Preparation and Evaluation of Mouth Dissoliving Film of Fluoxetine HCL

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***Abstract*—Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor used for treating depression, obsessive-compulsive disorder, and panic disorder. Its bitter taste and first-pass metabolism limit patient compliance, especially in pediatric and geriatric populations. The objective of this study was to formulate and evaluate mouth dissolving films of Fluoxetine HCl with enhanced palatability and rapid onset of action.**

The films were prepared by the solvent casting method using HPMC E5 as the primary film-forming polymer due to its good filmogenic and mucoadhesive properties. Doshion P 542, an ion exchange resin, was incorporated as a taste masking agent to complex with Fluoxetine HCl and mask its intense bitterness. Glycerin was used as a plasticizer to provide adequate flexibility and folding endurance. The prepared drug-resin complex was dispersed into the polymeric solution and cast into films.

The formulated films were evaluated for thickness, weight variation, folding endurance, surface pH, disintegration time, drug content, in-vitro dissolution, and taste evaluation. FTIR and DSC studies confirmed drug-excipient compatibility and successful taste masking through complexation. The optimized batch exhibited a disintegration time of <25 seconds and released >95% drug within 4 minutes in phosphate buffer pH 6.8. Taste panel studies showed significant bitterness reduction compared to pure drug. The films also demonstrated adequate mechanical strength and stability.

Thus, mouth dissolving films of Fluoxetine HCl prepared using HPMC E5 and taste-masked with Doshion P 542 by solvent casting method offer a promising approach for rapid drug delivery with improved patient acceptance. For use of Fluoxetine HCl or any prescription medication, consult a healthcare professional to ensure it is appropriate and safe for your condition.

I. INTRODUCTION

Depression and related psychiatric disorders are among the most prevalent health conditions globally, requiring long-term therapy with high patient compliance. Fluoxetine hydrochloride, a selective serotonin reuptake inhibitor, is a first-line agent for treating major depressive disorder, obsessive-compulsive disorder, panic disorder, and bulimia nervosa. However, conventional oral tablets of Fluoxetine HCl exhibit several drawbacks including bitter taste, extensive first-pass hepatic metabolism leading to reduced bioavailability, delayed onset of action, and difficulty in swallowing for paediatric, geriatric, and dysphagic patients. These factors often result in poor patient adherence to therapy.

Mouth dissolving films have emerged as a novel drug delivery system that disintegrates rapidly in the oral cavity without water, allowing direct absorption of the drug through the oral mucosa. This bypasses first-pass metabolism and provides faster onset of action, making it ideal for psychiatric drugs where quick relief is desirable. The solvent casting method is the most widely used technique for film preparation due to its simplicity, low cost, and ability to produce films with good uniformity and mechanical properties. A major challenge in formulating oral films of Fluoxetine HCl is its extremely bitter taste, which can lead to patient non-compliance. To address this, ion exchange resins such as Doshion P 542 are employed as taste masking agents. Doshion P 542 is a weak cation exchange resin that forms an insoluble drug-resin complex with the drug, preventing drug release in the oral cavity and thereby masking bitterness. The complex dissociates in the acidic environment of the stomach, releasing the drug for absorption. HPMC E5 is a low viscosity grade hydroxypropyl methylcellulose polymer that serves as an excellent film former due to its good water solubility, film-forming capacity, and acceptable mechanical strength. When combined with suitable plasticizers, it yields flexible films with rapid disintegration.

Therefore, the present work focuses on the development of mouth dissolving films of Fluoxetine HCl using HPMC E5 as the film-forming polymer and Doshion P 542 as the taste masking agent by solvent casting method, with the aim of achieving rapid disintegration, effective taste masking, and improved patient compliance. For medical conditions requiring Fluoxetine HCl, always consult a healthcare professional for proper diagnosis and treatment guidance.

