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Research Article

In vivo Evaluation of Fluvoxamine Maleate Mouth Dissolving Films by Design of Experiment

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ABSTRACT

Fluvoxamine, an antidepressant belonging to serotonin reuptake inhibitor (SRI) class, 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 (CCD), employed to examine the effects of amount of hydroxypropyl methylcellulose (HPMC) E15 (A), amount of eudragit RL 100 (B), amount of polyethylene glycol (PEG 4000) (C) on response variables tensile strength, disintegration time and cumulative % drug released. A 27 formulations prepared according to CCD and evaluated for physicochemical parameters and *in vitro* dissolution studies. Fluvoxamine mouth dissolving films formulated by employing solvent-casting method using HPMC E15, eudragit RL100, and PEG 4000. CCD is employed to optimize the effective dosage of formulation superdisintegrants. FF15 with a maximum tensile strength of 55.63 ± 1.37 mg, least disintegration time of 10 ± 1.85 seconds, and highest drug release of 98.29 ± 1.87 % is chosen as an optimal formulation with maximum content uniformity and folding endurance. From *in vivo* bioavailability studies, Cmax and Tmax of the fluvoxamine optimized mouth dissolving film formulation were significant ($p < 0.05$) compared to the fluvoxamine marketed product formulation. $AUC_{0-\infty}$ infinity for the optimized formulation was higher (733.84 ± 2.04 ng.h/mL) than the fluvoxamine marketed product formulation (485.67 ± 1.54 ng.h/mL). Statistically, AUC_{0-t} of the optimized mouth dissolving film formulation was significantly higher ($p < 0.05$) than fluvoxamine marketed product formulation. *In vivo* pharmacokinetic studies in rabbits confirmed the quick release and increase in bioavailability for fluvoxamine from optimized mouth dissolving film formulation as compared to the fluvoxamine marketed product formulation.

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] These are novel drug delivery systems that rapidly disintegrate and dissolve in saliva within few seconds, even in the absence of water, thus facilitating rapid drug absorption. The oral cavity offers direct entry of the drug into the systemic distribution, thus avoiding 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 reuptake 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 15 hours, with a range from 9 to 28 hours.[3]

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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 HPMC E 5, eudragit RL 100, polyethylene glycol (PEG) 4000, sucralose, aspartame purchased from Signet Chemicals Corporation Pvt. Ltd. Mumbai, India.

Experimental

Preparation of Fluvoxamine Mouth Dissolving Film

Fluvoxamine mouth dissolving formulation prepared by employing solvent casting method. Initially, the polymers soaked in water overnight for attaining uniformity in dispersion. Plasticizer added to these solutions and stirred continuously for 4-5 hours, leaving it undisturbed for 1-hour to obtain aqueous layer I (Table 1). 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 petridish with an area of 63.642 cm^2 and dried at 50–55°C for 24 hours. The obtained films peeled off and cut to 2×2 cm^2 size.[5]

Experimental Design

A 3^3 BBD was employed for optimizing the main, interaction, and quadratic effects of formulation components on characteristics of SNEDDS.[6] Seventeen experiments run

Table 1: Formulation of fluvoxamine mouth dissolving films

F.NO	*Fluvoxamine (mg)*	*HPMC E 5 (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

randomly for chosen independent variables, including 5 repetitions at center (asterisk-marked) obtained from 3 factor, 3-level BBD, and their subsequent responses noted are specified in Tables 1 and 2.

The BBD matrix obtained using Design Expert® software (Version7.0, Stat-Ease Inc., Silicon Valley, CA, USA), the second-order quadratic equations are as:

$$Y = \beta_1 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_1 X_2 + \beta_5 X_2 X_3 + \beta_6 X_1 X_3 + \beta_7 X_1^2 + \beta_8 X_2^2 + \beta_9 X_3^2$$

Y - Level of the measured response

β_0 – intercept

β_1 to β_9 - regression coefficient

X_1, X_2, and X_3 - main effects

X_1X_2, X_2X_3, and X_1X_3 - interaction between the main effects

X_1^2, X_2^2, and X_3^2 - quadratic terms of independent variables.

