IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
September 2019 Vol.:16, Issue:2

Development and Evaluation of Oral Dispersible Film of Fluoxetine Hydrochloride Using Pullulan

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ISSN 2349-7203
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Submission: 25 August 2019
Accepted: 30 August 2019
Published: 30 September 2019

www.ijppr.humanjournals.com

Keywords: Oral Dispersible film, Pullulan, Glycerin, Solvent casting, Fluoxetine Hydrochloride, Serotonin Reuptake Inhibitor

ABSTRACT

The present study intended to formulate the oral dispersible film of Fluoxetine hydrochloride using pullulan as a polymer and to evaluate it with the different parameters. The drug-excipients studies were carried out to determine any type of incompatibilities by using Fourier transmission infrared spectroscopy (FT-IR). The oral dispersible films were prepared using the solvent casting method using pullulan as a polymer. Glycerin was used as a plasticizer. The prepared films were evaluated for the parameters like physical appearance, thickness, folding endurance, *In-vitro* disintegration, mechanical properties, surface pH, drug content uniformity, taste evaluation, *In*-vitro dissolution test, and stability study. The X5 formulation was found to be stable and appropriate in its evaluation parameters than compared to other formulations. The folding endurance was found to be 259±2.53, disintegration time was found to be 04±0.69, the thickness was found to be 0.081±0.003, tensile strength was found to be 5.55, the % elongation was found to be 27.50, the maximum percentage drug release was found to be 95.80 % in 30 minutes. The drug content was found to be 99.86 with a surface pH of 6.8. In the stability studies of the formulation, the product was found to be stable for 90 days. The oral dispersible film is simple to administer and very much effective for the patients and the prepared film of fluoxetine hydrochloride proves to be a potential candidate for safe and effective oral dispersible drug delivery.

INTRODUCTION

The oral route of administration continues to be most preferred route due to various advantages including ease of administration, avoidance of pain, versatility and are administered in the form of both solid dosage forms (powders, pills, etc.) and liquid dosage forms (elixirs, syrups, emulsions, mixtures). The major disadvantage of this route is the difficulty in swallowing or chewing solid dosage forms, particularly in pediatric and geriatric patients. Due to fear of throat choking many pediatric and geriatric patients are unwilling to take these solid preparations. To overcome these difficulties, Oral Dispersible films have been introduced to make it easier for the patients to administer the drug by themselves and without any expertise in medicine administration. Oral film drug delivery is a better alternative against oral solid tablets because of its fear of taking and the risk of choking for certain patient populations even it has short disintegration/dissolution times and also the oral availability of many drugs are very poor because of the pH stomach, the presence of enzymes, extensive first-pass metabolism these can also be solved by making oral films. Due to all these types of complications, the pharmaceutical industry opted for the better alternative of a drug delivery system in the form of oral dispersible films [1].

Fluoxetine belongs to the class of selective serotonin reuptake inhibitor (SSRI). It blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on 5HT1A autoreceptors, which leads to an increase in 5-hydroxytryptamine levels and enhances the mood of the patients. Fluoxetine is used to treat depression, major depressive disorder, bulimia nervosa (a binge eating disorder) obsessive-compulsive disorder (OCD), panic disorder, and pre-menstrual dysphoric disorder (PMDD). The bioavailability of selective-serotonin reuptake inhibitor complex is concerning 60-80% and having 94-95% of protein binding with a biological half-life of 1-3 days and it's a BCS category I drug [2-3].

The present study aimed to prepare the oral dispersible film of fluoxetine hydrochloride with different percentage of pullulan to form the film with glycerin as a plasticizer.

MATERIALS AND METHODS

Fluoxetine Hydrochloride was procured from Yarrow Chem., Mumbai. Pullulan was obtained fromHayashibara.Co. Ltd, Okaya, Japan. Mannitol and citric acid were procured from S.D Fine, Mumbai. All other chemicals were of analytical grade.