Advantages of Mouth Dissolving Film: -

1. No water needed
2. Rapid onset of action
3. Bypasses first-pass metabolism
4. Improved patient compliance
5. Effective taste masking
6. Accurate and uniform dosing
7. Portable and convenient
8. Reduced chocking risk
9. Better stability

10. Discreet administration
11. Fast disintegration

II. MATERIALS AND METHODS

Pure sample of Fluoxetine HCL by Swapnroop Drugs & Pharmaceutical, C. Sambhajinagar, HPMC E5 by Destiny Chemicals, Vadodara, Doshion P 542 by Doshion Polyscience Pvt. Ltd., Ahmedabad, Glycerine Research lab Fine Chem Industries, Mumbai. All other chemicals and reagent used were of Jinentra Scientifics, Jalgaon.

Preparation of Mouth Dissolving Film by Solvent Casting Method: -

1) Weighed all ingredient accurately.
2) (Day 1st): - Solution 1 was prepared by dissolving film forming polymer HPMC E5 in distilled water, add Glycerine stirred the solution & kept aside to remove entrapped air bubble. Solution II was prepared by dissolving Taste masking agent Doshion p-542 in distilled water, stir the solution and kept aside for overnight.
3) (Day 2nd): – In solution II add Fluoxetine HCL, stirred solution properly & kept aside Fluoxetine HCL- Doshion P-542 solution for 1 hr.
4) After that solution I and solution II were mixed and stirred properly. Then add Aspartame, citric acid, flavoring & coloring agent mixed and stirred solution and kept aside to removed entrapped air bubbles.
5) Casted the solution by dragger & drag the film on the surface of TDP/ODF film former machine at temperature 70°C by solvent casting method.
6) The film was removed carefully from surface of the machine & cut into desired size & shape (2×2cm) & evaluated for various parameters.

Fig No: -1 Mouth Dissolving Film of Fluoxetine HCL

UV Estimation of Fluoxetine HCL: -

Method of Phosphate Buffer pH 6.8: -

Dissolve 28.80 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate in sufficient water to produce 1000 ml.

Preparation of Fluoxetine HCL Primary Stock Solution (100 µg/ml):-
Weigh accurately 10 mg of Fluoxetine HCl and transfer into 100 ml of volumetric flask. Add some quantity of phosphate buffer pH 6.8 and shake solution to dissolve Ivabradine Hydrochloride then finally make the volume up to 100 ml by using phosphate buffer pH 6.8.
Determination of UV Spectrum: -
Fluoxetine HCl (100 µg/ml) was prepared in phosphate buffer pH 6.8. The solution was scanned under the double beam UV visible spectrophotometer (Shimadzu – 1800) and spectrum was recorded in the wavelength ranges between 200 – 400 nm.
Parameters set for plotting of calibration curve: -
1. Solvents - Phosphate Buffer pH 6.8
2. λmax for Fluoxetine HCl - 226 nm

Preparation Standard of Calibration Curve of Fluoxetine HCL: -
The stock solution of Fluoxetine HCl was prepared by dissolving 10 mg Fluoxetine HCL in phosphate buffer pH 6.8 and final volume was made up to 100 ml to obtained concentration 100 µg/ml. From this stock solution, pipette out 0.2,0.4,0.6,0.8,0, 1.0 ml of solution transfer each into 10 ml volumetric flask & made up the volume up to 10 ml with phosphate buffer pH 6.8 to get 2,4,6,8,10 µg/ml concentration dilutions of Fluoxetine HCL respectively. The absorbance of this solution was measured by UV spectrophotometer at λmax 226 nm. Plotted the graph of absorbance of Fluoxetine HCl against concentration in MS Excel and determined to find straight line equation & correlation coefficient for calculation of percent drug dissolved. The calibration curve of Fluoxetine HCL in phosphate buffer pH 6.8

Table No1: - Preparation of Solution for Calibration Curve of Fluoxetine HCL in Phosphate Buffer

Sr No	Volume Of Stock Solution Taken (ml) and Diluted Upto 10 ml	Concentration (µg/ml)
1	0.2	2
2	0.4	4
3	0.6	6
4	0.8	8
5	1.0	10

Evaluation Parameter of Mouth Dissolving Film: -
1. General Appearance
2. Weight Variation
3. Thickness
4. Folding Endurance
5. Surface pH
6. Wetting time
7. Drug Content
8. Disintegration time

9. In-vitro Dissolution Study

❖ General Appearance: -

I. Texture
II. Colour
III. Odour
IV. Surface

❖ Weight Variation: -

The weight variation was determined by the Digital weighing balance. The weight of three film from the formulation individually was measured & calculate the average weight.