Evaluation of Fluvoxamine Mouth Dissolving Film

Thickness uniformity,[7] Drug content uniformity,[8] Folding endurance (FE),[9] Surface pH,[10] Tensile strength (TS),[11] and Disintegration time (DT) were performed according to the reported procedures

Cumulative Percentage Drug Release (CDR): The drug release of fluvoxamine mouth dissolving films is analyzed in saliva fluids of pH 6.8 used as dissolution medium followed by stirring at 37 ± 5°C at 100 rpm speed. The samples of dissolution medium withdrawn at various intervals spectrophotometrically at 271 nm.[12]

Pharmacokinetic Studies of Fluvoxamine in Rabbit Plasma

Animal Preparation

Twelve New Zealand white rabbits of either sex rabbits were (weighing 2–3 kg) selected for this study; all the animals were healthy during the experiment. Animals were maintained at room temperature 25°C, RH 45%, and 12 hours alternate light and dark cycle with 100% fresh air exchange in animal rooms, uninterrupted power and water supply, and rabbits were fed with standard diet and water ad libitum [13]. An *in vivo* pharmacokinetic study was conducted following the ethical guidelines for investigations in laboratory animals and approved by the Institutional Animal Ethics Committee (IAEC NO:.....).

Study Design

Rabbits were randomly divided into 2 groups, each group contains six animals. The rabbits selected for the study were housed in separate cages and had no medication for two weeks before the study. They were denied food and water during the study. The cages of rabbits were placed in 18 hours light/6 hours dark conditions. One group of rabbits received the marketed formulation (Luvox 25 mg tablets), whereas the other received mouth dissolving film. The film was carefully placed on the rabbit tongue with the help of a body restraint device in which the animals head was exposed and lifted apart the gums with a wooden tongue depressor. The film was placed in the mouth by wetting the mouth with a small amount of water. Also, the innovator applied a gentle tension to restrain the mouth from ensuring the complete disintegration of the film. For pharmacokinetic study, the blood samples were obtained from the peripheral vein of each rabbit at the interval of 0, 1, 2, 3, 4, 5, 7, 9, 12, and 24 hours. Marketed product tablets were crushed and mixed with carboxymethylcellulose (CMC) 1%W/V solution, ensuring that rabbits consumed all the dose. The drug was prepared in a solution form and was administered through the feeding tube orally.

HPLC Analysis

The apparatus used for HPLC was a Model 880-PU chromatography pump (Jasco, Tokyo, Japan) equipped with a Model 876-UV ultraviolet detector set at 254 nm wavelength and a Rheodyne Model 7120 injector (Rheodyne, Cotati, CA, USA) with an effective volume of 100 mL. The HPLC columns (150' 4.6 mm i.d.) used Grand Pack C18-5, Grand Pack C8-5, Grand Pack C4-5, and Grand Pack C2-5 of 5 mm particle size (MASIS, Owani, Japan); the end-cappings were carried out under the same condition for several stationary phases, for basic examination of suitable condition for chromatographic separation of fluvoxamine. The analytical column used was a Grand Pack C4-5. The mobile phase consisted of 0.5% potassium dihydrogen phosphate (pH 2.5)–acetonitrile (75:25, v/v). A flow rate of 1 mL/min was used at ambient temperature. Before mixing, the pH of 0.5% potassium dihydrogen phosphate was adjusted with 50% phosphoric acid, and the mobile phase was degassed ultrasonically before use. The retention times of fluvoxamine and internal standard moperone (IS) were 22.01 and 15.08 minutes, respectively.[14]

Pharmacokinetic Analysis

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration (C_{max}), time to attain $C_{max,}$ i.e., T_{max} and $t_{½}$ values, the area under plasma concentration-time curve from zero to the last sampling time (AUC_{0-t}), the area under plasma concentration-time