Standard calibration curve of Fluoxetine Hydrochloride in Phosphate buffer 6.8:

From solution having concentration 100 µg/ml aliquots of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5 ml were pipette out into 10ml volumetric flasks. The volume was made up to the mark with Phosphate buffer 6.8 to get the final concentration of 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 µg/ml respectively. The absorbance of each concentration was measured at 216.00nm.

Drug-Excipients Interaction studies:

The drug-excipients interaction study was carried out by using FTIR spectrophotometer.

FTIR spectroscopy studies:

The FTIR spectroscopy was employed to further characterize the possible interaction between drug and excipients in the solid-state on an Infrared spectrophotometer (Shimadzu Affinity-l) by conventional KBr plate method. 5mg of drug sample was mixed with 500 mg of powdered potassium bromide. The mixture was passed with 25.000psipressurein a press to form a small pellet. IR spectrum of drug was recorded in the frequency range of 400-4000 cm^{-1}. The significant peaks were recorded and were matched with standard FTIR.

Calculation of dose:

Loading dose:

Radius of Petri plate = 6cm.

Area of circle = πr^2

$\therefore 3.14 \times 3^2 = 28.26\ cm^2$

Now dose is 10mg and the cut film is of $3\times2\ cm^2 = 6\ cm^2$

$\therefore$ $6\ cm^2$ = 10mg so, $28.26\ cm^2$ =?

=28.26×10/6 = **47mg**

Preparation of Oral Dispersible Film:

Oral Dispersible Film's of Fluoxetine Hydrochloride were prepared using pullulan as polymer by solvent casting method. Pullulan was dissolved in 8ml of distilled water using magnetic

stirrer, similarly, mannitol was dissolved in remaining 2ml of hot water and to this sucralose was added. The drug was dissolved in a polymer solution and also plasticizer and citric acid were added to the polymeric solution. The solution was allowed to stand for 30 min to allow deaeration to take place and also to remove all the air bubbles. The solution was casted on a petri plate and dried at room temperature for 24 hours. The film was removed and cut into the required size of 3×2 cm^2. In this way, four films of each batch were prepared [4-5].

Table No. 1: Formulation of Oral Dispersible Film (Formulation plan).

Batch No.	Drug (mg)	Pullulan (mg)	Glycerin (mg)	Mannitol (mg)	Sucralose (mg)	Citric Acid (mg)	Water (ml)
X1	47	400	100	40	20	20	10
X2	47	400	120	40	20	20	10
X3	47	400	140	40	20	20	10
X4	47	500	125	50	25	25	10
X5	47	500	150	50	25	25	10
X6	47	500	175	50	25	25	10
X7	47	600	150	60	30	30	10
X8	47	600	180	60	30	30	10
X9	47	600	210	60	30	30	10

Evaluation of Oral Dispersible Films:

a) Physical appearance: This parameter was checked simply with a visual inspection of films and evaluation of texture by feel or touch.

b) Weight variation &Thickness of films: The weight of each film strip was taken on an electronic balance and then the average weight was calculated [6-7].

The thickness of the films was measured using screw gauge with a least count of 0.01mm at different spots of the films. The thickness was measured at three different spots of the films and the average was taken [7].

c) Folding endurance of films: The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the film (approximately 3x2 cm^2) at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance [8-9].

d) *In-vitro* disintegration time of films: In vitro disintegration time is determined visually in a Petri dish of 10 ml artificial saliva with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates [10].

e) Mechanical Properties: The Film was evaluated for the measurement of mechanical properties using tensile strength apparatus. Film of dimension 3 x 0.5 size was held between two clamps at a distance of 2.5 cm. The Film was pulled by the clamp as weight is applied through one end [11].

$$\text{Tensile strength} = \frac{\text{Load Failure} \times 100}{\text{Strip thickness} \times \text{Strip Width}}$$

Percentage Elongation was calculated by the following equation:

$$\text{Percentage Elongation} = \frac{\text{Increase in length} \times 100}{\text{Original length}}$$

f) Surface pH of films: Surface pH was determined by the films were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode near the surface of films and allowing equilibrate for l min. Reading was recorded in pH meter [12-13].

