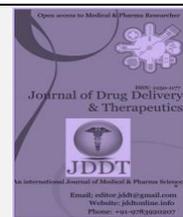
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Research Article

## Formulation, Development and Evaluation of Fast Dissolving Oral Film of a Selective Serotonin-Reuptake Inhibitor (SSRI) Escitalopram Oxalate

Nitesh Yadav\*, Pushendra Soni, Lavakesh Kumar Omray

Radharaman Institute of Pharmaceutical Sciences, Bhopal (M.P.), India

### ABSTRACT

The purpose of this research was to develop fast dissolving oral film of Escitalopram oxalate. Fast dissolving oral film offers a solution for paediatrics, geriatrics; psychiatric or mentally ill people and those have difficulty in swallowing tablets/capsules resulting in improved patient compliance. Selective serotonin reuptake inhibitors (SSRIs), which are broad spectrum antidepressants that are effective for major depressive disorder and several anxiety disorders. Escitalopram Oxalate is highly selective, more effective and better than other SSRIs. The prepared formulations were evaluated for Thickness, Weight uniformity, Folding Endurance, Percentage of Moisture Content, Drug Content Analysis, Disintegrating time and *In vitro* dissolution study. Stability studies were carried out with optimized formulation F5 which was stored for a period of one, two and three months at 40±2°C temperature and 75±5% relative humidity for a period 3 months. Thus it can be concluded that Escitalopram oxalate fast dissolving films could be commercially exploited for the treatment of panic disorder using Escitalopram oxalate with merits of faster onset of action, avoidance of extensive first pass metabolism, low dosage regimen, enhanced bioavailability and improved patient compliance.

**Keywords:** Escitalopram oxalate, Fast dissolving oral film, Evaluation

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### \*Address for Correspondence:

Nitesh Yadav, Radharaman Institute of Pharmaceutical Sciences, Bhopal (M.P.), India

### INTRODUCTION

Escitalopram oxalate is a newer antidepressant used for the treatment of panic disorder. Escitalopram oxalate is S(+) enantiomer of the racemic bicyclic phthalene derivative of citalopram, which is chemically S(+)-1-[3(dimethylamino)propyl]-1-p-fluorophenyl-5-phthalene carbonitrile<sup>1-2</sup>.

Escitalopram oxalate acts by increasing intrasynaptic levels of the neurotransmitter serotonin by blocking the reuptake of the neurotransmitter into the neuron. Its half-life is about 27-32 hours. It is metabolized in the liver, especially by the CYP3A4 and CYP2C19 after oral administration. Its bioavailability is 80% and protein binding is approximately 56%. It is poorly soluble in water so its absorption is less. It is acidic and its pKa value is 4.19 which is satisfactory for selection of drug. The Log Partition coefficient value is 3.45. The t<sub>max</sub> value of Escitalopram oxalate is 4hr after multiple dosing. The dose of 5-20mg once a day and is used for treatment of depression<sup>3</sup>.

This is seen to afflict nearly 45% of the general population. Particularly, the difficulty is experienced by pediatric and

geriatric patients<sup>3</sup>. To overcome these problems, orodispersible film have been developed, which has good dose uniformity, easy administration and serves as the first choice of dosage form for paediatrics, geriatrics and travelling patients. Fast-dissolving oral films (FDFs) showed a great potential over other dosage forms for the delivery of drugs since they provide distinct advantages including rapid disintegration and dissolution in the oral cavity thus increase bioavailability with faster onset of action and avoidance of first-pass effect<sup>4</sup>. Due to high permeability of oral mucosa, it allows direct access of drug to the systemic circulation and avoids the first pass metabolism<sup>5</sup>. FDFs represent an advantageous dosage form, especially for geriatric and pediatric patients<sup>6-7</sup>.

### MATERIALS AND METHODS

#### Materials

Escitalopram oxalate was obtained as a gift sample from Pharmaceutical Company. HPMC was procured from Qualikems fine chem Pvt Ltd Vadodhara. PEG400, sodium starch glycolate, croscarmellose sodium was obtained from S.D fine chemicals limited, Mumbai. Citric acid, ethanol was

obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid,  $\text{KH}_2\text{PO}_4$ ,  $\text{NaOH}$  was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

### Standardization of Escitalopram oxalate by UV-Visible spectrophotometry

#### Determination of $\lambda_{\text{max}}$ of Escitalopram oxalate

The  $\lambda_{\text{max}}$  of Escitalopram oxalate was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer (Labindia 3000+). Accurately weighed 10 mg of drug was dissolved in 10 ml of Phosphate buffer pH 6.8 solutions in 10 ml of volumetric flask. The resulted solution (1000 $\mu\text{g}/\text{ml}$ ) was used to prepare the concentration 10 $\mu\text{g}/\text{ml}$ . The spectrum of this solution was recorded in 200-400 nm range using U.V. spectrophotometer (Labindia-3000+) <sup>8</sup>. After the complete scan  $\lambda_{\text{max}}$  of Escitalopram oxalate was found 232 nm.

