth dissolving formulation prepared by employing solvent casting method. 27formulations were made, which was shown in Table 1. Initially ,the polymers soaked in water over night for attaining uniformity in dispersion. Plasticizer added to these solutions and stirred continuously for 4-5hours, leaving it un disturbed for 1-hour to obtain aqueous layer I. The fluvoxamine, lactose, and aspartame dissolved in distilled water to obtain aqueous layer II. The two aqueous layers mixed for 1-hour, followed by sonication for 30 min. The obtained mixture is layered on petri dish with an area of 63.642cm^{2}and dried at 50–55°C for 24 hours. The obtained films peeled off and cut to2×2cm^{2}size [5].

RESPONSE SURFACE METHODOLOGY

About 27 FDOFs (FF1-FF27) were formulated and optimized by 3^3 response surface method(RSM) with 3 variables at 3 different levels of polymers by using Design of experiment(DoE) software[6].
Study type: Response surface
Design type: central composite
Design mode: quadratic

EVALUATION OF FDOF FILMS[7,8,9,10]

Thickness uniformity

The digital Vernier Calliper(0.01mm least count) was used to analyze patch thickness. The measurement done at various tactical points of FDF and averaged.

Weight uniformity

Weight variation evaluated by separately weighing chosen films and values averaged.

Drug content uniformity[11]

The films dissolved in PB with continuous stirring for an hour. The drug concentration analyzed with the help of VU spectrophotometer at $\lambda_{max}$of 271 nm.

Folding endurance

The films subjected to repeated folding at one single point till it breaks and the number noted.

Surface pH of film

The FDOF was dissolved in 2 ml of PB and pH measured using pH meter.

Tensile strength

The FDOF (2 × 2 cm^2) with no air bubbles were fixed between 2 clamps that are 3 cm apart. A cardboard was fixed on clamp surface with the help of double sided tape. The strips were pulled by

Table 1 : Formulation of fluvoxamine mouth dissolving films

F.NO	Fluvoxamine(mg)	HPMC E5 (mg)	Eudragit RL100 (mg)	PEG 4000 (mg)	Lactose (mg)	Aspartame (mg)	Flavor (ml)	Water (ml)
FF1	25	20	30	25	10	04	0.1	10
FF2	25	30	30	25	10	04	0.1	10
FF3	25	20	40	25	10	04	0.1	10
FF4	25	30	40	25	10	04	0.1	10
FF5	25	20	30	35	10	04	0.1	10
FF6	25	30	30	35	10	04	0.1	10
FF7	25	20	40	35	10	04	0.1	10
FF8	25	30	40	35	10	04	0.1	10
FF9	25	20	35	30	10	04	0.1	10
FF10	25	30	35	30	10	04	0.1	10
FF11	25	25	30	30	10	04	0.1	10
FF12	25	25	40	30	10	04	0.1	10
FF13	25	25	35	25	10	04	0.1	10
FF14	25	25	35	35	10	04	0.1	10
FF15	25	30	40	30	10	04	0.1	10
FF16	25	20	35	25	10	04	0.1	10
FF17	25	25	35	30	10	04	0.1	10
FF18	25	20	30	25	10	04	0.1	10
FF19	25	25	40	25	10	04	0.1	10
FF20	25	20	35	25	10	04	0.1	10
FF21	25	25	35	30	10	04	0.1	10
FF22	25	25	35	25	10	04	0.1	10
FF23	25	30	35	35	10	04	0.1	10
FF24	25	20	30	30	10	04	0.1	10
FF25	25	25	35	35	10	04	0.1	10
FF26	25	20	40	25	10	04	0.1	10
FF27	25	20	35	35	10	04	0.1	10

placing weights in pan till it breaks and the force applied was noted. The force was measured when the films breaks.

Disintegration Time (DT)

The films (2X2 cm^2) were rested on Petri dish containing 10 ml PHB and the taken for the film to break was recorded.

Cumulative Percentage Drug Release (CDR)

Dissolution profile of fast dissolving films of Fluvoxamine was carried out in a beaker containing 30ml of the stimulated salivary fluid pH (6.8) as a dissolution medium, maintained at 37±5ºC.The medium was stirred at 100 rpm. Aliquotes of the medium were withdrawn at regular intervals of 1 min. And the same amount was replaced with fresh medium. Samples were analyzed for cumulative percentage drug release spectrophotometrically at 271nm. Three trials were carried out for all the samples and average was taken.