❖ Thickness: -

The thickness of film was determined by digital vernier calliper or by micrometre screw gauge to ensure the uniformity in the thickness of film. The thickness of the film was measured at five separate locations four at corner & one is the middle; then mean value was calculated.

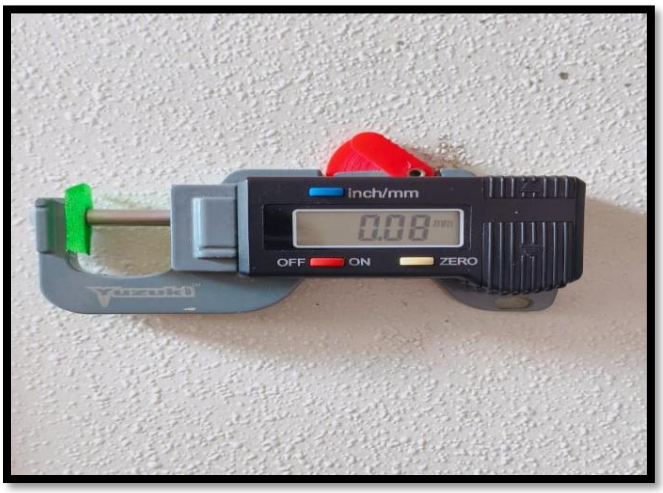

Fig No2: - Thickness of mouth dissolving film

❖ Folding Endurance: -

Folding Endurance was determined by repeated folding of the film at the same place till it breaks. The no of time the film was folded without breaking. The greater the folding endurance valve, greater the film mechanical strength.

❖ Surface pH: -

The surface pH was determined by using digital pH meter. The film was placed in petri dish & moistened with 0.50ml of distilled water. After that bringing the electrode of pH meter into contact with the surface of the film & allowing equilibration for 1min; the pH was measured.

❖ Wetting time: -

A circular paper was placed in the petri dish. 6ml of 1.1% W/V methylene blue solution was added to the petri dish. The film was placed on the surface of tissue paper. The time required for the dye to appear on the surface of the film was noted as the wetting time.

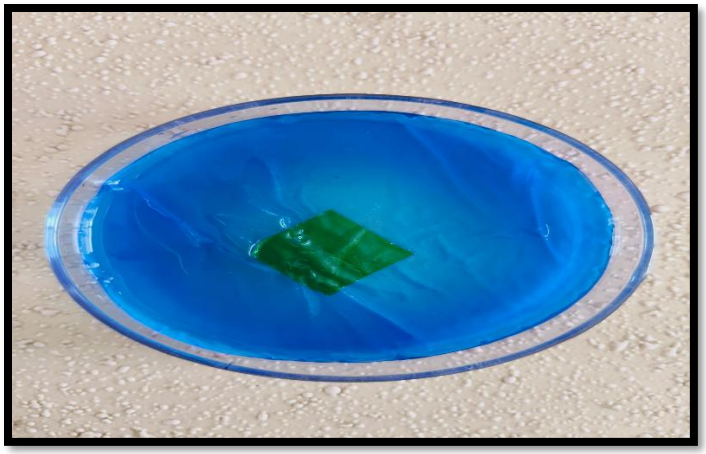

Fig No3: - Wetting time of mouth dissolving film

❖ Drug Content: -

Take a film and dissolve in phosphate buffer pH 6.8 in volumetric flask & make up the volume upto 100ml. After that filter the solution using Whatman filter paper & then withdraw 0.5 ml solution & diluted to 10ml with phosphate buffer pH 6.8. Take absorbance of the dilution using UV spectrophotometer & calculate the drug content.