#### Preparation of calibration curve:

From stock solutions of Escitalopram oxalate 1 ml was taken and diluted up to 10 ml. from this solution 0.5, 1.0, 1.5, 2.0 and 2.5 ml solutions were transferred to 10ml volumetric flasks and make up the volume up to 10 ml with Phosphate

buffer pH 6.8, gives standard drug solution of 5, 10, 15, 20, 25 $\mu\text{g}/\text{ml}$  concentration.

### Formulation development of oral film of Escitalopram oxalate

#### Solvent casting technique

Drug (Escitalopram oxalate) containing fast dissolving films were fabricated by the solvent casting method. The optimized amount of HPMC was dissolved in 5ml of water and stirrer continuously for 1 hour, optimized amount of plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm \* 10 films area and was dried at controlled room temperature (25°-30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use. Formulations were prepared using HPMC K15, PEG-400, SSG and CCS at different drug: polymer ratios. The compositions of the formulations were shown in table 1.

Table 1: Formulation of Escitalopram oxalate oral fast dissolving films

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6
Escitalopram oxalate	120	120	120	120	120	120
HPMC	300	600	900	300	600	900
PEG-400	150	150	150	150	150	150
SSG	200	300	400	-	-	-
CCS	-	-	-	200	300	400
Mannitol	100	100	100	100	100	100
Citric acid	100	100	100	100	100	100
DM water qs to (ml)	30	30	30	30	30	30

#### Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm<sup>2</sup> films present whole plate = 12
- Each film contains 10 mg of drug.
- 12 no. of films contains mg of drug? = 10×12 = 120mg
- The amount of Escitalopram oxalate added in each plate was approximately equal to 10mg.

#### Evaluation

The formulations were evaluated by the following tests <sup>9-12</sup>.

#### Thickness

Randomly 10 films were selected and thickness was measured using vernier calliper at three different places.

#### Weight variation

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

#### Folding endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.

### Percentage of moisture content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

### Drug content analysis

The patches (n = 3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 232nm.

### Disintegrating time

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time. Three super disintegrating agent were selected for this work. The film of (2.5\*2.5 cm) size (unit dose) was placed on a petridish containing 10 ml of distilled water. The time required for the film to break was noted as cursive *in vitro* disintegration time.

### In vitro dissolution study

The *in vitro* dissolution test was performed using the USP dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at  $37 \pm 0.5^\circ\text{C}$ ; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery ( $2.5 \times 2.5 \text{ cm}^2$ ) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2 and 5 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45  $\mu\text{m}$  membrane filter and the concentration of the dissolved Escitalopram oxalate was determined using UV-Visible spectrophotometer at 232nm. The results were presented as an average of three such concentrations.

### Stability studies

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at  $40 \pm 2^\circ\text{C}$  temperature and 75 $\pm$ 5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method.

## RESULTS AND DISCUSSION

To check solubility of drug in other solvent like water, ethanol, methanol, 0.1 N HCl, 0.1 N NaOH, Chloroform and 6.8 pH Phosphate buffer. Melting point was determined by Melting point apparatus (Chemiline CL-725) and found to 150-151 $^\circ\text{C}$ . The  $\lambda_{\text{max}}$  found for Escitalopram oxalate is 232.0 nm. Various methods are available for casting of oral films. This is fast disintegrating oral film hence on the laboratory scale solvent casting technique was adopted for formulation of films. In the present work, fast dissolving oral films of Escitalopram oxalate were prepared by solvent casting method with a view to enhance patient compliance, for the treatment of depression. Fast dissolving oral films were disintegrated in the mouth and were dissolved within a matter of few seconds without need of water. Fast dissolving oral films were prepared using different concentration of superdisintegrants and evaluated. Different formulations (F1-F6) were prepared using varying amount of SSG and CCS. The prepared formulations were evaluated for Thickness, Weight uniformity, Folding Endurance, Percentage of

Moisture Content, Drug Content Analysis, Disintegrating time and *In vitro* dissolution study. Stability studies were carried out with optimized formulation F5 which was stored for a period of one, two and three months at  $40 \pm 2^\circ\text{C}$  temperature and 75 $\pm$ 5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of film was found to slightly decrease at higher temperature.

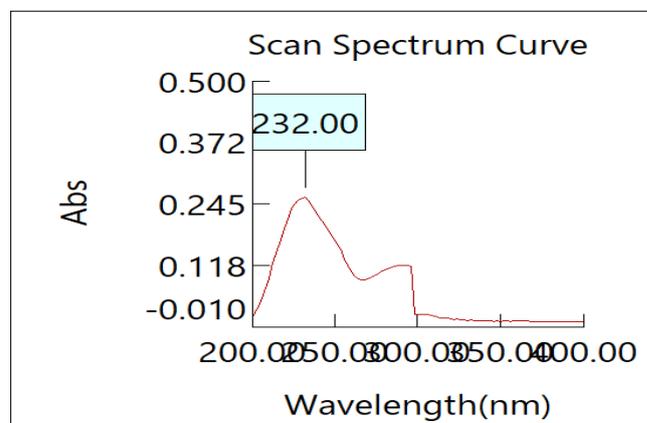


Figure 1: U.V. Spectra of Pure Drug (Escitalopram oxalate)