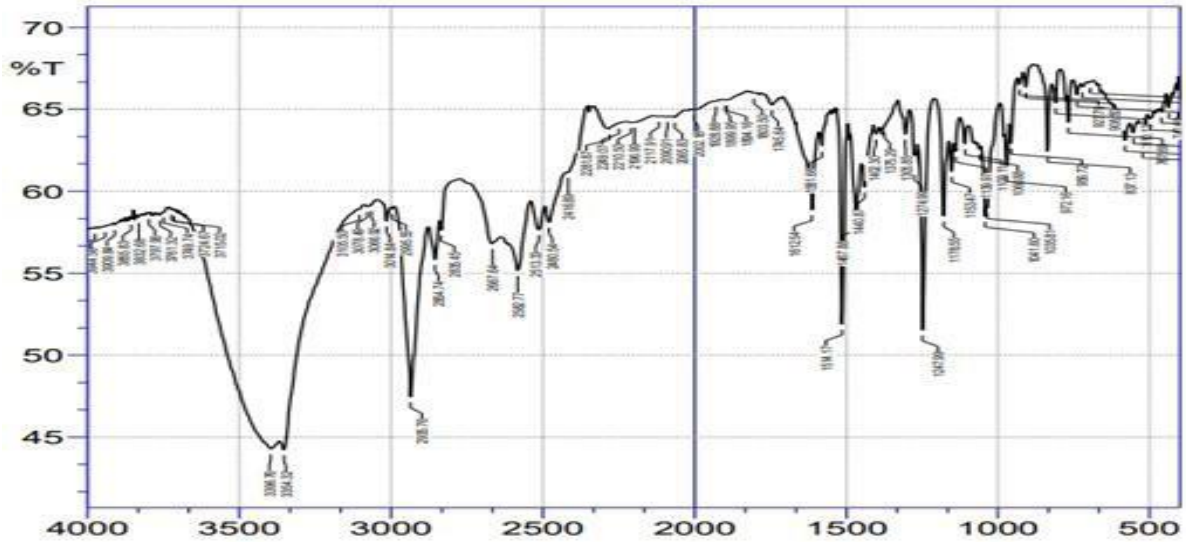

Figure 1: FTIR of pure drug fluvoxamine

Characterization of Fluvoxamine Mouth Dissolving Films

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectrophotometer (Schimadzu FTIR 8400S, Japan) was used to record the FTIR spectra of pure drug and formulated films in4,000 to 400cm^{-1} range[12]

Stability Studies

Stability testing was conductedat40°C±2°C/75%RH±5% RH for 3months using stability chamber (Thermo Lab, Mumbai)as per the referred procedure [13]

RESULTS

Drug Authentication Study

The presence of broadband at 3396–3354cm^{-1} for NH_3 stretching and OH stretching, 2935–2582 cm^{-1} for aliphatic C-H stretching, 1700cm^{-1} for C=O in COOH 1514cm^{-1} for C=N stretching, 950–650cm^{-1} multiple bands 1,4-disubstituted benzene ring indicates the purity of fluvoxamine sample.(Figure 1)

Physico-chemical Evaluation of Fluvoxamine Mouth Dissolving Films

The results of all parameters tested were within acceptable ranges and tabulated the values in Table 2.

The thickness of all 27formulations ranges from 0.10 ± 0.22 to 0.21 ± 0.50 mm. Lower standard deviations of film thickness demonstrate uniformity in film thickness. The minimum thickness of 0.10 ± 0.22 mm was observed for the FF15 formulation.

The tensile strength of all 27 film formulations lies within17.5±1.48to55.63±1.37gmwith a maximum value of 55.63 ± 1.37 demonstrated by FF15 indicating that film scan with stand ware and tare.

The folding endurance of all 27 formulations ranged between 246±1.38to292±1.44. Formulations containing a higher polymer concentration exhibited higher folding endurance of 292, indicating that the films with stand folds.

The drug content uniformity of all formulations varies between95.18±1.89to99.43±0.21. The highest value recorded for FF15 indicating that the film releases the drug uniformly on dissolution.

The pH on the acid or alkaline side causes oral mucosa. The pH of all formulated films is within 6.11±0.60to6.72±0.56, ensuring no irritation.

The DT(sec)of formulations FF1toFF27ranged between 10–25 seconds. The least disintegration time of10 seconds was recorded for FF15 indicating the faster dissolution of film.

Table 2: Evaluation of Fluvoxamine FDOF (FF1-FF27)

F.NO	Thickness (mm)	Tensile Strength (gm)	Folding Endurance	#Content uniformity (%)	Surface pH	DT (Sec)
FF1	0.16±0.05	32.8±1.13	265±1.14	96.11±1.63	6.25±0.37	62±1.23
FF2	0.12±0.14	29.5±1.27	278±1.22	97.45±1.06	6.16±0.11	79±1.51
FF3	0.19±0.36	44.9±1.10	252±1.17	98.16±1.23	6.36±0.39	52±1.40
FF4	0.13±0.90	51.2±1.16	263±1.69	96.16±1.01	6.53±0.12	63±1.19
FF5	0.14±0.23	39.0±1.78	246±1.38	95.21±1.22	6.39±0.19	77±1.25
FF6	0.15±0.14	23.7±1.55	275±1.19	98.27±0.39	6.23±0.35	50±1.87
FF7	0.17±0.64	35.1±1.34	269±1.13	95.18±1.89	6.52±0.40	57±1.63
FF8	0.14±0.28	50.5±1.66	253±1.15	97.77±1.58	6.35±0.77	35±1.37
FF9	0.17±0.19	17.5±1.48	266±1.28	95.75±1.63	6.29±0.11	56±1.19
FF10	0.15±0.11	23.6±0.96	284±1.29	97.89±1.47	6.16±0.87	78±1.24
FF11	0.16±0.18	48.5±1.75	263±1.49	96.47±1.38	6.45±0.17	44±1.19

