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NANOSUSPENSION BASED SUBLINGUAL FILM OF FLUVOXAMINE MALEATE

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ABASTRACT

The primary objective of this study was to enhance the solubility of the BCS Class II drug, fluvoxamine maleate, by formulating it as a nanosuspension for incorporation into a sublingual film. The intention was to bypass hepatic first-pass metabolism, thereby improving bioavailability, ensuring faster onset of action, and increasing patient compliance. Nanosuspension were prepared using the Solvent-Antisolvent precipitation using PVPK-30 as a Stabilizer. Then solvent casting method was used to prepare sublingual film of theire suspension with HPMC E5 and Glycerol as polymer and plasticizer, respectively. The optimization of Sublingual film was done by 3^2 Full Factorial design. The independent variables were Concentration of film forming agents and plasticizer concentration. The optimized batch showed improved Disintegration time and cumulative drug release, and physical stability over time.

KEYWORDS: Fluvoxamine Maleate, Nanosuspension, Sublingual Film, Full Factorial Design, Solvent-Antisolvent precipitation method, Solvent Casting method, Disintegration time, Depression.

INTRODUCTION

Depression or Major Depressive Disorder (MDD) is a significant mental health condition characterized by persistent sadness, loss of interest in daily activities, and a wide range of emotional and physical symptoms. Fluvoxamine Maleate Drug suffers from poor solubility and low oral bioavailability (53%) due to first pass metabolism. As Nanosuspension could offer benefits like enhanced solubility, bioavailibility and dissolution rate. Sublingual film dosage forms provide an efficient vehicle for delivering these nanosuspension which will bypass the first pass metabolism and enhance patient compliance.

3^2 Full factorial design, a statistical optimization technique, is ideal for pharmaceutical formulation development.

MATERIALS AND METHODS

Fluvoxamine Maleate is provided as a gift sample from TORRENT PHARMACEUTICALS and exepients were PVPK-30 from Research Lab Fine Chem Industries, HPMC E5 from Seva fine Chemicals, Citric Acid from Sisco Research lab, Glycerol from Sisco Research lab, Crosscarmellose sodium, Sucralose, and Orange oil was provided by oxford lab fine chem LLP.

Formulation of Nanosuspension of Fluvoxamine maleate

Solvent-Antisolvent precipitation method was employed to prepare Nanosuspension of Fluvoxamine Maleate. Drug and different Stabilizers were taken in 1:1, 1:2 w/w ratio. A 20:80 ratio were taken for solvent (Methanol) and Antisolvent phase (Water). Drug was dissolved into Methanol and another antisolvent phase was prepared by dissolving stabilizer into water. Methanol solution was injected using the syringe into the Antisolvent phase under continuous stirring for 2 hours and allowed to complete evaporation of methanol. These nanosuspension was subjected to ultrasonication to reduce particle size.

Batch	Drug : Stabilizer	Ratio
N1	Drug: PVPK-30	1:1
N2	Drug: PVPK-30	1:2
N3	Drug: SLS	1:1
N4	Drug: SLS	1:2

Drug Amount according to one petri plate

Characterization of Nanosuspension

Particle size and PDI: Fluvoxamine maleate nanosuspension was determined using dynamic light scattering (DLS) method by Particle size analyzer (Malvern zeta sizer). For analysis nanosuspension is

diluted and sonicate for 2 minutes. The obtained PDI values gives idea about particle size distribution. Theire values range from 0.000 to 1.000, which demonstrates that lower the value, the narrower the size distribution.

Zeta potential: The zeta potential of nanosuspension was diluted and analysed using electrophoretic light scattering method which measured at 90° Scattering angle at 25°C Malvern zeta sizer. It determines stability of suspension.

