

SOLUBILITY ENHANCEMENT OF ESCITALOPRAM OXALATE USING HYDROTROPE

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ABSTRACT

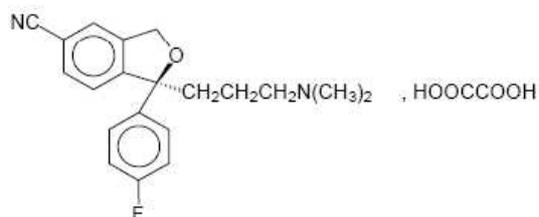
Escitalopram oxalate is a potent inhibitor of serotonin (5-HT) uptake that exhibit antidepressant activity. In spite of oxalate form it is sparingly soluble in water. The efficacy and bioavailability of Escitalopram oxalate is limited by its poor aqueous solubility and dissolution rate. The effect of hydrotropic (niacinamide) on the solubility of escitalopram oxalate was investigated. The saturation solubility indicate that enhancement in solubility was more than eight folds in 2M niacinamide compared to distilled water. Tablets of escitalopram oxalate with and without niacinamide were prepared and dissolution study was performed. Dissolution studies indicate that dissolution rate was remarkably increased with tablet containing niacinamide compared to tablets without niacinamide.

Keywords: Hydrotropy, Niacinamide, Escitalopram oxalate, Solubility enhancement.

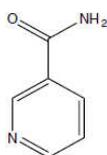
INTRODUCTION

Hydrotropes are a diverse class of molecules first described by Neuberg [1,2] almost a century ago. They are characterized by an amphiphilic molecular structure and an ability to dramatically increase the solubility of sparingly soluble organic molecules in water, often by several orders of magnitude [3,4]. The most common molecular characteristics of a hydrotropic molecule are a saturated hydrocarbon ring and an ionic moiety; however, hydrotropes can adopt many forms. Hydrotropes includes urea, nicotinamide, resorcinol, sodium benzoate, p-hydroxy benzoic acid, caffeine, proline HCl, procaine HCl, pyrogallol, sodium 3-hydroxy-2-naphthoate, sodium cumene sulfonate and many more [5].

Escitalopram, the *S*-enantiomer of Citalopram is a selective Serotonin Reuptake Inhibitor (SSRI). Escitalopram is given for the treatment of depression and some anxiety disorders including panic disorder, obsessive compulsive disorder, and social anxiety disorder. It is given orally as the oxalate although doses are expressed in terms of the base; escitalopram oxalate 12.8 mg is equivalent to about 10 mg of escitalopram [6]. In spite of oxalate form it is sparingly soluble in water [7]. Hydrotropic solubilization of a wide variety of drugs has been demonstrated [8-16] in the literature and a number of mechanisms have been reported [17-28]. The present study was aimed to investigate the effect of niacinamide (hydrotrope) on the solubility of Escitalopram oxalate, and to attempt formulation in tablets. Tablets were also studied for dissolution and chemical stability.



Escitalopram oxalate



Niacinamide

MATERIALS AND METHODS

Materials

Escitalopram oxalate obtained as a gift sample by Lupin Ltd. Jammu, India. All the other chemicals and reagents were of analytical grade obtained from Research Lab, Mumbai.

Methods

Preparation of calibration curve of drug

The calibration curve of Escitalopram oxalate was prepared in 80% v/v methanol at 238 nm using double-beam spectrophotometer (Jasco 530 V). Accurately weighed 50 mg of Escitalopram oxalate was transferred to a 50 mL volumetric flask containing 40 mL 80% v/v methanol. The flask was shaken for 5 minutes to solubilize the drug and volume was made up to 50 ml using 80% v/v methanol. Using this stock solution, various standard solutions of concentrations 2, 4, 6, 8 and 10 µg/mL were prepared using 80% v/v methanol as solvent. Absorbances of these solutions were noted against corresponding reagent blanks at 238 nm to obtain the calibration curve [29].