### G) Calibration curve of Escitalopram oxalate at $\lambda_{\text{max}}$ 232nm

Observation table:

Table 2: Calibration curve of Escitalopram oxalate in Phosphate buffer pH 6.8

S. No.	Conc. ( $\mu\text{g/ml}$ )	Absorbance
1.	2	0.207
2.	4	0.378
3.	6	0.534
4.	8	0.685
5.	10	0.871

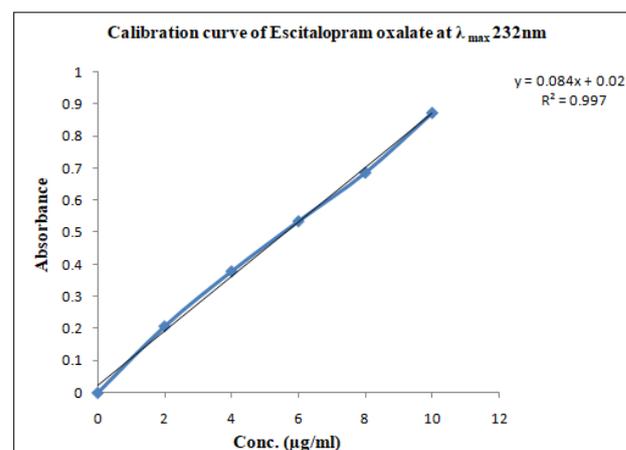


Figure 2: Calibration Curve of Escitalopram oxalate in Phosphate buffer pH 6.8 at 232nm

**Table 3: Result of general appearance, thickness, weight variation and % assay**

Formulation code	General Appearance	Thickness* ( $\mu\text{m}$ )	Weight* (mg)	(%) Assay*
F1	Translucent	0.09 $\pm$ 0.01	85	96.65 $\pm$ 0.12
F2	Translucent	0.10 $\pm$ 0.02	122	97.56 $\pm$ 0.21
F3	Translucent	0.12 $\pm$ 0.02	153	96.45 $\pm$ 0.14
F4	Translucent	0.08 $\pm$ 0.01	86	97.45 $\pm$ 0.32
F5	Translucent	0.12 $\pm$ 0.02	125	99.85 $\pm$ 0.14
F6	Translucent	0.13 $\pm$ 0.02	155	98.85 $\pm$ 0.25

\*Average of three determination (n=3)

**Table 4: Result of folding endurance, disintegrating time, tensile strength &% of moisture content**

Formulation code	Folding endurance*	Disintegration time (Sec.)*	Tensile strength (kg/cm <sup>2</sup> )*	Moisture Content (%)*
F1	More than 100	88 $\pm$ 4	0.658 $\pm$ 0.008	2.23 $\pm$ 0.12
F2	More than 100	80 $\pm$ 5	0.698 $\pm$ 0.006	2.10 $\pm$ 0.14
F3	More than 100	73 $\pm$ 3	0.712 $\pm$ 0.007	1.85 $\pm$ 0.13
F4	More than 100	66 $\pm$ 5	0.612 $\pm$ 0.006	1.65 $\pm$ 14
F5	More than 100	50 $\pm$ 4	0.756 $\pm$ 0.005	1.21 $\pm$ 12
F6	More than 100	60 $\pm$ 5	0.763 $\pm$ 0.004	1.92 $\pm$ 11

\*Average of three determination (n=3)

**Table 5: Results of *In-Vitro* release study of optimized formulation F3**

S. No.	Time (Min.)	Cumulative % Drug release
1.	1	33.45 $\pm$ 0.45
2.	2	67.85 $\pm$ 0.65
3.	5	96.65 $\pm$ 0.32

**Table 6: Characterization of stability study of optimized film (F3)**

Characteristic	Time (Month)			
	Initial	1 Month	2 Month	3 Month
% Assay*	99.12 $\pm$ 0.45	98.45 $\pm$ 0.32	98.12 $\pm$ 0.45	98.05 $\pm$ 0.65

\*Average of three determination (n=3)

## CONCLUSION

Fast dissolving oral films were prepared using different concentration of superdisintegrants and evaluated. Different formulations (F1-F6) were prepared using varying amount of SSG and CCS. The prepared formulations were evaluated for thickness, weight uniformity, folding endurance, percentage of moisture content, drug content analysis, disintegrating time and *In vitro* dissolution study. Stability studies were carried out with optimized formulation F5 which was stored for a period of one, two and three months at 40 $\pm$ 2 $^{\circ}$ C temperature and 75 $\pm$ 5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of film was found to slightly

decrease at higher temperature. Results of evaluation parameters of optimized and validated Escitalopram oxalate oral fast dissolving films revealed good mechanical strength, uniformity of content, optimum surface pH, faster disintegration time, almost complete drug dissolution or release and good stability up to three months. Thus it can be concluded that Escitalopram oxalate fast dissolving films could be commercially exploited for the treatment of panic disorder using Escitalopram oxalate with merits of faster onset of action, avoidance of extensive first pass metabolism, low dosage regimen, enhanced bioavailability and improved patient compliance.

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