Table 2: 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)	$18 + 9X_1 + 13\ X_2 + 5\ X_3 + 3X^2_1 - 5X_1X_3 - 11\ X^2_2 - 2\ X_2X_3 - 3\ X^2_3$
CDR (Y_3)	$71.32 - 2.84\ X_1 + 21.18\ X_2 - 18.56\ X_3 + 0.47X^2_1 - 12.19X_1X_3 + 06.75\ X^2_2 - 34.65\ X_2X_3 + 2.40\ X^2_3$

curve from zero to infinity ($AUC_{0-\infty}$). AUC_{0-t} was calculated by the linear trapezoidal rule and $AUC_{0-\infty}$ from the following formula

$$AUC_{0-\infty} = AUC_{0-t} + C_t / K_E$$

Characterization of Fluvoxamine Mouth Dissolving Films

Fourier transform infrared spectroscopy: FTIR spectrophotometer (Schimadzu FTIR 8400S, Japan) was used to record the FTIR spectra of pure drug and formulated films in the 4000–400 cm^{-1} range.[15]

Stability Studies

Stability testing was conducted at 40°C ± 2°C/75% RH ± 5% RH for 3 months using stability chamber (Thermo Lab, Mumbai) as per the referred procedure.[16]

Results

Drug Authentication Study

The presence of broadband 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 1514 cm^{-1} for C=N stretching, 950–650 cm^{-1} multiple bands 1,4-disubstituted benzene ring indicates the purity of fluvoxamine sample. (Fig. 1)

Physico-chemical Evaluation of Fluvoxamine Mouth Dissolving Films

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

The thickness of all 27 formulations 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 within 17.5 ± 1.48 to 55.63 ± 1.37 gm with a maximum value of 55.63 ± 1.37 demonstrated by FF15 indicating that films can withstand ware and tare.

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

The drug content uniformity of all formulations varies between 95.18 ± 1.89 to 99.43 ± 0.21. The highest value