Saturation solubility studies

For equilibrium solubility determination at room temperature, the excess solute method was employed. Sufficient excess amounts of drug were added to screw capped 10 mL glass vials containing distilled water, 0.5 M niacinamide, 1 M niacinamide, 1.5M niacinamide and 2 M niacinamide solutions separately. The vials were shaken mechanically for 12 hrs at room temperature in an orbital flask shaker (Khera Instruments Pvt. Limited, Delhi, India). The solutions were allowed to equilibrate for the next 24 hrs and then transferred into Eppendorf tubes and centrifuged for 30 min at 2000 rpm (Remi Instruments Limited, Mumbai, India). The supernatant of each vial was filtered through Whatman filter paper. Filtrates of saturated solutions of Escitalopram oxalate were analyzed by spectrophotometric method using a double beam UV-visible spectrophotometer (Jasco 530 V), measuring the absorbance of appropriately diluted solutions against the respective reagent blanks at 238 nm.

Drug excipient compatibility study

IR spectra for drug and drug with excipients were recorded in a FTIR (IR Affinity-1 FTIR, Shimadzu) with KBr pellets.

Preparation of tablets

The general formula of the tablets prepared using escitalopram oxalate is given in Table 1.

Compressed tablets each containing 10 mg of escitalopram were prepared by wet granulation method. All the ingredients (except talc and magnesium stearate) were passed through #60 mesh, appropriate quantities weighed and dry blended for 5 minutes in the mortar. Batch F2 contain niacinamide where as batch F1 does not contain niacinamide. The granulating fluid, PVP in alcohol (10% w/v) was added and mixed thoroughly to form dough mass. The mass was passed through #10 mesh to obtain wet granules. The wet granules were dried at 45°C for 2 h. Then the dried granules were passed through #16 mesh. Then talc and magnesium stearate were passed through #60 mesh, appropriate quantities weighed and blended with dry granules for 2 minutes.

Table 1: Table shows composition of tablets

Ingredients	F1	F2
Escitalopram oxalate*	12.8 mg	12.8 mg
Lactose	108.2 mg	99.2 mg
Niacinamide	-	9 mg
Starch	22.5 mg	22.5 mg
Talc	5 mg	5 mg
Magnesium stearate	1.5 mg	1.5 mg
PVP in alcohol	q.s	q.s.
Total (mg)	150	150

12.8 mg of escitalopram oxalate is equivalent to 10 mg of Escitalopram

Evaluation of Powder Blend

Bulk Density (D_b)

Apparent bulk density was determined by pouring pre-sieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by

$$D_b = M / V_0$$

Where, M is the mass of powder and V_0 is the Bulk volume of the powder.

Tapped density (D_t)

It was determined by placing a graduated cylinder, containing a known mass of drug excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by

$$D_t = M / V_t$$

Where, M is the mass of powder and V_t is the tapped volume of the powder.

Angle of repose

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained. Diameter of heap, D, was measured. The angle of repose, θ , was calculated by formula

$$\tan \theta = h / r$$

$$\theta = \tan^{-1} (h / r)$$

Where, θ is the angle of repose, h is the height in cm and r is the radius.

Carr's Index (I)

It is expressed in percentage and is expressed by

$$I = (D_t - D_b) \times 100 / D_t$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Hausner ratio

It is expressed by $H = D_t / D_b$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Evaluation of tablets

Thickness

Thickness of tablet was determined by using digital vernier caliper.

Hardness

The crushing strength of the tablets was measured using a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability

Twenty tablets were weighed and placed in a Roche friabilator (Electrolab, India). Twenty preweighed tablets were rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured as per the following formula,

$$\text{Percentage friability} = (\text{Initial weight} - \text{Final weight}) \times 100 / \text{Initial weight}$$

Disintegration time

The time required for disintegration of 3 tablets per batch was carried out in USP disintegration test apparatus (Model ED2L, Electrolab, Mumbai, India) containing 900 mL distilled water at 37 ± 0.5 °C. The mean disintegration time was calculated.