g) Drug content uniformity study of films: The films were tested for drug content uniformity by UV-Spectrophotometric method. Films of 3×2 cm^2 were cut from three different places from the casted films. Each film was placed in 10 ml volumetric flask and diluted with Phosphate buffer 6.8 up to 10 ml. The absorbance of the solution was measured at 216 nm using UV/visible spectrophotometer (Shimadzu UV-l800). The percentage of drug content was determined [14-18].

h) *In-vitro* Dissolution Study: *In-vitro* dissolution of Fluoxetine Hydrochloride Oral dispersible films was studied in USP XXIV dissolution test apparatus 900ml Phosphate buffer 6.8 solutions was used as dissolution medium. The stirrer of the apparatus was adjusted to rotate at 50 pm. The temperature of the dissolution medium was maintained at 37± 0.5°C throughout the experiment. One film was used in each test. Samples after the dissolution medium (5ml) was withdrawn using a syringe. The solution was filtered with Whatman filter paper. Samples were withdrawn after 2, 5, 10, 15, 20, 25, 30-minute intervals

of time and analyzed for drug release by measuring the absorbance at 216 nm. The volume withdrawn at each time interval was replaced with a fresh quantity of dissolution medium Cumulative percent Fluoxetine Hydrochloride released was calculated and Plotted against time [19].

i) Stability Study: The need of stability testing is to test the product and also to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of various environmental factors such as temperature, light, humidity, and enables recommended Storage conditions, retest periods and shelf lives to be established [20].

In the present study, stability studies were carried out at Room Temperature and Accelerated testing: 40°C ± 2°C / 75 % RH ± 5% RH for 3 months for the optimized formulation. The optimized formulation was analyzed for the Physical appearance, Drug content, Disintegration Time.

RESULTS AND DISCUSSION

RESULTS

1) From the standard calibration curve, it was observed that the drug obeys Beer's law. The drug showed good linearity with the regression of co-efficient (R^2) of 0.999 and the equation for this line obtained was found to be 0.042x-0.002.

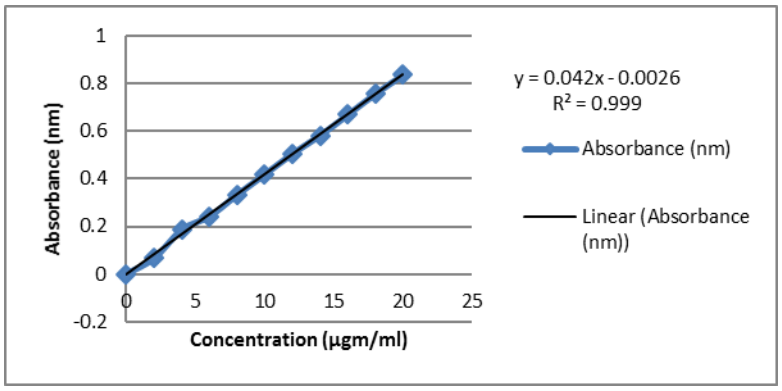

Figure No. 1: Standard Calibration curve of Fluoxetine Hydrochloride

2) The peaks obtained in the FT-IR spectroscopy of pure drug Fluoxetine Hydrochloride and the optimized formulation was matched with the standard values for the compatibility and it shows no interaction between them as they are compatible with each other.

