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Original Article

# Formulation and Evaluation of Escitalopram Oxalate Orodispersible Tablets using Sublimation Technique

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ABSTRACT

**Objective:** Orodispersible tablets dissolve or disperse rapidly in a matter of seconds after placement in the mouth lacking of water can alleviate the problem of swallowing tablets. The current study was to formulate and evaluate orodispersible tablets of Escitalopram oxalate generally used in the treatment of major depressive disorder and generalized anxiety disorder. **Experimental Approach:** Drug excipient compatibility study checked by FTIR and DSC shows no any interaction between drug and excipients. Tablets were prepared by sublimation technique. A $3^2$ full factorial design was applied to study the combined effect of two independent variables as the amount of Camphor ($X_1$) and Kyron T-314 ($X_2$). The disintegration time ($Y_1$), wetting time ($Y_2$) and %CDR at 5 min ($Y_3$) were selected as dependent variables. **Results and Discussion:** The blends were examined for pre-compression and post-compression parameters. The results indicated that the concentration of Camphor ($X_1$) and Kyron T-314 ($X_2$) significantly affect the disintegration time ($Y_1$), wetting time ($Y_2$) and %CDR at 5 min. ($Y_3$). Batch S9 containing Camphor (17 mg) and Kyron T-314 (10 mg) shows less disintegration time (17 sec.), less wetting time (15 sec.) and good drug release (100.23%) at 5 min. compared to other batches. **Conclusion:** Batch S9 was selected as optimized batch. Stability study conducted as per ICH guidelines and the optimized batch S9 was found to be stable. This approach is effective, economical and industrially feasible.

**Keywords:** Orodispersible tablets, Escitalopram oxalate, Sublimation, Camphor, Kyron T-314, $3^2$ Full Factorial Design.

## 1. INTRODUCTION

Introduction of a therapeutic substance into the body to improve its efficacy and safety is known as a drug-delivery system which interfaces between the patient and the drug. The drug may be introduced into the human body by various routes, but oral route has been one most popular and used route for both conventional as well as novel drug delivery because of the low cost of therapy, pain avoidance, self-medication, ease of ingestion, leading to high levels of patient compliance, and it did not require sterile conditions[1,2]. However, this form of dosage has some limitation like motion sickness (kinetosis), sudden episodes

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of allergic attacks or coughing and unavailability of water, but one important drawback is 'Dysphagia' or difficulty in swallowing. This is seen to afflict nearly 45% of the general population. Particularly, the difficulty is experienced by pediatric and geriatric patients[3].

To overcome these problems, orodispersible tablets (ODT) have been developed, which has good hardness, dose uniformity, easy administration and serves as the first choice of dosage form for pediatrics, geriatrics and travelling patients. ODTs are also known as "fast-melting, fast-dissolving, oral disintegrating or disperse". It can be defined as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed under the tongue[4,5].

Orodispersible Tablet has a pleasing mouth feel, and it's not required water to swallow[6]. ODT easily dissolved or disintegrates in saliva within a few seconds (15 s to 3 min) without the need for drinking water or chewing, leaves no residue in the mouth when administered and less sensitive to environmental conditions like temperature, humidity[7]. Some ODT tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are called true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed as fast-disintegrating tablets, as they may take about one minute to disintegrate completely.

Escitalopram oxalate is the pure (S) enantiomer of racemic citalopram and is a selective serotonin reuptake inhibitor (SSRI). Escitalopram is used in the treatment of depression and anxiety. It is approved for the treatment of major depressive disorder and generalized anxiety disorder; other indications include social anxiety disorder, panic disorder and obsessive compulsive disorder. 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 tmax value of Escitalopram oxalate is 4hr after multiple dosing. The dose of 5-20mg once a day and is used for treatment of depression.[3]

The present study was undertaken to develop orodispersible tablets of Escitalopram oxalate with shorter disintegration time, greater drug release and lesser friability with a prospect of assisting various patients who have difficulty in swallowing conventional dosage forms.

## 2. MATERIALS AND METHODS

Escitalopram oxalate was obtained as a gift sample from Intas Pharm Ltd., Ahmedabad, Gujarat. Microcrystalline cellulose and Kyron T-314 were procured from Accent Microcell Pvt. Ltd., Ahmedabad, Gujarat and Corel Pharm Chem., Ahmedabad, Gujarat respectively. Aspartame, Camphor, Magnesium stearate, and Talc were purchased from S. D. Fine Chemicals, Mumbai, India. All other chemicals were of analytical reagent grade.

**Drug-Excipient Compatibility Study by FTIR[4]**

Infrared spectra of the drug and excipients were recorded by a KBr pellet method using Fourier Transform Infrared Spectrophotometer. A base line correction was made using dried KBr and then the spectra of mixture of drug and excipients with KBr were recorded. The samples were prepared by the KBR pellet press method.