FF12	0.14±0.20	37.1±1.12	255±1.69	97.81±1.22	6.11±0.60	50±1.40
FF13	0.17±0.13	21.5±1.49	268±1.29	96.45±1.47	6.28±0.89	72±1.73
FF14	0.14±0.29	42.4±1.18	260±1.41	95.65±1.11	6.43±0.28	58±1.87
FF15	0.10±0.22	55.63±1.37	292±1.44	99.43±0.21	6.72±0.56	29±1.85
FF16	0.14±0.12	26.1±1.37	253±1.30	96.85±1.39	6.44±0.96	63±1.81
FF17	0.12±0.13	37.5±1.39	277±1.38	97.56±1.44	6.35±0.29	70±1.56
FF18	0.13±0.20	46.7±1.13	256±1.58	95.68±01.7	6.17±0.22	48±1.12
FF19	0.18±0.15	42.9±1.14	283±1.17	97.34±1.55	6.28±0.19	57±1.33
FF20	0.14±0.26	39.1±1.77	279±1.30	96.31±1.24	6.16±0.49	76±132
FF21	0.15±0.39	25.2±1.30	258±1.49	97.23±0.87	6.37±0.41	35±1.27
FF22	0.13±0.49	19.5±1.19	264±1.51	96.36±1.61	6.13±0.85	43±1.61
FF23	0.20±0.58	25.7±1.10	275±1.51	97.45±1.38	6.23±0.62	58±1.49
FF24	0.17±0.98	19.9±1.14	261±1.23	96.29±1.62	6.19±0.46	41±1.31
F25	0.13±0.46	42.2±1.37	258±1.41	97.36±1.55	6.62±0.14	53±1.39
FF26	0.18±0.59	53.5±1.44	286±1.54	95.38±1.45	6.34±0.25	62±1.40
FF27	0.21±0.50	33.6±1.58	255±1.30	96.89±1.13	6.28±0.51	35±1.77

Cumulative Percentage Drug Release (CDR)

The drug release of all 27-fluvoxamine mouth dissolving film formulations varied from 79.24±1.13%to98.29±1.87%. Maximum drug release exhibited for FF15 (98.29±1.87%) within 10min is higher than that of pure drug 86.78 ±1.53 %. (Fig.2-5)