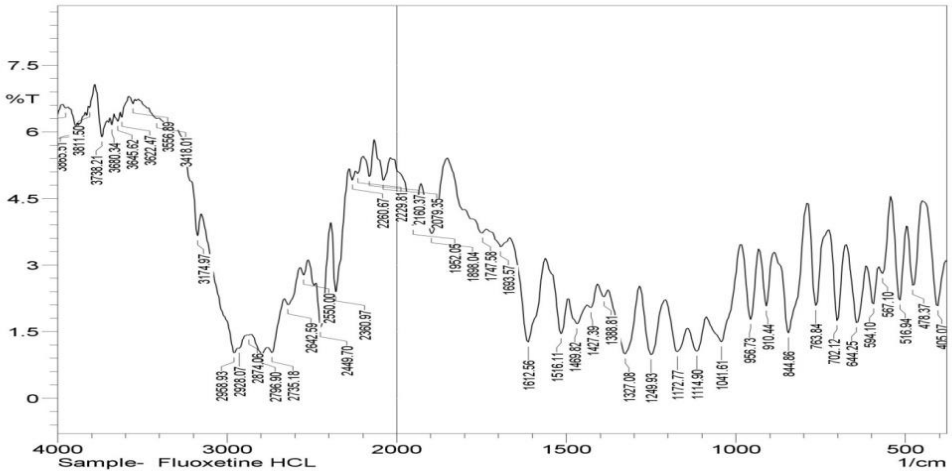

Figure No. 2: FT-IR Spectrum of pure drug Fluoxetine Hydrochloride

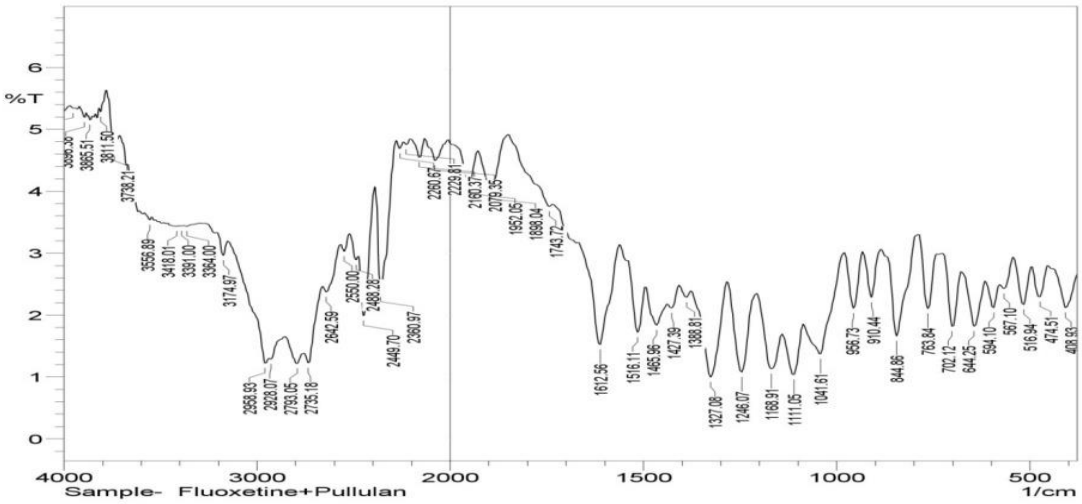

Figure No. 3: FT-IR Spectrum of Optimized Formulation (X5)

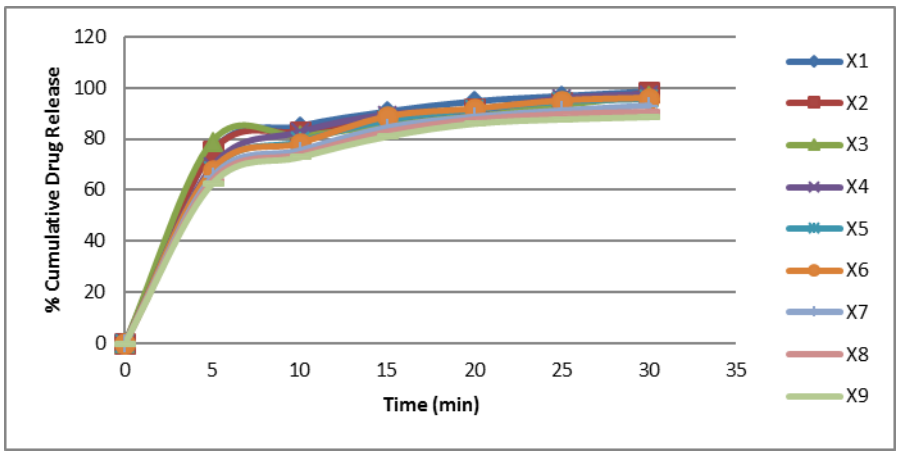

Figure No. 4: % Cumulative Drug Release of X1-X9 formulation.