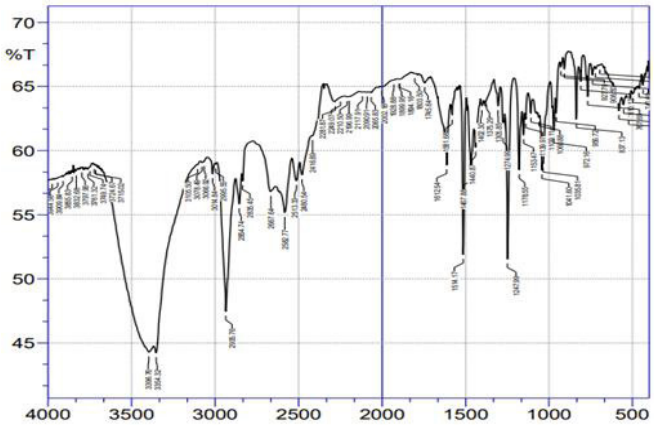

Fig. 1: FTIR of pure drug fluvoxamine

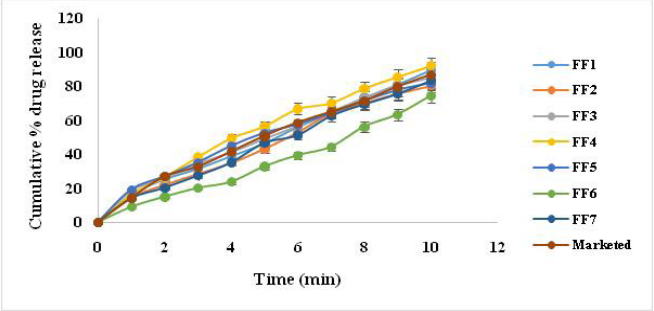

Fig. 2: *In vitro* CDR profile of formulations FF1-FF7

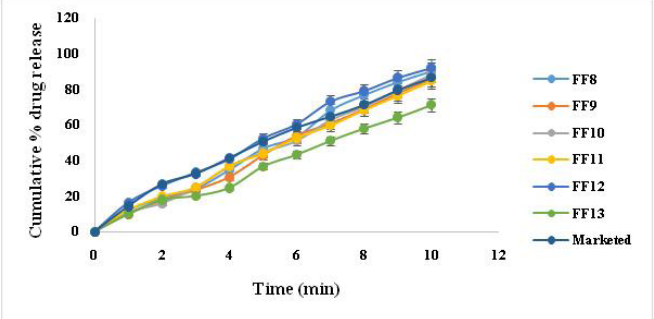

Fig. 3: *In vitro* CDR profile of formulations FF8-FF13

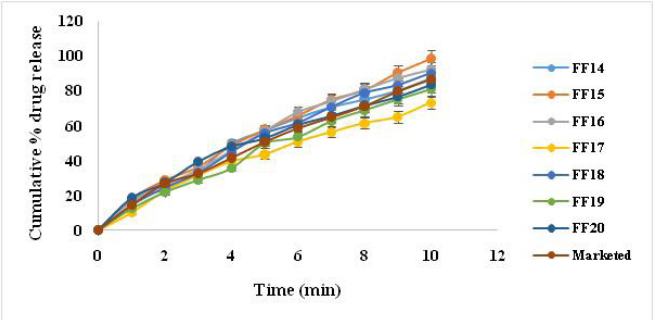

Fig. 4: *In vitro* CDR profile of formulations F14-F20

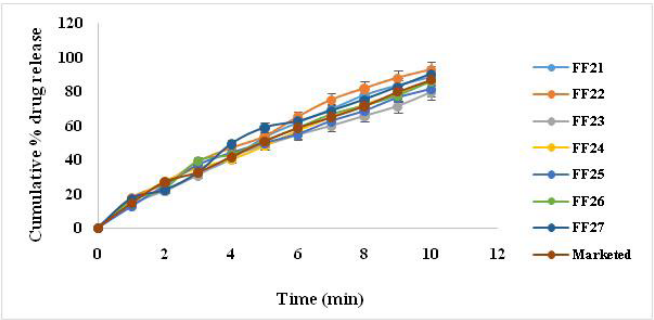

Fig. 5: *In vitro* CDR of formulations FF21-FF27

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 ± 0.60 to 6.72 ± 0.56, ensuring no irritation.

The DT (sec) of formulations FF1 to FF27 ranged between 10–25 seconds. The least disintegration time of 10 seconds was recorded for FF15 indicating the faster dissolution of film.

Design of Experiment

Effect on tensile strength (Y1): The tensile strength of all formulations ranged between 17.5-55.63 nm. The quadratic model generated indicated that the amount of HPMC E15 (A) amount eudragit RL 100 (B) and PEG 4000 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 (Table 2). The factorial equation for droplet size showed a good correlation coefficient (0.9997). The influence of effects is understood using contour and 3D plots (Figs. 6 and 7).

Effect on disintegration time (Y2): The DT of all films ranged between 10–25 sec. The quadratic model generated revealed that the amount of eudragit RL 100 and PEG 4000 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 model is 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 and 9).

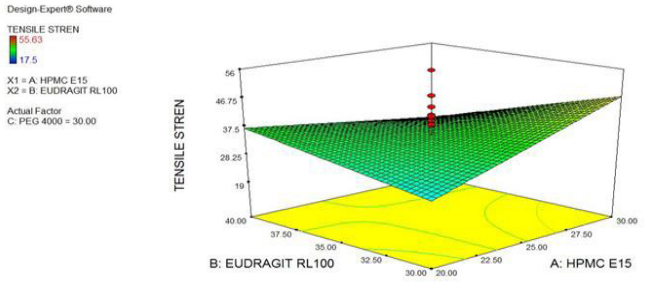

Fig. 6: Response 3D surface plot depicting the influence of amount of HPMC E15 and amount of Eudragit RL 100 on tensile Strength fixed C

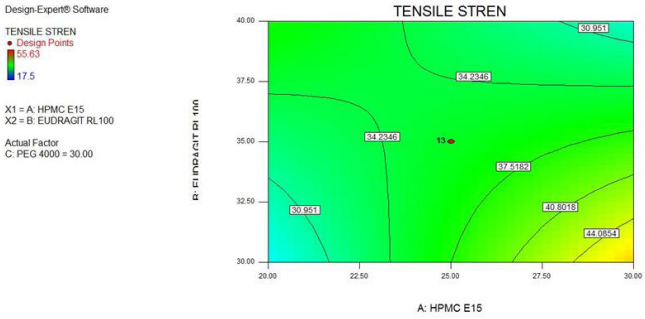

Fig. 7: Contour plot depicting influence of amount of HPMC E15 and amount of Eudragit RL 100 on tensile strength fixed level of C