FTIR Study: identification of drug- polymer compatibility by FTIR Fourier transform Infra-red (FT-IR) is the tool for solid state characterization of pharmaceutical solids. The identification of the drug was done by (FT-IR) spectroscopic method using Alpha Bruker FTIR spectrophotometer. The drug was mixed with suitable amount of KBr and converted into pellets using KBr press at 20 psi for 10 min. The disc thus prepared was placed in a sample compartment and scanned at transmission mode in the region of 4000 to 400 cm-1. The IR spectrum of the drug and drug with PVPK-30, HPMC E5, Glycerol, Crosscarmelose sodium, Sucralose, Citric Acid and Orange oil thus obtained was compared with standard spectra of the drug.

Formulation of Optimized Nanosuspension loaded Sublingual film

Solvent casting method was employed to prepare sublingual film containing nanosuspension of drug. All the water soluble polymers (film forming agent)are dissolved in suitable volume of water to form homogenous and viscous solution with the help of magnetic stirrer. Sucralose, Crosscarmelose Sodium, Citric acid and Orange Flavour were added and stirred till the complete dissolving of all ingredients and After that plasticizer was added. Then previously prepared Nanosuspension was added to the mixture with continuous stirring. Both the solutions are mixed together until homogenous. The solution is then spread on a glass petri plate and allowed to dry in hot air oven at 50°C. After complete drying of the film it was cut into 2×2 cm^2 and stored in aluminum foil.

Evaluation of Nanosuspension loaded Sublingual Film

Physical appearance and texture: Physical appearance is checked by visual inspection Surface texture is examined by touch.

Thickness: The thickness of the drug loaded films was measured with the help of micrometer screw gauge at different strategic locations like four corners and center of the each film. Mean SD was calculated. The standard range for film thickness should not be less than 5 %. This is essential to assure uniformity in the thickness of the film as this was directly related to the accuracy of dose.

Surface pH: The prepared strip is placed in Petri dish and they are wetted using 0.5ml distilled water. The pH is measured by bringing the electrode in contact with the surface of the oral film and allowing equilibrating for 1 min. The study performed on three films of each formulation and mean ± SD was calculated. pH 6.8 is considered best for the film as it is the pH of the oral cavity and is considered to be tolerated the best.

Weight Uniformity: Weight variation is studied by individually weighing 3 randomly selected film strips using Analytical balance and calculating the average weight. It should not deviate significantly from average weight.

Folding Endurance: It is measured manually for the prepared oral film. It involves repeatedly folding the film at a same point until it breaks.

Disintegration time: There are currently no official guidelines in Pharmacopoeias for the determination of disintegration time of ODFs. Hence, Petridish method is used. Each strip was placed in glass Petri dish containing 10 ml simulated salivary fluid with slight swirling at every 10s. The time taken by the film to completely disintegrate is noted.

Moisture Content: The percentage moisture loss was carried out to check integrity of the film at dry conditions. film from each batch were weighed and kept in Hot Air Oven at 105°c for 2 hours. The strips were taken out and reweighed. The percentage moisture absorption was calculated by.

% Moisture content = [Initial weight –Final weight] X 100 / Initial weight.

In vitro dissolution test: The in vitro dissolving experiments were carried out with beaker method. A 150 ml glass beaker containing 125 ml phosphate buffer pH 6.8 as the dissolution medium. A magnetic stirrer bar was used to stirr the medium at 200 rpm. At 1 ,2 ,3 ,4 and 5 min. 5 ml samples were extracted and replaced with 5 ml of new dissolving media. UV absorbance at 244 nm was used to analyses the samples.

Re-dispersion Study: The same techniques were applied to measure the particle size nanosuspension after being re-dispersed from the film. To evaluate how well the nanoparticles could be re-dispersed, square film samples (2 × 2 cm^2) were placed in a suitable amount of distilled water and gently shaken to allow the films to disintegrate and form a fine nanosuspension which will be analysed further.

Total 4 preliminary trial batches were prepared to select drug to Stabilizer ratio to get narrowest and stabilized particle size and 8 trial batches were taken for selecting film forming agent and plasticizer concentration. Batch B1-B8 were checked with Disintegration time and Folding Endurance and then the selected batch B6 was Selected.