Table No. 2: Evaluation of Films

Batch No.	Appearance	Folding Endurance	Disintegrationtime (sec)	Thickness (mm)	Tensile Strength (gm/mm^2)	%Elongation
X1	Transparent	83±0.57	09±0.57	0.063±0.0018	5.09	13.33
X2	Transparent	136±1.52	10±0.58	0.066±0.008	4.80	16.66
X3	Transparent	125±1.02	11±0.57	0.068±0.0008	4.49	20.02
X4	Transparent	185±1.15	11±0.68	0.077±0.0008	5.65	20.5
X5	Transparent	257±2.51	04±0.69	0.079±0.001	5.52	26.66
X6	Transparent	201±1.59	13±0.57	0.082±0.001	4.89	30.08
X7	Transparent	166±1.59	15±0.57	0.086±0.0013	6.98	26.33
X8	Transparent	223±1.61	16±0.57	0.089±0.002	6.29	30.10
X9	Transparent	210±1.53	18±0.68	0.092±0.0012	6.03	36.66

Table No. 3: Evaluation of Final Formulation.

Formulation Batches	Drug Content	Surface pH
X1	98.15	6.6
X2	98.53	6.5
X3	98.40	6.6
X4	97.10	6.7
X5	99.90	6.8
X6	98.02	6.5
X7	98.40	6.8
X8	96.50	6.7
X9	98.10	6.8

Table No. 4: *In*-vitro Dissolution study of the prepared films.

Time (min)	Batch no.								
	X1	X2	X3	X4	X5	X6	X7	X8	X9
0	0	0	0	0	0	0	0	0	0
5	75.15	72.25	78.96	69.25	67.81	67.88	65.16	63.92	62.67
10	85.01	83.02	81.05	82.71	79.09	78.16	75.42	74.02	72.99
15	90.72	87.10	85.19	89.52	87.60	88.68	84.49	82.90	81.11
20	94.71	91.71	89.13	91.22	91.79	91.72	88.65	87.68	86.20
25	96.79	94.18	93.00	95.94	94.91	94.93	91.11	89.83	87.86
30	98.60	98.27	96.86	97.55	95.80	95.90	92.98	90.67	88.79

Kinetics of drug release: To analysis, the mechanism for the release and release rate kinetics of the formulated dosage form, the data obtained from conducted studies were fitted into Zero order, First order. In this by comparing the values obtained, the best-fit model was found to be First order equation was selected.

Table No. 5: Kinetics of the Optimized Formulation

Formulation	Zero Order	First Order	Best Fit Model
X5	0.705	0.970	First Order Equation

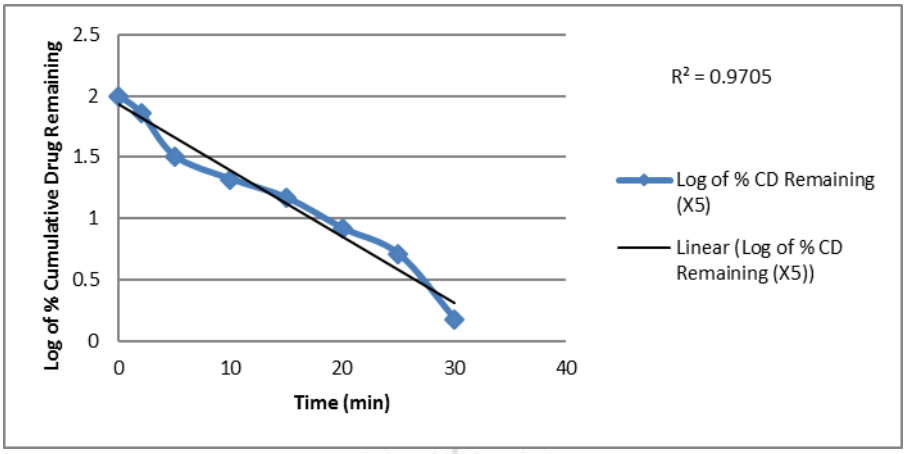

Figure No. 5: Log % of Cumulative Drug Remaining of X5 vs Time (First order equation).