❖ Disintegration time: -

To determine the disintegration time, take a film place in beaker containing 20ml distilled water. The time taken by the film to disintegration or break was noted as disintegration time.

❖ In-vitro Dissolution study: -

The dissolution study of mouth dissolving was performed using USP type-II (Paddle Apparatus) with rotating speed 50 rpm & using 900ml of phosphate buffer pH 6.8, at 37±0.5℃ temperature. A 5ml sample was withdraw at specific time interval (2,4,6,8,10 min) & replacement with fresh dissolution medium in same amount to maintain sink condition. The samples were filtered through Whatman filter paper No-42. The dilutions was analyzed at λmax 226nm using UV-spectrophotometer. The drug release was plotted against time to determine the release profile of various batches.

❖ Dissolution Profile: -

Dosage: - Fluoxetine HCL
Strength of film: - 10mg
Instrument: - Dissolution Tester (USP) TDT– 08L
Apparatus: - USP Type II (Paddle)
Dissolution: - Phosphate Buffer pH 6.8.
Volume of Dissolution Medium: - 900ml
Temperature: - 37±0.5℃
Rotation speed: - 50 rpm
Wavelength: - 226nm
Aliquotes sampling time: - 0, 2, 4, 6, 8, 10

Sampling volume: - 5ml

III. RESULTS & DISCUSSION

Optimization: -

- The word optimize means 'to make as perfect.
- In terms of sentence, it is defined as choosing a best element from some set of available alternatives.
- Optimization is the process of determining the best way to use existing resources while considering all of the factors that influence decisions in any experiment. The final product not only meets bioavailability requirements, but also practical mass production criteria. Modern optimization techniques based on experimental designs are an essential aid in formulation development because they aid in developing the best possible formulation under a given set of conditions, saving significant time, money, and development effort.

Central Composite Design (CCD): -

Central composite design also known as Box-Wilson design; the central composite design (CCD) is the most often used design for quadratic models. Central composite design (CCD) is a statistical optimization method commonly used in pharmacy and pharmaceutical research. The design comprises of a combination of a two-level factorial points (2^n), axial or star points (2n) and a Central point. The axial point for a two-factor problem includes, ($\pm\alpha$, 0) and (0, $\pm\alpha$) where α is the distance of the axial points from the centre. A two-factor CCD is identical to a 3^2 FD with the rectangular experimental domain at $\alpha = \pm 1$, On the other hand, the experimental domain is spherical in shape for α is $\sqrt{2} = 1.414$. During the development of pharmaceutical products, the CCD is often used in response surface optimization and is widely used to study the relationship between multiple variables and their effect on the response or outcome of interest. The Central Composite Design (CCD) was employed to systematically study the experimental design to investigate the effect of two independent variables (factors), i.e., concentration of HPMC E5 (X1) & Concentration of Doshion P-542(X2) on the dependant variables, i.e. Percentage Drug Release (Y1) & Disintegration Time (Y2). In these study conc. of HPMC E5 (X1) & conc. of Doshion P-542 (X2) was considered as formulation variables which varied, as required by experimental design & the number of other excipients were kept constant. The Percentage Drug Release (Y1) & Disintegration Time (Y2) were selected as response variables. All analysis were performed by using the Design Expert Version 13.0.5.0 software. CCD involves the design and execution of a series of experiments, with different combinations of factors and levels, based on a set of predetermined criteria. The design typically includes both factorial points and axial points. Factorial points represent extreme or minimum/maximum levels of the factors, while axial points help estimate curvature and interaction effects. The response or outcome of interest is measured for each experimental condition. The collected data from CCD experiments are then analyzed using statistical techniques such as regression analysis, analysis of variance (ANOVA), and

response surface modelling. These analyses help identify the key factors that significantly affect the response, optimal factor levels for desired outcomes and any interactions between factors.