Drug content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 12.8 mg of escitalopram oxalate was dissolved in 100 ml of 0.1 N HCl, filtered, diluted suitably and analyzed for drug content at 238 nm using UV-Visible spectrophotometer (Jasco 530 V). Drug content of the tablets was calculated using the standard calibration curve.

Dissolution studies

Dissolution rates of tablets were studied using USP type II dissolution rate test apparatus. 0.1 N HCl was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. A temperature of 37 ± 0.5 °C was maintained throughout the experiments. Samples (5 ml) of dissolution medium were withdrawn at known time intervals and replaced with same volume of distilled water after each withdrawal. The samples were analyzed for drug release by measuring the absorbance of appropriately diluted sample solutions with 0.1 N HCl at 238 nm wavelength. Calculations for amounts of drug released were done using regression equation.

Chemical stability studies

Tablets of batch F2 were packed in aluminium foil and kept in 10 ml amber colored glass vials which were plugged and sealed. Vials were kept at room temperature, at 40°C with 75% RH. The samples were withdrawn after regular interval of one month for three months and drug contents were determined by UV spectrophotometer method. The initial drug content for each formulation was considered as 100%.

RESULT AND DISCUSSION

Saturation solubility studies

The solubility determination of escitalopram oxalate was carried out in distilled water, 0.5 M, 1M, 1.5M, and 2M niacinamide solutions. The results of solubility studies are presented in Table 2. It seems from the results that the aqueous solubility of Escitalopram oxalate was increased more than eight times in 2M niacinamide solutions. It is concluded that the solubility of Escitalopram oxalate increases by niacinamide solutions.

Table 2: Table shows results for saturation solubility studies

Solvent	Solubility (mg/mL)
Distilled Water	35.78
Niacinamide (0.5M) solution	105.58
Niacinamide (1M) solution	163.28
Niacinamide (1.5 M) solution	220.91
Niacinamide (2M) solution	281.0

Drug excipient compatibility study

The IR spectrum showing percentage transmission (T%) versus wave number of Escitalopram oxalate and Escitalopram oxalate with

excipients are shown in fig. 1 and 2 respectively. IR spectra shows characteristic peaks of C-N bending and C-O at 1222.87 and 1103.28 cm^{-1} , respectively. Also cyano (CN) group at 2250 cm^{-1} . From the figure it is evident that Escitalopram oxalate with other tablet excipients undergoes no chemical reaction and no interaction seen.