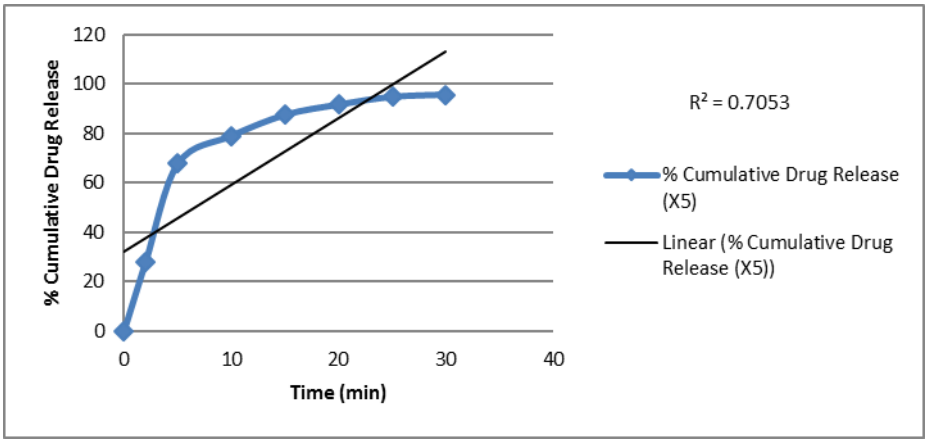

Figure No. 6: % Cumulative Drug Release of X5 vs Time (Zero order Equation)

Stability Study: The stability studies of optimum formulation revealed that there is no significant reduction in drug content, Disintegration time, the appearance was observed over a period of 3months.

No significant change was observed in drug content and disintegration time at room temperature and as well as on accelerated stability studies at40°C ± 2°C / 75 % RH ± 5% RH. Hence formulation X5 was found to be stable for 90 days.

Table No. 6: Stability Study for X5 Formulation

Stability (Room Temp)	Appearance	Drug Content (%)	Disintegration time(sec)
0 Days	Transparent	98.98	12
15 Days	Transparent	98.90	12
30 Days	Transparent	98.85	12
45 Days	Transparent	98.71	12
60 Days	Transparent	98.60	11
75 Days	Transparent	98.50	11
90 Days	Transparent	98.41	10

Table No. 7: Stability Study for X5 Formulation (Accelerated Study)

Stability (40°C ± 2°C / 75 % RH ± 5% RH)	Appearance	Drug Content (%)	Disintegration time(sec)
0 Days	Transparent	98.98	12
15 Days	Transparent	98.90	12
30 Days	Transparent	98.83	12
45 Days	Transparent	98.75	11
60 Days	Transparent	98.65	11
75 Days	Transparent	97.64	10
90 Days	Transparent	97.40	10

Scanning Electron Microscopy:

The SEM study was carried out to study the surface morphology of the prepared film.