Table No2:-Independent Variables and their levels of Central Composite Design: -

Independent variable	Unit	Levels				
		-α	Low	Medium	High	+α
HPMC E5	%	37.9289	40	45	50	52.0711
Doshion P-542	%	1.17157	2	4	6	6.82843

Table No3:-Dependent (Response) Variable of Central Composite Design

Response Variable	Actual Coded Values	Unit
% Drug Release	Y1	%
Disintegration Time	Y2	Seconds

Table No 4:-Factor Combination as per the Chosen Experimental Design: -

Experimental No	HPMC E5		Doshion P-542	
	Coded	Actual%	Coded	Actual%
FLU1	0	45	+1	4
FLU2	+1	50	-α	6
FLU3	0	45	+1	6.82843
FLU4	-1	40	-1	2
FLU5	-α	37.9289	0	4
FLU6	+α	52.0711	0	4
FLU7	0	45	0	4
FLU8	+1	50	-1	2
FLU9	-1	40	-α	6
FLU10	0	45	-α	1.17157

Graphical Representation:

A) % Drug Release:

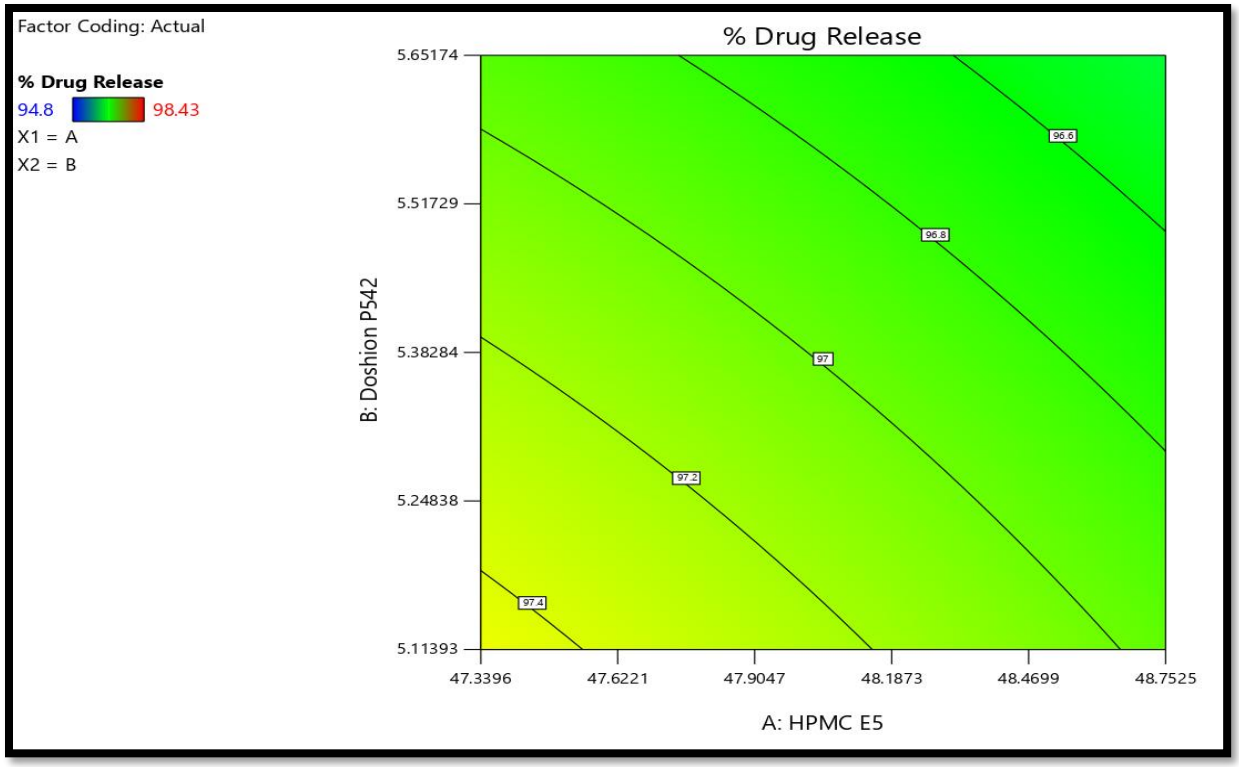

Fig No4:-Response Surface Contour Grapgh Showing the influence of HPMC E5 (x1) and Doshion (X2) on % Drug Release (Y1)