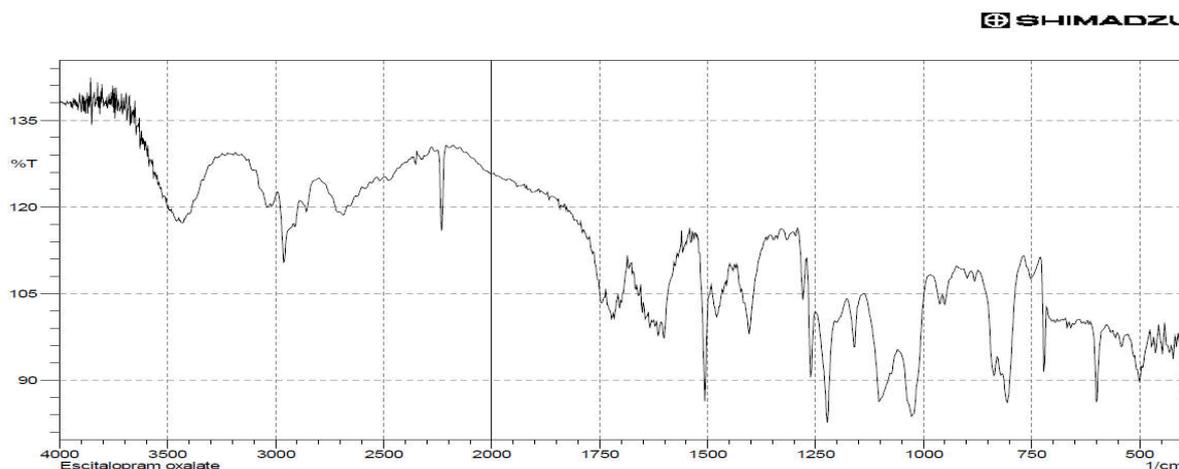


Fig. 1: It shows IR spectra of Escitalopram oxalate

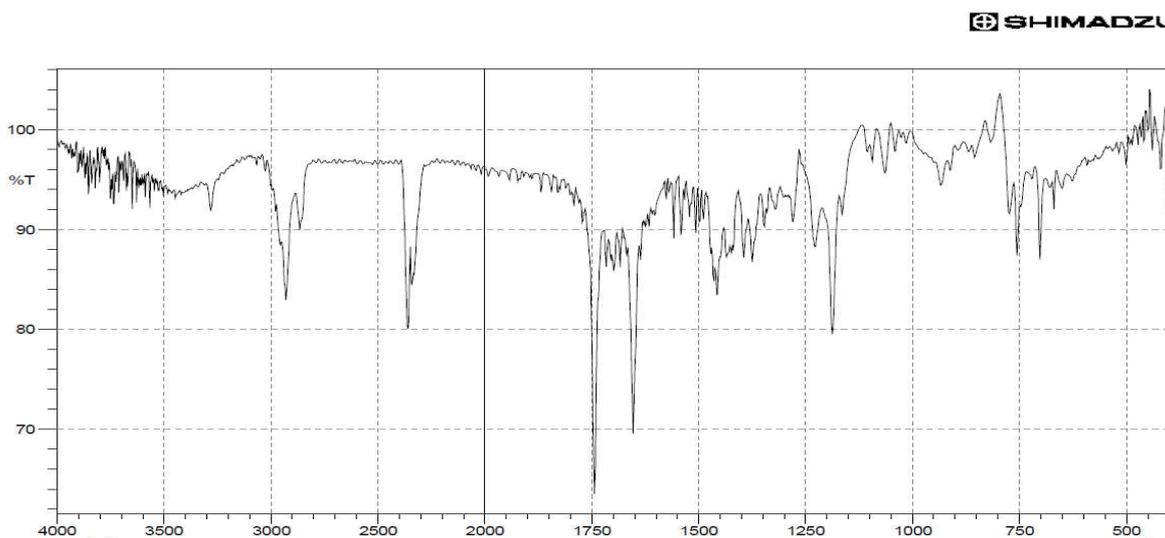


Fig. 2: It shows IR spectra of escitalopram oxalate with excipients

Evaluation of tablets powder blends

Tablets powder blends were evaluated for bulk density, tapped density, angle of repose, carr's index, and Hausner ratio (Table 3) showing good flow and compressibility.

Table 3: Table shows results for evaluation of powder blends

Formulations	F1	F2
Bulk density (g/cm^3)	0.57 ± 0.17	0.55 ± 0.12
Tapped density (g/cm^3)	0.68 ± 0.13	0.71 ± 0.11
Angle of repose (θ)	29.32 ± 0.16	29.98 ± 0.23
Carr's index	16.18 ± 0.32	16.50 ± 0.28
Hausner ratio	1.19 ± 0.18	1.05 ± 0.25

n=3

Evaluation of tablets

Two different batches (F1 and F2) of escitalopram oxalate tablets were formulated and prepared by wet granulation methods as per the formulae given in Table 1. The physical properties of the prepared tablets are summarized in Table 4. All the tablets prepared

were found to contain the drug in the range of $100 \pm 2\%$. Hardness of the tablets was in the range $3-4 \text{ kg}/\text{cm}^2$. Percentage weight loss in the friability test was less than 0.76% in all the cases. Disintegration time of the tablets was in the range of 7-8 minutes. Thickness of the tablets was in the range of 2.70 to 2.81mm. Both the batches of tablets prepared fulfilled the official (IP) specification for weight variation. As such all the tablets prepared were of good quality with regard to drug content, weigh variation, friability, hardness and disintegration time and fulfilled the official (IP) specifications of uncoated tablets.