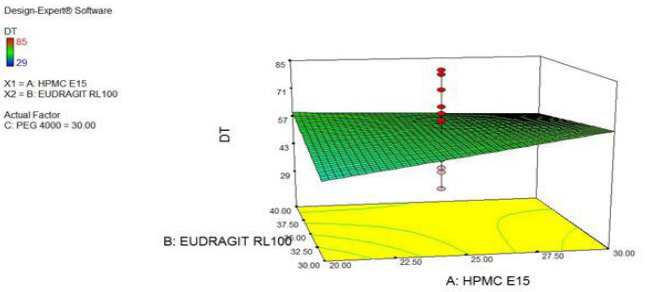

Fig. 8: Response 3D surface plot showing the influence of amount of HPMC E15 and amount of eudragit RL 100 on DT time fixed level of C

Table 3: Accelerated stability study of formulation FF15

	Temperature Maintained at 40 ± 2°C; Relative Humidity (RH) Maintained at 75% ± 5%RH			
Parameters	*Initial*	*After 1month*	*After 2months*	*After 3months*
Tensile Strength (%)	55.63 ± 1.37	55.63 ± 1.53	55.61 ± 1.42	55.58 ± 1.35
CDR (%)	98.29 ± 1.87	98.21 ± 1.68	98.18 ± 1.37	98.11 ± 1.22
Disintegration time (Sec)	6 ± 1.69	6 ± 1.78	6 ± 1.55	6 ± 1.24

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

		Predicted values			*Observed values*			
Independent variable	*Nominal values %*	*Tensile Strength (Y1) (nm)*	*DT (Sec) (Y2)*	*CDR (Y3)*	*Batch*	*Tensile Strength (Y1) (nm)*	*DT (Y2)*	*CDR in 10 min (Y3)*
Amount of HPMCE5 (A)	25				1	19.3	20	97.66
Amount of Eudragit RL 100 (B)	35	17.5	10	98.29	2	20.8	25	96.23
Amount of PEG 4000 (C)	30				3	22.5	15	97.17

Effect on cumulative % drug released (Y3): The CDR ranged between 72.15 to 98.29%. The quadratic model generated revealed that the amount of HPMC E15, amount of eudragit RL 100, and PEG 4000 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 (Table 4). The mathematical model generated for percent drug release in 10 minutes (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.

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-Expert software. 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.

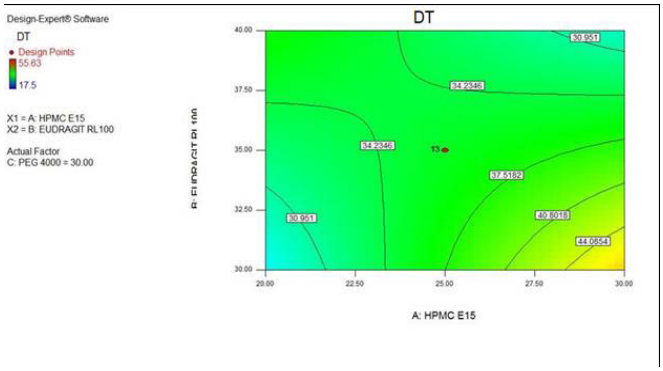

Fig. 9: Contour plot showing the influence of amount of HPMC E15 and amount of eudragit RL 100 on DT fixed level of C

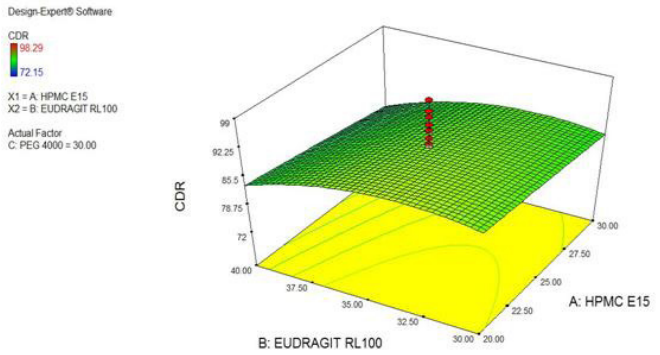

Fig. 10: Response 3D surface plot showing the influence of amount of HPMC E15 and amount of eudragit RL 100 on CDR fixed level of C

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 broadband 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 1514 cm^{-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 (Table 3).