Based on the results of the Preliminary batches, a statistical design was applied to optimize the final formulation. It was observed that the concentration of Film forming agents and Plasticizers significantly influenced the physico chemical properties of the formulation. Hence, a 3^2 full factorial design was implemented, considering Film forming agents concentration and Plasticizer concentration as independent variables, while Disintegration time and % In- vitro Drug Release were selected as dependent variables. The independent variables were studied at three levels : low (-1), intermediate (0) and high (1) to evaluate their impact on the critical quality attributes. 3^2 factorial design was applied as per below;

Independent Variables		Dependent Variables	
X1 (mg)	**X2 (mg)**	**Y1 (Sec)**	**Y2 (%)**
Concentration of film forming agent (HPMC E5)	Concentration of Plasticizer (Glycerol)	Disintegration Time	In- vitro drug release (After 10 minutes)

Coded values are as follows

Levels	Coded value	Independent Variables	
		X1 (mg)	X2 (mg)
Low	-1	15	2
Intermediate	0	20	4
High	1	25	6

Design Layout and Data Transformation for Batches

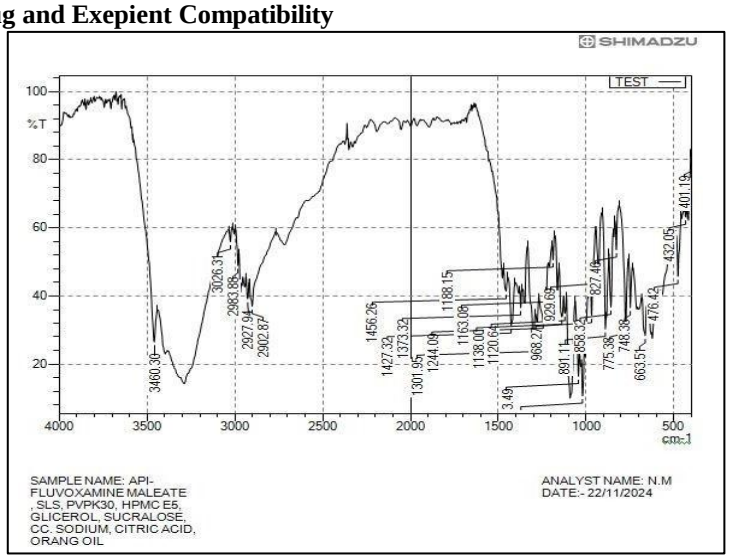
Batch no	Coded Value		Actual Value	
	Concentration of film forming agent (HPMC E5)	Concentration of plasticizer (GLYCEROL)	X1 (mg)	X2 (mg)
F1	+1	-1	25	2
F2	+1	+1	25	6
F3	-1	0	15	4
F4	-1	+1	15	6
F5	+1	0	25	4
F6	-1	-1	15	2
F7	0	+1	20	6
F8	0	0	20	4
F9	0	-1	20	2

9 batches (F1–F9) were formulated using with **HPMC E5 (X_1)** and **Glycerol (X_2)** as independent variables. The actual values for each batch were calculated from coded levels ensuring precise formulation adjustments.