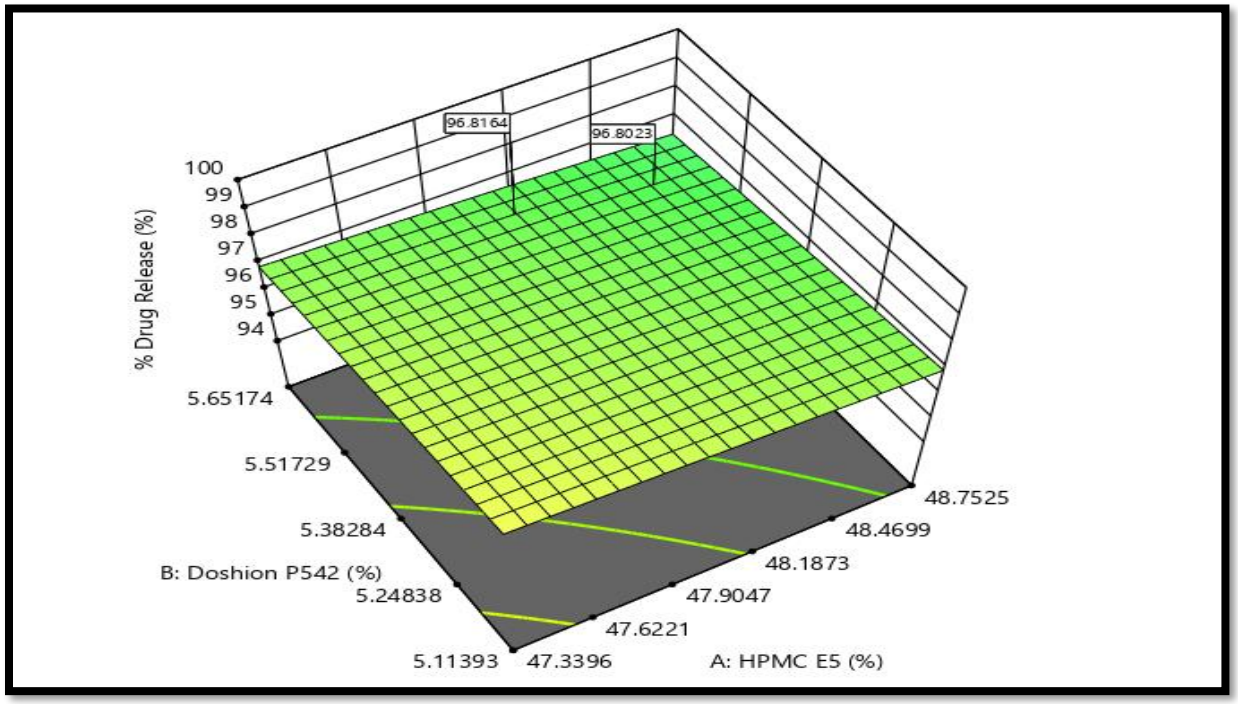

Fig No5:-3D Response Surface Graph Showing the influence of HPMC E5 (x1) and Doshion (X2) on % Drug Release (Y1)