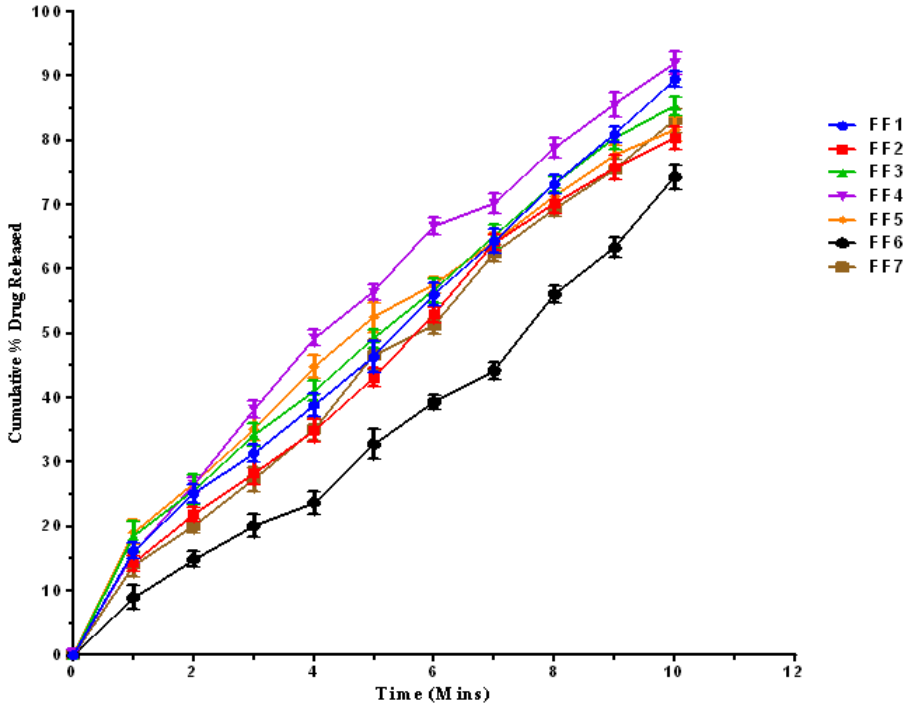

Figure2: Dissolution profile ofFF1-FF7

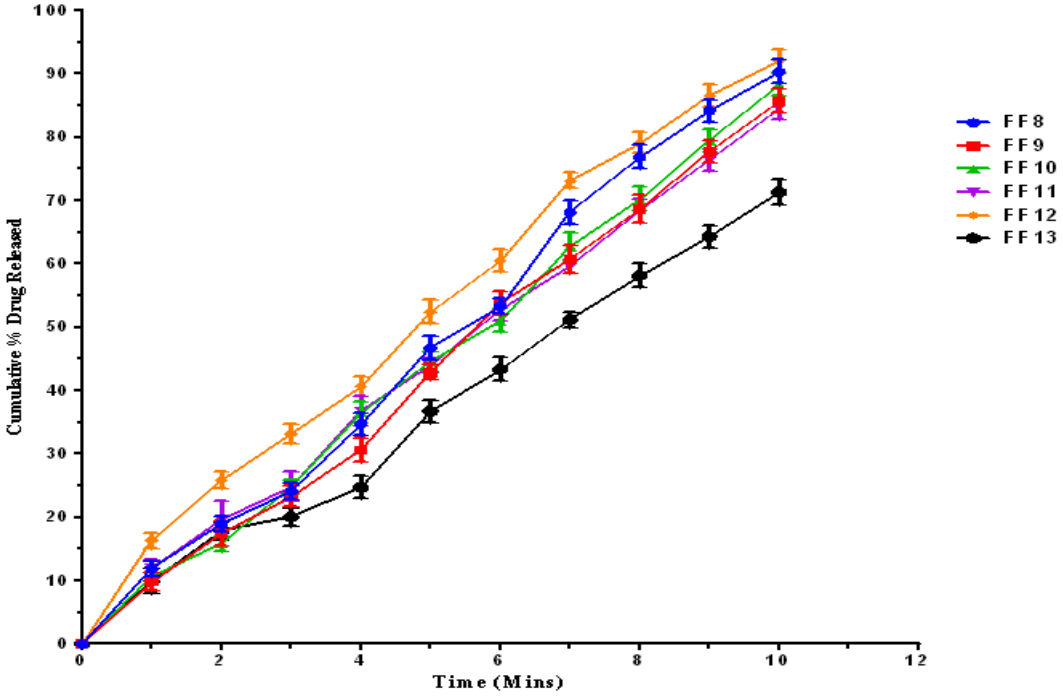

Figure 3:Dissolution profile ofFF8-FF13

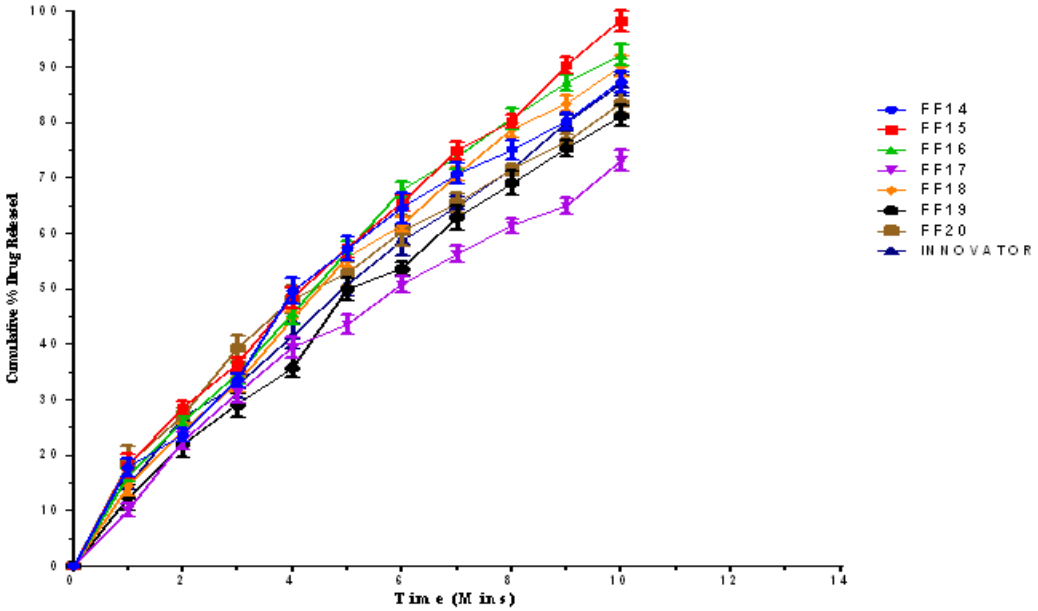

Figure 4: Dissolution profile ofFF14-FF20

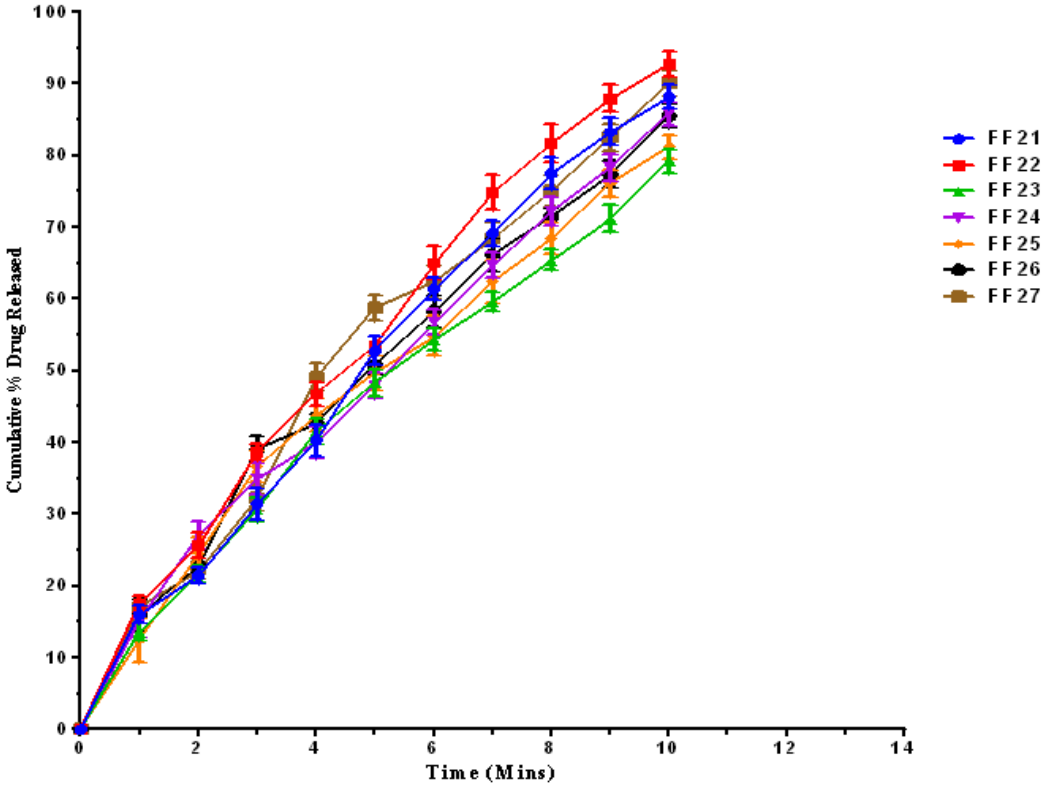

Figure 5: Dissolution profile ofFF21-FF27

Design of Experiment and Statistical Analysis

Based on CCD, the effect of one factor (PEG 4000) on other two factors (HPMC E15, Eudragit RL 100) is explained., and evaluated the main effects, interaction effects, and quadratic effects of the process variables on the tensile strength, disintegration time, and cumulative % drug released.

All responses substituted into second quadratic equation and the adequacy of the model verified by ANOVA, using Design-Expert software. For all the three responses, the quadratic model generated the highest F value, hence, considered as fitting model. All of the responses exhibited a significant lack-of-fit F value ($p > 0.05$), further supporting the adequacy of the model fit. The R2 value signifies the measure of the amount of variation around the mean (Table 3).

Table 3: Regression equations of the fitted models

Response	Equation
Tensile Strength (Y1)	$14.38 + 08.75\ X_1 - 6.33\ X_2 - 1.15\ X_3 - 0.48X^2_1 + 1.59X_1X_3 + 13.54\ X^2_2 - 3.15\ X_2X_3 + 2.79\ X^2_3$