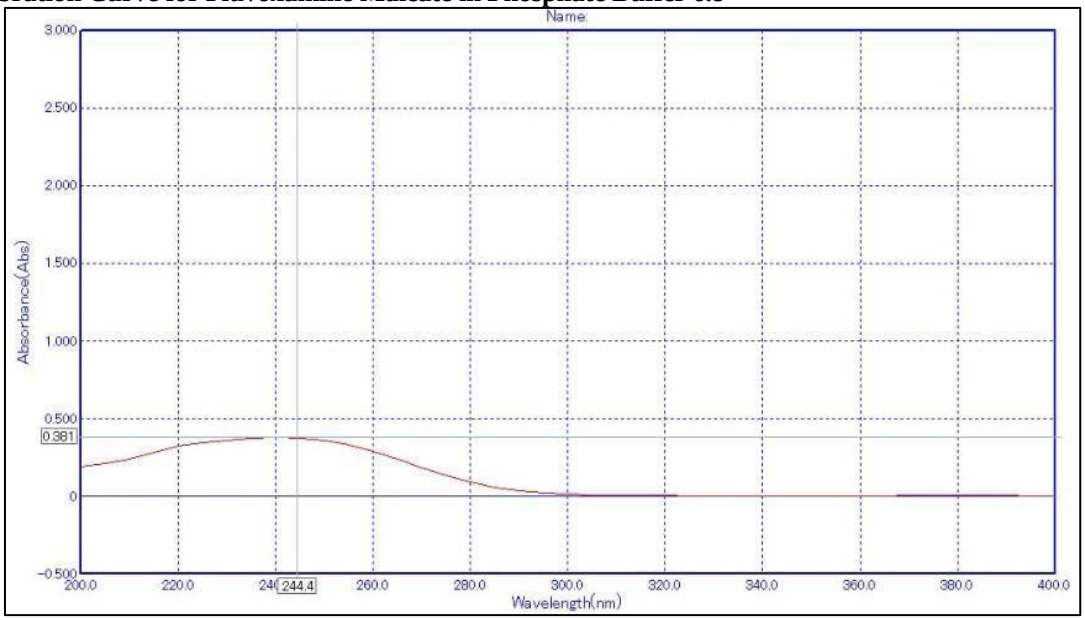
The optimised Nanosuspension is loaded into sublingual film with each containing 25 mg equivalent of fluvoxamine maleate.

RESULT AND DISCUSSION

1. FTIR Study for Drug and Exepient Compatibility

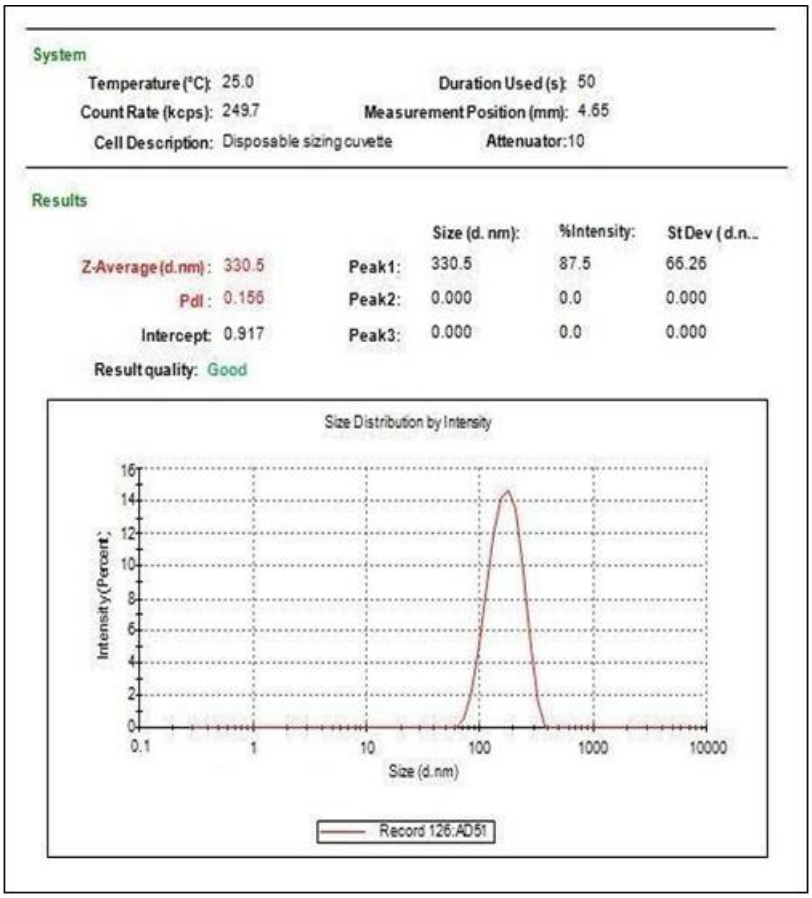


2. Calibration Curve for Fluvoxamine Maleate in Phosphate Buffer 6.8



3. Results for Nanosuspension

PARAMETERS	1:1 N1	**1:2 N2**	1:1 N3	1:2 N4
Particle size(nm)	740.10	**330.50**	1410.00	1787.50
PDI	0.280	**0.156**	0.400	0.425