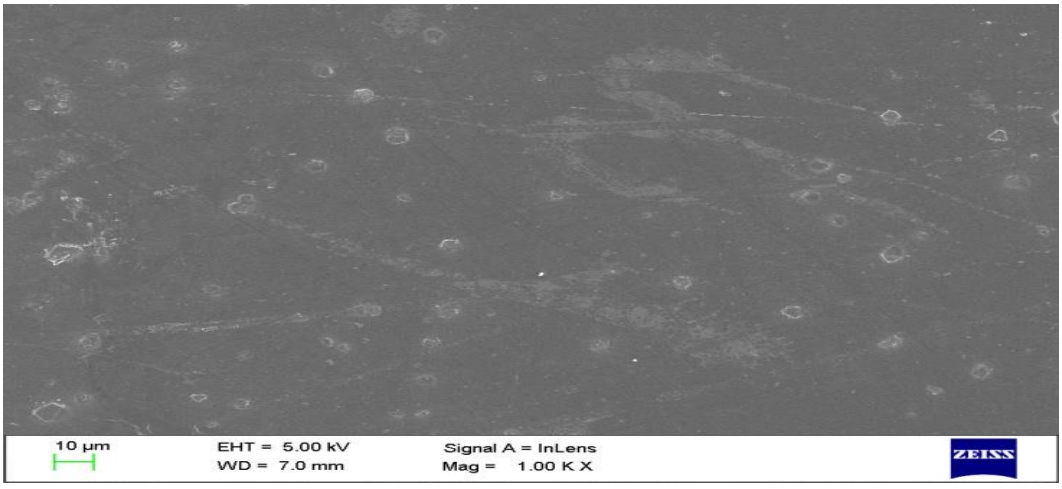

Figure No. 7: Surface Morphology of the prepared film at 1000X

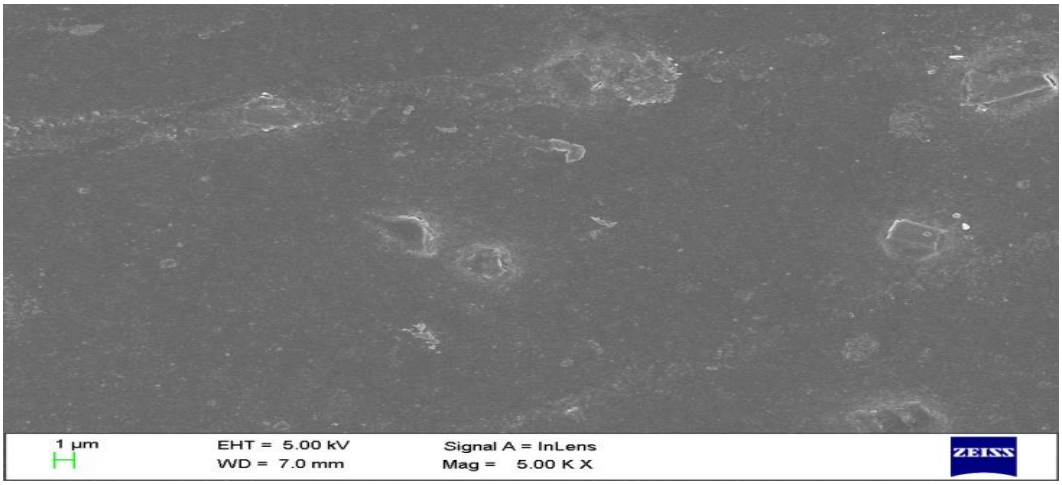

Figure No. 8: Surface Morphology of the prepared film at 5000X

DISCUSSION

An oral dispersible film of Fluoxetine hydrochloride was prepared using pullulan with glycerin as a plasticizer by solvent casting method. The results of the present study show that the oral dispersible film can decrease the disintegration time due to which it can give a rapid release of the drug in the body.

It is concluded that the oral dispersible film of Fluoxetine hydrochloride gives an effective fast release of the drug (i.e. up to 70 % of the drug gets released in 5 minutes). When compared with the % drug release of the market formulation in tablet formulation its was found that only 78.5% of the drug gets released in 30min and also when evaluated for the marketed fast dissolving tablet the drug release of 90.14% was found to be in 30min, while the oral dispersible film shows a release of 95.80% of the drug.

The optimized formulation was chosen from the various evaluation parameters tested and so the X5 formulation was found to be optimized.

The compatibility study done by FT-IR shows that there is no drug-excipient interaction. The stability study of the optimized formulation shows that the prepared oral dispersible film was stable for 90 days.

Finally, it can be concluded that the Fluoxetine hydrochloride oral dispersible film can be a better alternative for the tablet type of dosage form.

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