Disintegration Time (Y2)	$18 + 9X_1 + 13\ X_2 + 5\ X_3 + 3X^2_1 - 5X_1X_3 - 11\ X^2_2 - 2\ X_2X_3 - 3\ X^2_3$
% Cumulative drug released (Y3)	$71.32 - 2.84\ X_1 + 21.18\ X_2 - 18.56\ X_3 + 0.47X^2_1 - 12.19X_1X_3 + 06.75\ X^2_2 - 34.65\ X_2X_3 + 2.40\ X^2_3$

Effect on tensile strength(Y1): The tensile strength of all formulations ranged between 17.5-55.63nm.The quadratic model generated indicated that the amount of HPMC E15 (A) amount eudragit RL 100 (B) and PEG4000 possess a significant influence on tensile strength. The theoretical (predicted) and observed values are in reasonably good agreement, as seen from Table 3. The mathematical model generated for tensile strength (Y1)was significant with an F-value of 981.80, indicating that the model is significant. There exists a 0.01% chance that a “Model F-value” this large might be due to noise (Table2). The factorial equation for droplet sizes how eda good correlation coefficient(0.9997).The influence of effects is understood using contour and 3D plots (Figs. 6 and 7).

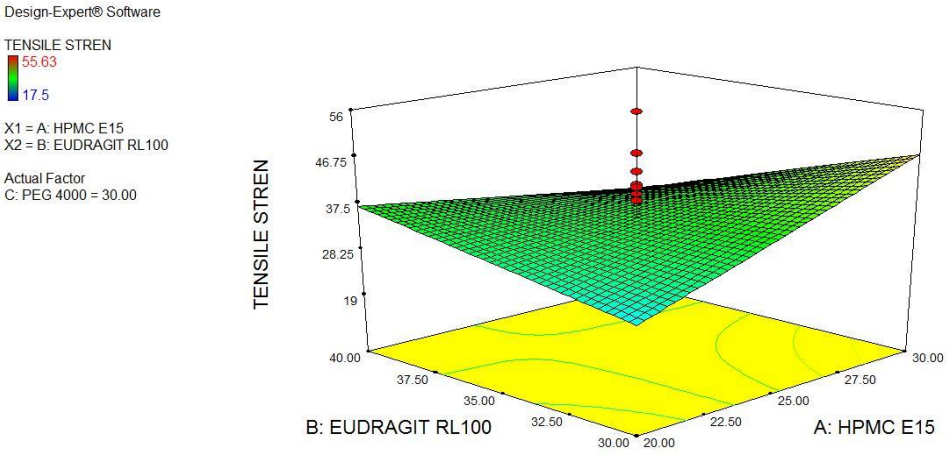

Figure 6. Response 3D surface plot showing the influence of amount of HPMC E15 and amount of Eudragit RL 100 on Tensile Strength fixed level of C