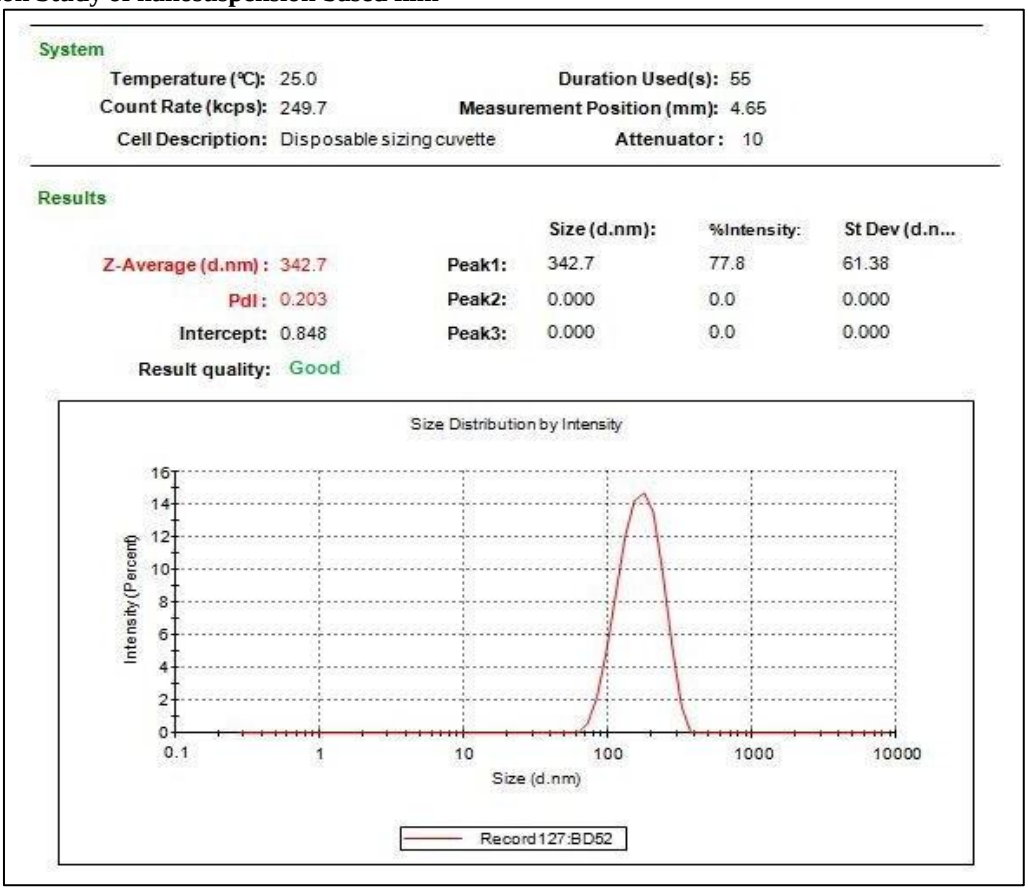
Among the four Trial batches of nanosuspension, Batch N2 exhibited the smallest particle size and polydispersity index (PDI) respectively 330 nm and 0.156, indicating a relatively narrow size distribution.