Pharmacokinetic Parameters Comparison for Fluvoxamine Marketed Product and Optimised Mouth Dissolving Film

Figs. 13–15 show the plasma concentration-time curve in rabbits after a single oral dose of Fluvoxamine optimized mouth dissolving film formulation compared to fluvoxamine marketed product. Pharmacokinetic parameters of fluvoxamine after oral administration of

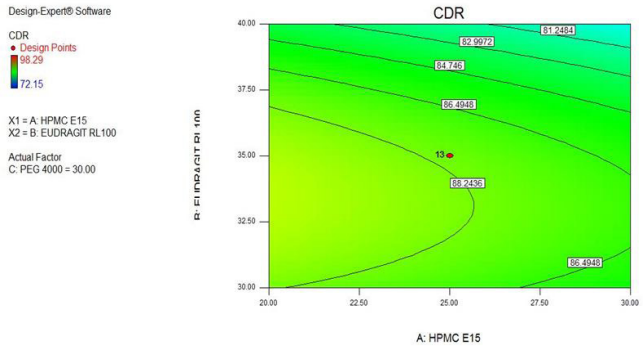

Fig. 11: Contour plot showing the influence of amount of HPMC E15 and amount of eudragit RL 100 on CDR at fixed level of C

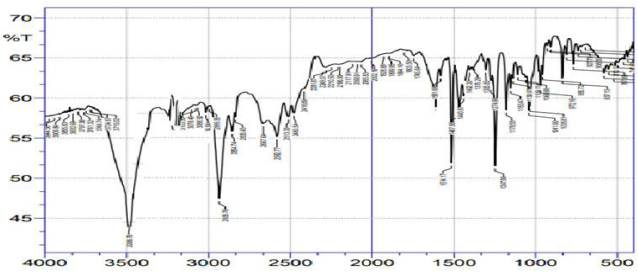

Fig. 12: FTIR of optimized fluvoxamine mouth dissolving film (FF15)

Table 5: Pharmacokinetic parameters of fluvoxamine optimised mouth dissolving film formulation and marketed product in rabbit plasma

Pharmacokinetic parameters	*Fluvoxamine marketed product*	*Fluvoxamine – optimized mouth dissolving film formulation*
C_{max} (ng/mL)	15.75 ± 0.12	25.38 ± 0.08
AUC_{0-t} (µg. h/mL)	430.28 ± 0.99	653.18 ± 0.65
AUC_{0-inf} (µg. h/mL)	485.67 ± 1.54	733.84 ± 2.04
T_{max} (h)	2 ± 1.65	0.5 ± 0.92
$t_{1/2}$ (h)	11.65 ± 0.02	7.092 ± 0.04

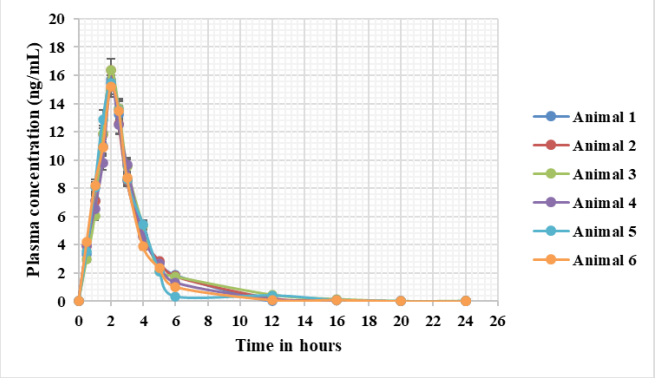

Fig. 13: Plasma concentration-time profile of fluvoxamine marketed product in rabbit plasma