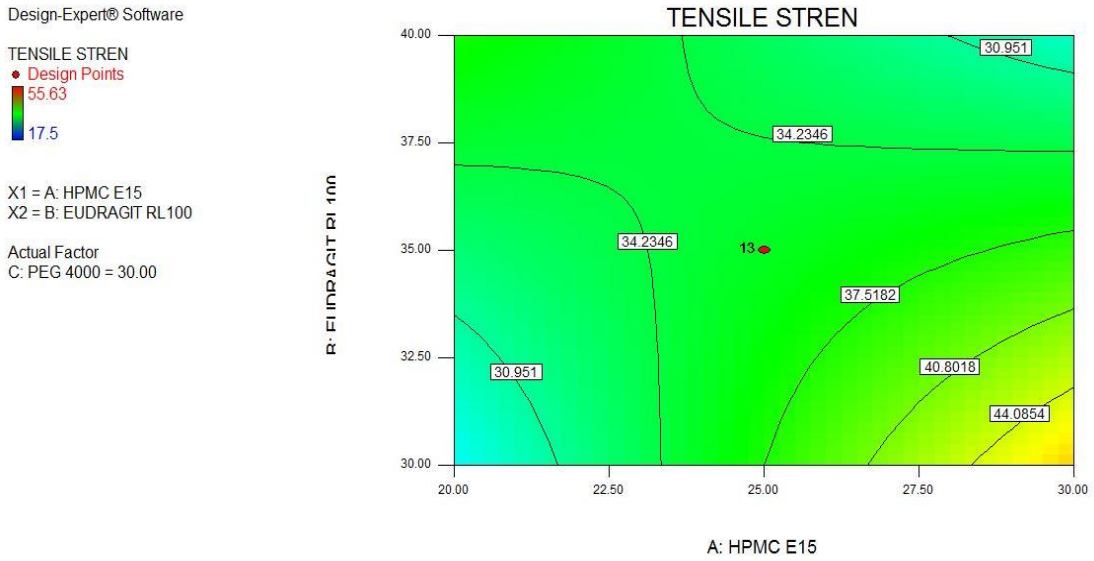

Figure 7: Contour plot showing the influence of amount of HPMC E15 and amount of Eudragit RL 100 on Tensile Strength fixed level of C

Effect on disintegration time(Y2): The DT of all films ranged between 10–25sec.The quadratic model generated revealed that the amount of eudragit RL100 and PEG4000 significantly influences the DT (Table 2). The theoretical (predicted) values and the observed values were in reasonably good agreement (Table 4). The mathematical model generated for disintegration time (Y2) was significant, with an F-value of 0.0133 implies the modelis significant. The factorial equation for disintegration time showed a good correlation coefficient (0.9994). The influence of the main and interactive effects of factors on DT was further elucidated using contour and 3D response plots (Figs.8 and9).

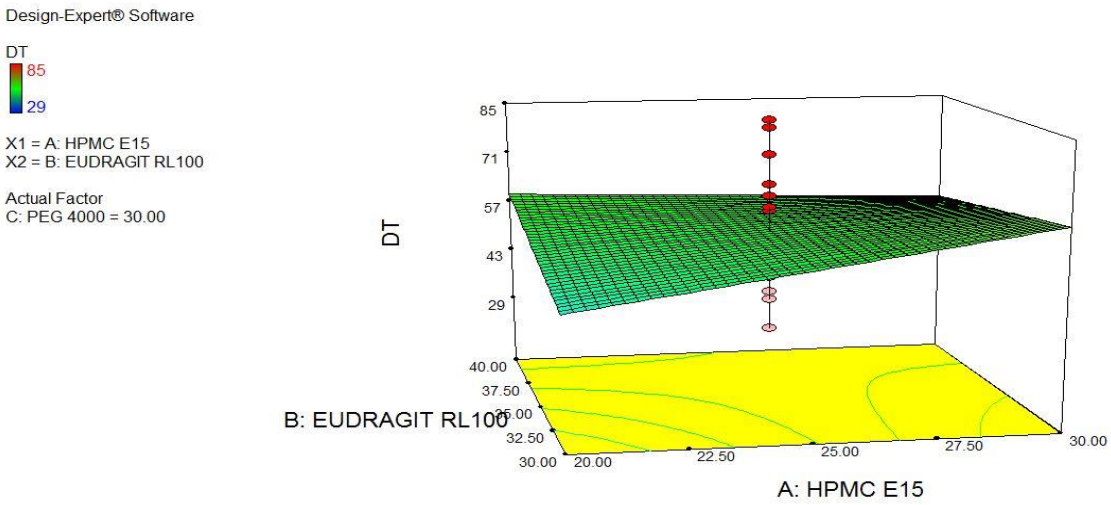

Figure 8: Response 3D surface plot showing the influence of amount of HPMC E15 and amount of Eudragit RL 100 on Disintegration Time fixed level of C

Effect on cumulative %drug released(Y3): The CD Rranged between 72.15 to 98.29%. The quadratic model generated revealed that the amount of HPMCE15, amount of eudragitRL100, and PEG4000 has a significant influence on the cumulative percent drug (Table 2). The theoretical (predicted) values and the observed values were in reasonably good agreement as seen (Table4). The mathematical model generated for percent drug release in 10minutes (Y3) was significant, with an F-value of 0.0163 implies the model is significant. The factorial equation for percent drug release showed a good correlation coefficient (0.9991).The interaction between A and B on percent drug release at a fixed C level is demonstrated in Fig. 10. The respective contour plots are as shown in Fig.11.