4. Results of the 3^2 Full Factorial Design Batches

Parameters	Thickness (mm)	Surface pH	Average Weight (mg)	Folding Endurance	% Moisture
F1	0.47±0.04	6.98±0.2	112.5±1.36	190±1.77	7.5±0.065
F2	0.49±0.01	7.25±0.3	116.59±1.39	210±2.38	7.8±0.15
F3	0.42±0.02	7.2±0.3	100.5±1.56	189±2.89	7.1±0.68
F4	**0.42±0.02**	**6.86±0.2**	**103.2±1.03**	**246±1.09**	**5.9±0.12**
F5	0.45±0.01	7.1±0.2	111.5±1.43	197±1.57	7.6±0.68
F6	0.40±0.01	6.85±0.1	101.9±1.3	192±1.25	6.2±0.02
F7	0.42±0.01	6.95±0.2	108.25±1.2	194±1.95	6.8±0.12
F8	0.43±0.06	7.05±0.1	107.6±1.2	192±1.52	7.2±0.07
F9	0.42±0.04	7.01±0.3	105.6±1.2	175±1.91	7.3±0.07

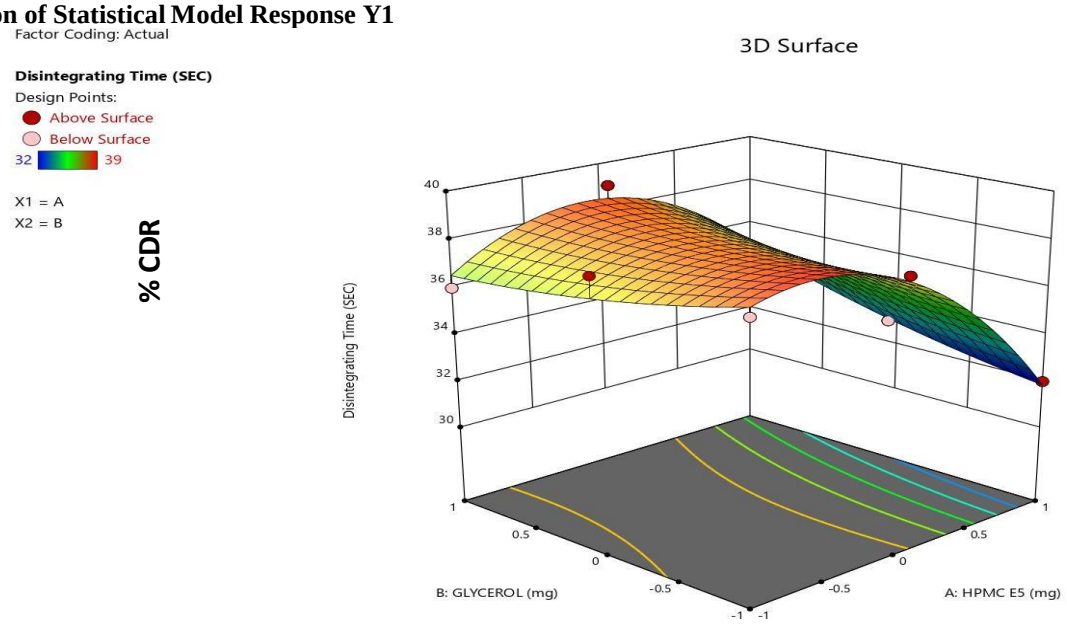
Parameters	Dt. Time (seconds)	In vitro drug release % (After 10 minutes)
F1	38.05±0.25	97.15±1.05
F2	45±0.85	96.87±0.79
F3	40.3±0.6	95.68±1.68
F4	**36±0.45**	**98.57±0.5**
F5	41.5±0.26	97.28±1.39
F6	33.9±0.9	95.65±0.95
F7	47.4±0.79	97.08±0.25
F8	42±0.36	95.77±0.77
F9	34±0.29	96.68±0.68