B) Disintegration Time:-

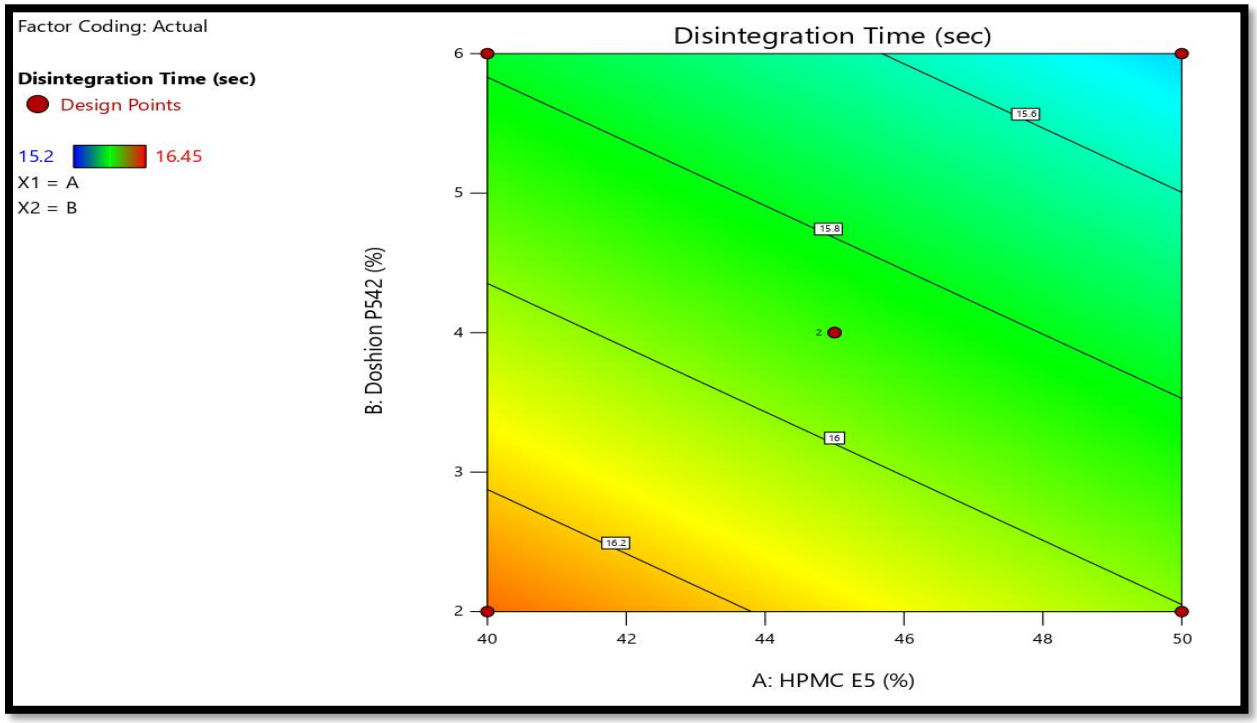

Fig No6:-Response Surface Contour Graph Showing the influence of HPMC E5 (x1) and Doshion (X2) on Disintegration Time (Y2)