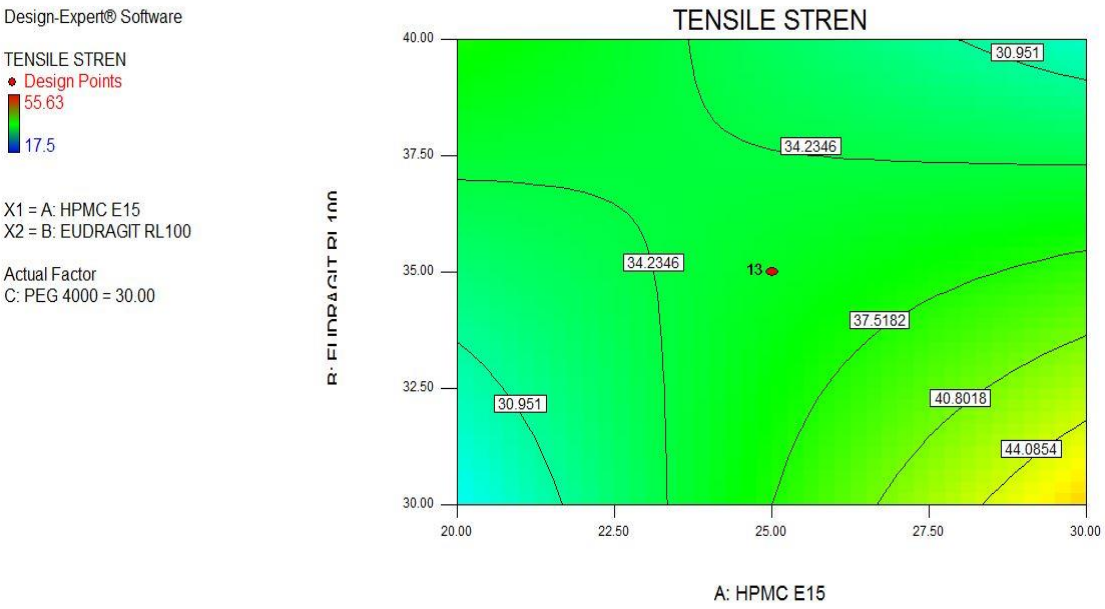

Figure 9: Contour plot showing the influence of amount of HPMC E15 and amount of Eudragit RL 100 on Disintegration Time fixed level of C

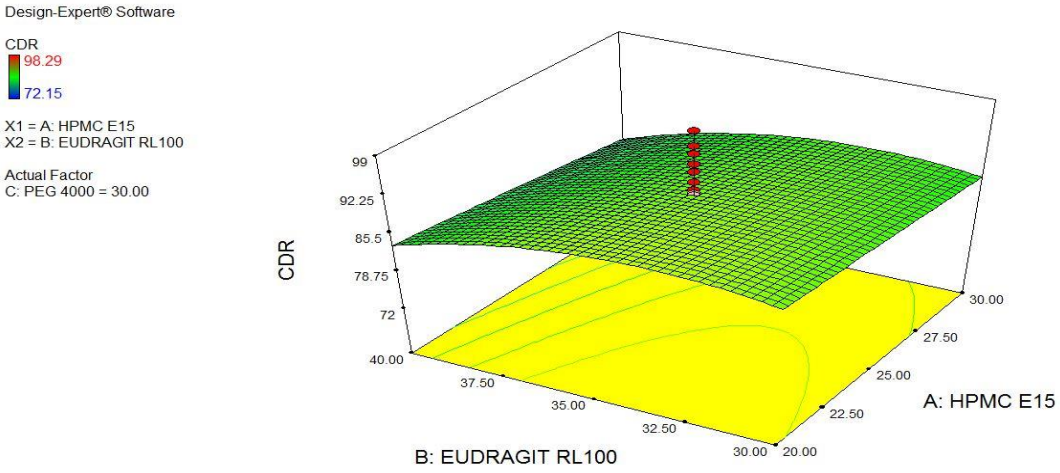

Figure 10: Response 3D surface plot showing the influence of amount of HPMC E15 and amount of Eudragit RL 100 on Cumulative percent drug released fixed level of C

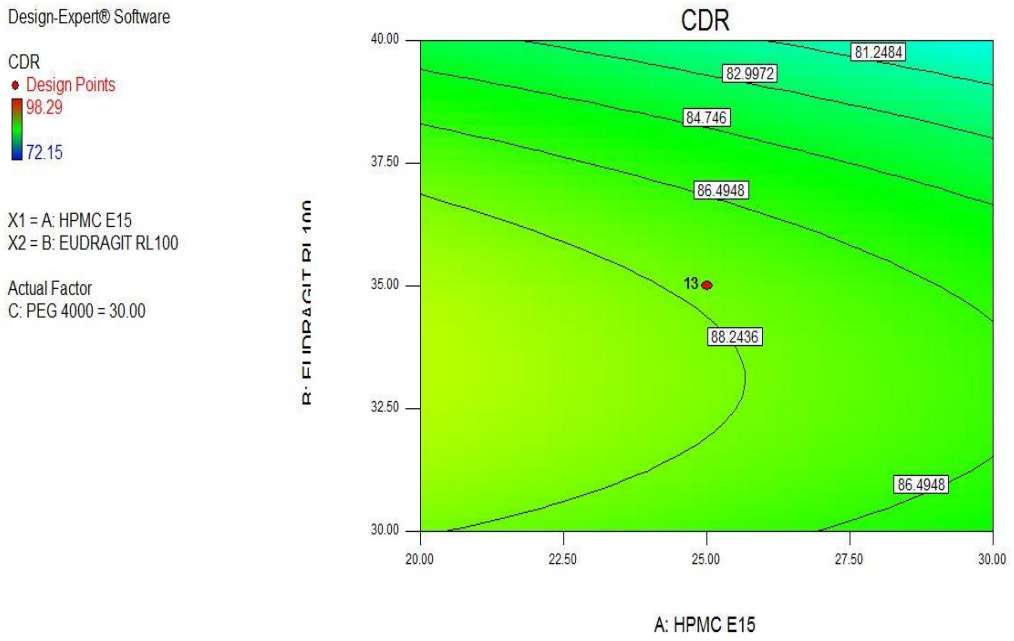

Figure 11: Contour plot showing the influence of amount of HPMC E15 and amount of Eudragit RL 100 on Cumulative percent drug released fixed level of C