Table 4: Table shows results for evaluation of tablets

Formulation	F1	F2
Thickness (mm)	2.79 ± 0.03	2.80 ± 0.04
Hardness (kg/cm^2)	3.5 ± 0.3	3.5 ± 0.4
Disintegration time (min.)	7.2 ± 0.43	6.8 ± 0.53
Weight variation (mg)	150 ± 2.08	150 ± 2.25
Drug content (%)	98.17 ± 2.74	98.95 ± 2.22
Friability (%)	0.65 ± 0.17	0.75 ± 0.15

n=3

Dissolution studies

From the results (Fig. 3) of dissolution rate study, it is evident that the tablets without niacinamide [F1] exhibited poor drug release profiles. Drug release profiles from tablets containing niacinamide [F2] were remarkably increased compared to tablets without niacinamide. As the initial rates of dissolution of drug from tablets containing niacinamide were significantly high as compared with initial dissolution rates from tablets without niacinamide, the quick onset of action and better extent of absorption is expected after oral administration of tablets containing niacinamide.

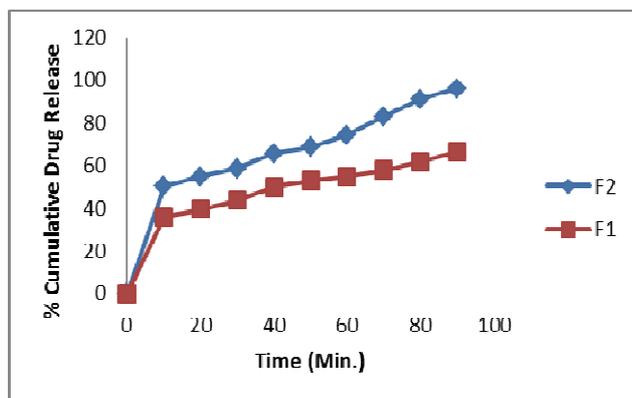


Fig. 3: It shows dissolution profile of escitalopram oxalate with and without hydrotrope

Chemical stability of escitalopram oxalate tablets

The results of chemical stability study (Table 5) showed that the residual drug content after regular interval of one month for three month at room temperature in F2 formulation was above 98%, showing very good chemical stabilities at room temperature. The residual drug contents after regular interval of one month for three month at 40°C/75% RH was above 95%, showing good chemical stabilities at moderate and high temperature.

Table 5: Table shows chemical stability data

Condition	Time (Months)	% Residual drug in formulation F2
Room temperature	1	99.23±0.72
Room temperature	2	98.87±0.56
Room temperature	3	98.51±0.63
40°C / 75 % RH	1	98.16±0.89
40°C / 75 % RH	2	97.24±0.66
40°C / 75 % RH	3	97.61±0.74

n=3

CONCLUSION

Most of the chemical entities that are being discovered are lipophilic and have poor aqueous solubility. Currently number of techniques addressed the poor solubility and dissolution rate of poorly soluble drugs. Hydrotropic solubilization was found to be excellent technique in the solubility and dissolution enhancement of sparingly water soluble drugs. Niacinamide was used as hydrotropic agent and Escitalopram oxalate tablets were prepared with and without niacinamide. Escitalopram oxalate tablets containing niacinamide show fast release of drug as compared with tablets prepared without niacinamide. The quick onset of action and better extent of absorption is expected after oral administration of these tablets.

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