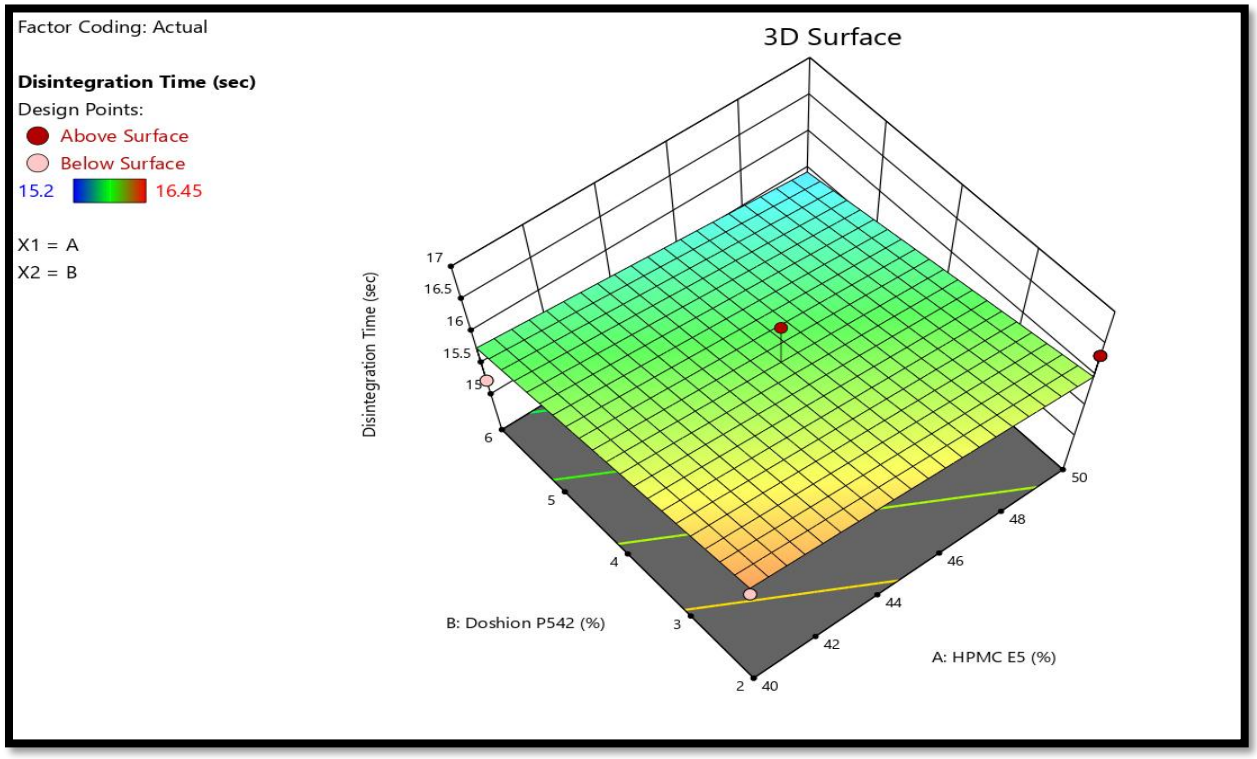

Fig No7: - 3D Response Surface Graph Showing the influence of HPMC E5 (x1) and Doshion (X2) on Disintegration Time (Y2)

Stability Study:

Short Term Stability Study for Optimized Batch (FLU1) :

Stability studies were carried out at 40°C ± 2°C and 75% RH ± 5% RH for 1 month. The film was observed for physical changes, weight variation, folding endurance, disintegration time, drug content & % drug release & other parameters. Mouth dissolving film of Fluoxetine HCL were found to be physically & chemically stable and showed no significant changes in terms of physical characteristics, formulation FLU1 was stable and retained their original properties with minor differences in drug content, % DR and other parameter which are in acceptable limits.

Table No5: - Stability Study of Optimized Batch of Fluoxetine HCl

Evaluation Parameters	Batches	
	Initial	One Month
Weight Variation (mg)	75.32	75.15
Thickness (mm)	0.080	0.080
Folding Endurance	103.23	103.20
Disintegration Time (s)	16.21	16.20
Drug Content (%)	98.10	98.13
Drug Release (%)	98.40	98.43

IV. CONCLUSION

Mouth dissolving films of fluoxetine HCl represent a promising patient-centric drug delivery system, especially for paediatric, geriatric, and psychiatric patients who face difficulty swallowing conventional tablets or have compliance issues.

The key strengths include rapid disintegration without water, potential for enhanced bioavailability via buccal absorption that bypasses first-pass metabolism, discreet administration, and improved acceptability through taste masking of fluoxetine's inherent bitterness. These features directly address noncompliance, which is a major challenge in depression therapy.

However, limitations such as dose-loading capacity, moisture sensitivity, need for specialized packaging, and technical challenges in taste masking and dose uniformity restrict their universal application. They are most suitable for low-to-moderate doses and patients who can follow the "no eating/drinking until dissolved" instruction.

Overall, fluoxetine HCl MDFs are a viable alternative to tablets and oral solutions when rapid onset, ease of administration, and improved compliance are priorities. With optimization of film-forming polymers, plasticizers, and taste-masking strategies, MDFs can enhance therapeutic outcomes in depression and related disorders, particularly in special patient populations.

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