Re-dispersion Study of nanosuspension based film

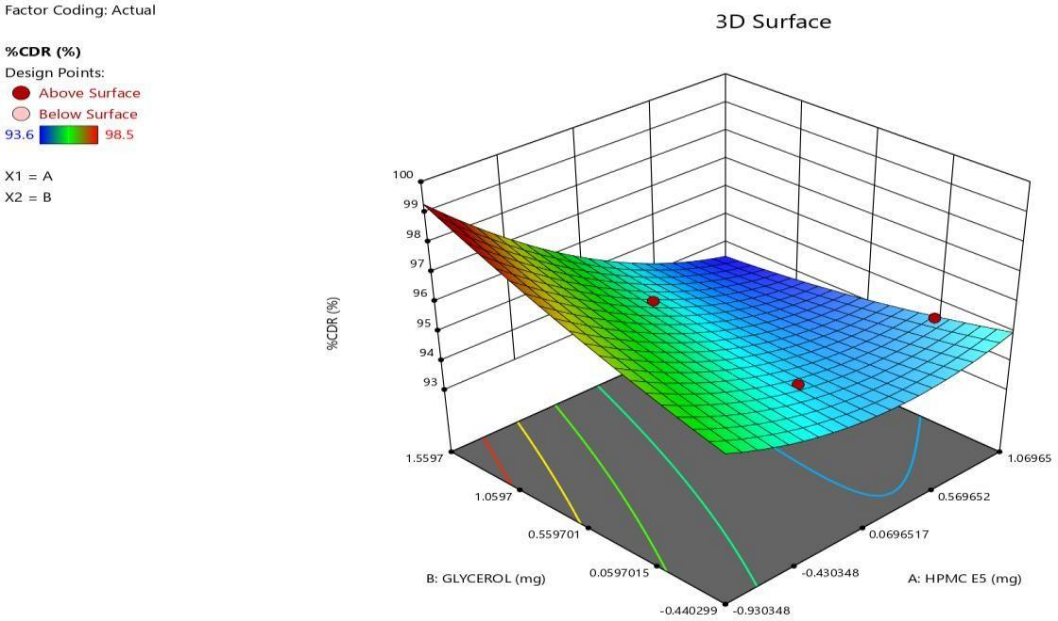


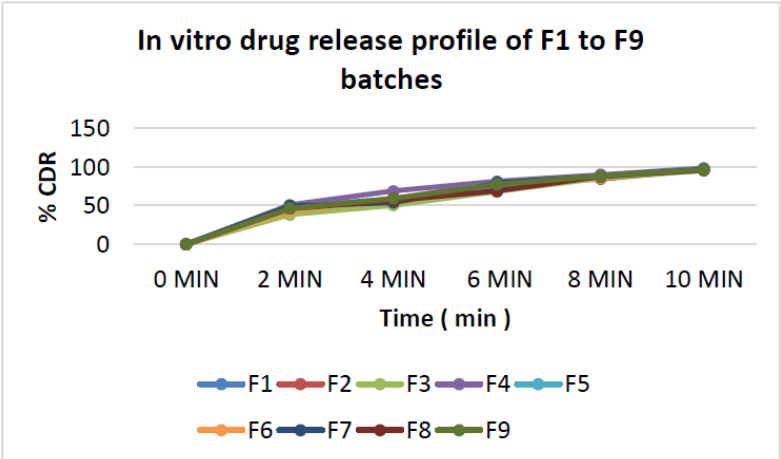
There was no significant difference in particle size between the fluvoxamine maleate nanosuspension (330.5 nm) and the re-dispersed particles from the optimized film (342.7 nm). The slight increase in size may be due to the coating effect of the polymer (HPMC E5) and plasticizer (glycerol) used in the film. Overall, these results suggest that the nanosuspension remained stable within the polymeric matrix.

Validation of Statistical Model Response Y1



Validation of Statistical Model Response Y2





CONCLUSION

The present study successfully developed and optimized a nanosuspension-based sublingual film of fluvoxamine maleate to improve solubility, patient compliance**,** and avoid first-pass metabolism**.** The optimized formulation (F4), prepared using HPMC E5 as film-forming agent and glycerol as plasticizer, demonstrated rapid disintegration (36 seconds) and high drug release (98.57% in 10 minutes). The use of PVP K-30 as a stabilizer in a 1:2 ratio resulted in stable nanosuspension with desirable physicochemical properties. The model was validated through checkpoint batches and exhibited high reproducibility and predictability. Stability studies confirmed that the formulation remained physically and chemically stable for at least one month under accelerated conditions. Although significant potential as a fast-acting, patient-friendly alternative for fluvoxamine maleate delivery via the sublingual route.

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