Optimization by Desirability Function

The responses: tensile Strength (Y1), disintegration time(Y2), and cumulative % drug released in 10 minutes (Y3) were transformed into the desirability scale. Among them, Y1 and Y2 are minimized, while Y3 is maximized. In the individual desirability function, Y_{max} and Y_{min} are considered the highest and objective function (D) calculated for each response combined to obtain global desirability value using Design-Experts of beware. The maximum function values are generated at X1:25, X2:35, and X3:30. Three batches of films formulated with optimized ratios were obtained and evaluated. They have existed descent agreement amongst predicted and observed values (Table 4). Hence the results were validated.

Characterization of Optimized Fluvoxamine Mouth Dissolving Film by FTIR

The FTIR spectra of optimized formulation FF15(Fig. 12) exhibited all characteristic peaks of pure fluvoxamine present in Fig.1 broad band at 3396–3354$cm^{-1}$for NH_3 stretching and OH stretching, 2935–2582 cm^{-1} for aliphatic C-H stretching, 1700 cm^{-1} for C=O in COOH 1514cm^{-1} for C=N stretching, 950 to 650 cm^{-1} multiple bands 1,4-disubstituted benzene ring indicating the absence of interaction between the drug, polymers, and plasticizer used.

Stability Study

The formulation FF15 was subjected to an accelerated stability study for 3 months adhering to ICH guidelines. The results indicate no significant alteration in appearance and flexibility. In addition, no significant variation in tensile strength, in vitro drug released, and disintegration time confirmed polymer stability (Table5).

Table 4: Optimized values obtained by the constraints applies on Y1, Y2 and Y3

Independent variable	Nominal values %	Predicted values						
		Tensile Strength (Y1) (nm)	Disintegration Time (Sec) (Y2)	%CDR (Y3)	Batch	Tensile Strength (Y1) (nm)	Disintegration Time (Y2)	Percent drug released in 10 min (Y3)
Amount of HPMC E5 (A)	25	17.5	29	98.29	1	19.3	32	97.66
Amount of Eudragit RL 100 (B)	35				2	20.8	35	96.23
Amount of PEG 4000 (C)	30				3	22.5	31	97.17

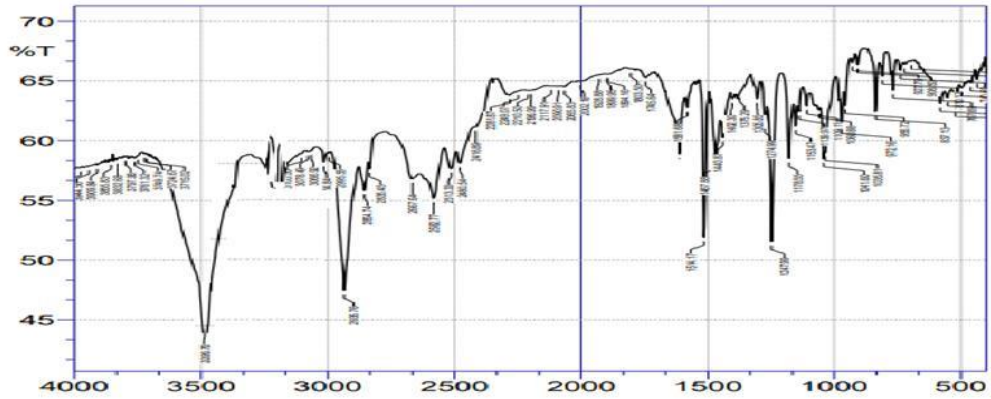

Figure 12: FTIR of pure fluvoxamine

Table 5: Parameters after stability study of FF15

Parameters	Temperature Maintained at 40 ±2^{0}C ; Relative Humidity (RH) Maintained at 75%±5%RH			
	Initial	After 1 month	After 2 months	After 3 months
Tensile Strength (%)	55.63±1.37	55.63±1.53	55.61±1.42	55.58±1.35
In Vitro Drug Released (%)	98.29±1.87	98.21±1.68	98.18±1.37	98.11±1.22
Disintegration Time (Sec)	29±1.69	29±1.78	29±1.55	29±1.24

DISCUSSION

The current research attempts to achieve faster dissolution fluvoxamine by formulation into mouth dissolving films using CCD 27 film formulations (FF1-FF27) prepared using direct compression techniques using HPMC E15 eudragit RL 100 and PEG 4000 in varying compositions followed by optimization using 33 CCD. The physicochemical properties of the film's formulations were evaluated and found within limits. Maximum drug dissolution exhibited by formulation FF15 within 10 minutes. Based on the results formulation FF15 was concluded as the best formulation. Based on DoE and desirability functions, the formulation comprising 25 mg of HPMC E15, 35 mg of eudragit RL 100, and 30 mg of PEG 4000 is chosen as the most optimal formulation with minimum tensile strength disintegration time and maximum cumulative % drug release. The developed formulations were stable over 3 months. From the above results, we can conclude that the developed formulation can be an innovative dosage form to improve the drug delivery, quick onset of action, as well as, improve patient compliance in the management of depression**.**

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