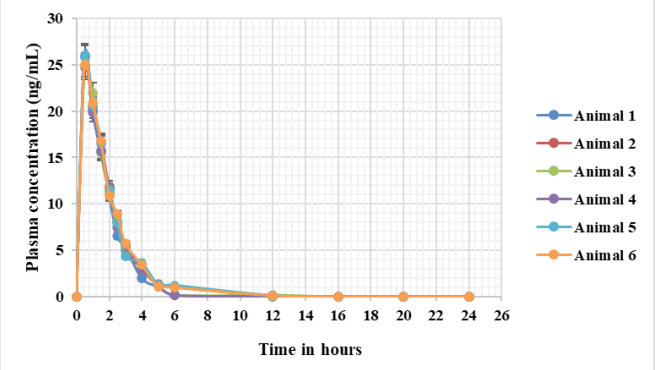

Fig. 14: Plasma concentration-time profile of fluvoxamine optimized mouth dissolving film optimised in rabbit plasma

the two formulations in rabbits are shown in Table 5. From pharmacokinetic studies, C_{max} of the fluvoxamine optimized mouth dissolving film formulation 25.38 ± 0.08 ng/mL was significant ($p < 0.05$) compared to the fluvoxamine marketed product formulation 15.75 ± 0.12 ng/mL. T_{max} of both fluvoxamine optimized mouth dissolving film formulation and fluvoxamine marketed product was 0.5 ± 0.92 hours and 2.0 ± 1.65 hours, respectively. $AUC_{0-\infty}$ an infinity of optimized formulation was higher (733.84 ± 2.04 ng.h/mL) than the fluvoxamine marketed product formulation 485.67 ± 1.54 ng.h/mL. Statistically, AUC_{0-t} of the optimized mouth dissolving film formulation was significantly higher ($p < 0.05$) than fluvoxamine marketed product formulation. A higher amount of drug concentration in blood indicated better systemic absorption

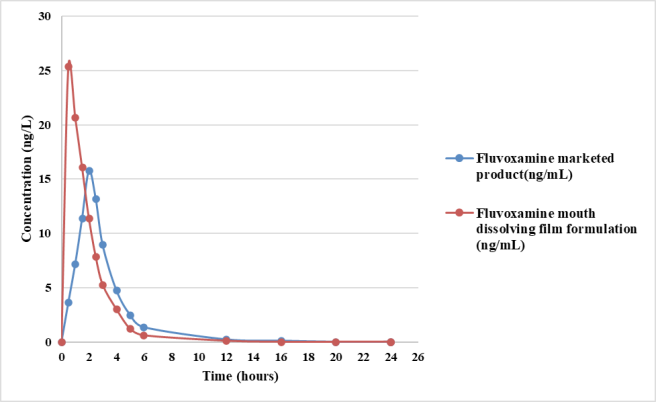

Fig. 15: Plasma concentration profiles of fluvoxamine optimised mouth dissolving film and marketed product in rabbit plasma

of fluvoxamine from optimized mouth dissolving film formulation when compared to the fluvoxamine marketed product, and also *in vivo* pharmacokinetic studies in rabbits confirmed the quick release and increase in bioavailability for fluvoxamine from optimized mouth dissolving film formulation as compared to the fluvoxamine marketed product formulation.

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 3^3 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 *in vivo* bioavailability studies, C_{max} of the fluvoxamine optimized mouth dissolving film formulation 25.38 ± 0.08 ng/mL was significant ($p < 0.05$) compared to the fluvoxamine marketed product formulation 15.75 ± 0.12 ng/mL. T_{max} of both fluvoxamine optimized mouth dissolving film formulation and fluvoxamine marketed product was 0.5 ± 0.92 h and 2.0 ± 1.65 h, respectively. $AUC_{0-\infty}$ infinity for the optimized formulation was higher (733.84 ± 2.04 ng.h/mL) than the fluvoxamine marketed product formulation (485.67 ± 1.54 ng.h/mL). Statistically, AUC_{0-t} of the optimized mouth dissolving film formulation was significantly higher ($p < 0.05$) than fluvoxamine marketed product formulation. *In vivo*, pharmacokinetic studies in rabbits confirmed the quick release and increase in bioavailability for fluvoxamine from optimized mouth

dissolving film formulation as compared to the fluvoxamine marketed product formulation. Hence mouth dissolving films of fluvoxamine were successfully formulated using CCD with bioavailability enhancement with a quick onset of action with higher patient compliance.

References

1. Dinge A, Nagarsenker MV. Formulation and Evaluation of Fast Dissolving Films for Delivery of Triclosan to the Oral Cavity. AAPS Pharm Sci Tech. 2008;9(2):349-356.
2. Saigal N, Baboota S, Ahuja A, Ali J. Fast-dissolving Intraoral drug delivery systems. Expert Opin Ther Pat. 2008;18(7):769-778.
3. Dell'Osso B, Allen A, Hollander E. Fluvoxamine: a selective serotonin re-uptake inhibitor for the treatment of obsessive-compulsive disorder. Expert Opin Pharmacother. 2005;6(15):2727-2740.
4. Schwartz BJ, Connor RE. Optimization technique in pharmaceutical formulations and processing.J Drugs Pharm Sci Modern Pharm. 1996;72:727-754.
5. Keshavarao KP, Dixit M. Formulation and Evaluation of Mouth Dissolving Film Containing Rofecoxib. IRJP. 2011;2(3): 273-278.
6. Montgomery, Douglas C. Design and Analysis of Experiments: Response surface method and designs, John Wiley and Sons, Inc. New Jersey. 2005, pp 210-256.
7. Cilurzo F, Cupone IE, Minghetti P, Selmin, Montanari L. Fast dissolving films made of maltodextrins. Eur J Pharm Biopharm. 2008;70 (3): 895–900.
8. Kulkarni AS, Deokule HA, Mane MS, Ghadge DM. Exploration of different polymers for use in the formulation of oral fast dissolving strips. J Current Pharm. Res 2010;2(1): 33-35.
9. Corniello C. Quick dissolving strips: from concept to commercialization. Drug Del Technol. 2006;6(2): 68–71.
10. Londhe VY, Umalkar KB. Formulation development and evaluation of fast dissolving film of telmisartan. Indian journal of pharmaceutical sciences. 2012;74(2):122–126.
11. El-Setouhy DA, El-Malak NSA. Formulation of a novel tianeptine sodium orodispersible film.AAPS Pharm Sci Tech. 2010;11(3):1018-1025.
12. Pankaj K, Ashok G, Bharat S, Shubhanjali S. Design and Comparative Evaluation of In-vitro Drug Release, Pharmacokinetics and Gamma Scintigraphic Analysis of Controlled Release Tablets Using Novel pH Sensitive Starch and Modified Starch- acrylate Graft Copolymer Matrices. Iran J Pharm Res. 2015;14(3):677–691.
13. Rocco Orlando, Sara De Martin, Laura Andrighetto, Maura Floreani, Pietro Palatini. Fluvoxamine pharmacokinetics in healthy elderly subjects and elderly patients with chronic heart failure. Br J Clin Pharmacol. 2010;69(3), 279–286
14. Tadashi Ohkubo, Ritsuko Shimoyama, Koichi Otani, Keizo Yoshida, Hisashi Higuchi, Tetsuo Shimizu High-Performance Liquid Chromatographic Determination of Fluvoxamine and Fluvoxamino Acid in Human Plasma. Analytical Sciences. 2003;19(6): 859–864
15. Choudhary DR, Patel VR, Patel HV, Kundawala AJ. Formulation and evaluation of quick dissolving film of levocetirizine dihydrochloride. International Journal of Pharmacy and Technology. 2011; 3(1): 1740–1749.
16. Vuppalapati L, Cherukuri S,Neeli V, Reddy Yeragamreddy P, Reddy Kesavan B. Application of Central Composite Design in Optimization of Valsartan Nanosuspension to Enhance its Solubility and Stability. Current Drug Delivery. 2016; 13(1): 143–157.

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