**$3^2$ Full Factorial Design [9, 10]**

A $3^2$ full factorial design was employed to systematically study the joint influence of the effect of independent variables concentration of Camphor ($X_1$) and Kyron T-314 ($X_2$) on the dependent variable i.e disintegration time ($Y_1$), wetting time ($Y_2$) and %CDR at 5 min. ($Y_3$) (Table 1). In this design, 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations. A statistical model incorporating interactive and polynomial terms is used to evaluate the response. Polynomial equation generated by this design is as follow:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where Y is the dependent variable, $b_0$ is the arithmetic mean response of the 9 runs, and $b_1$ to $b_2$ are the regression coefficients. The main effects ($X_1$ and $X_2$) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms ($X_1X_2$) show how the response changes when two factors are simultaneously changed. The polynomial terms ($X_1^2$ and $X_2^2$) are included to investigate nonlinearity. The response values are subjected to MLRA (Multiple linear regression analysis) to find out relationship between the factors used and response values obtained. After application of full factorial design and with the help of produced polynomial terms, amount of formulation variable was optimized.

**Formulation of Escitalopram oxalate Orodispersible Tablets by Sublimation Method[8]**

All of the formulation components other than lubricant and glidant were accurately weighed, passed through 60-mesh sieve and mixed in vertical blender for 30 min. Talc and magnesium stearate were passed through 80-mesh sieve, mixed with an above blend for 10 min and resultant blend was directly compressed into tablets. The amount of all tablet components other than a superdisintegrant and sublimating agent was kept constant. Round concave tablets of 200 mg in weight and 8 mm diameter were prepared using 10 station sided rotary tablet press (Karnavati Engineering). Table 2 outlines the compositions of various ODT formulations studied. Compressed tablets were subjected to the sublimation process in hot air oven at 60°C for 2 hr.

**Pre Compression Evaluations of Escitalopram Oxalate Orodispersible Tablets[5,6]**

Prior to compression, powder blends were evaluated for flow and compressibility parameters. The flow properties of powder were determined by angle of repose and compressibility by Carr's index and Hausner's ratio.

**Post Compression Evaluations of Escitalopram Oxalate Orodispersible Tablets**

The prepared tablets were evaluated for physical and chemical characteristics.

**Diameter[4]**

Tablets of each batch were selected and measured for diameter using vernier caliper.

**Thickness[4]**

The thickness of three randomly selected tablets was measured using vernier calipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined.

**Weight Variation[4]**

Uniformity of the weight test as described in the IP/BP was followed. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Using this procedure weight variation range of all batches of formulations was determined and recorded.

$$PercentageDeviation = \frac{IndividualWeight - AverageWeight}{IndividualWeight}$$

**Hardness[11]**

Five tablets were randomly selected from each batch and hardness of tablets was determined by using a Monsanto hardness tester. The mean values and standard deviation for each batch were calculated.

**Friability[11]**

The friability of tablets was performed in a Roche Friabilator. Five tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed.

$$F = \frac{Winitial - Wfinal}{Winitial} X\ 100$$

**Wetting Time[12]**

Six circular tissue papers of 10 cm diameter were placed in a Petri dish and 10 ml of water containing amaranth dye was added to it to identify complete wetting of tablet surface. A tablet was carefully placed on the surface of tissue paper in petri dish at ambient temperature. The time taken by water to reach the upper surface of the tablet and to completely wet the tablet was noted as wetting time. The study was performed in triplicate and time was recorded using stopwatch.

***In-vitro* Disintegration Time[12]**

The digital tablet disintegration test apparatus was used to determine *in vitro* disintegration time (DT) using distilled water at 37±2°. The time(s) taken by tablet for complete disintegration with no residue remaining in apparatus was recorded as mean ± SD.

***In-vitro* Drug Release Study[12]**

*In-vitro* release rate of Escitalopram oxalate from the formulated orally disintegrating tablets were determined using USP Type II (Paddle) apparatus. Dissolution studies were carried out according to USFDA Guidelines. The dissolution medium was selected 900 ml 0.1N HCl with a paddle speed of 50 RPM and medium temperature of 37±0.5ºC. Samples (5 ml) were withdrawn at suitable intervals, filtered and absorbance measured at 238 nm using UV-Visible Spectrophotometer.

**Drug Content[12]**

The drug content was carried out by weighing ten tablets from each batch and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate, powder was weighed accurately which was equivalent to specified weight of Escitalopram oxalate and dissolved in 100 ml volumetric flask containing 0.1N HCl and volume was made to 100 ml with solvent. The volumetric flask was shaken using a sonicator for 1 hr and after suitable dilution with 0.1 N HCl, the drug content was determined using UV-Visible Spectrophotometer at 238 nm.

**Stability Studies[13]**

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of an environmental factor such as temperature, humidity and enables recommended storage condition, re-test periods and shelf life to be established. Stability studies were carried out on optimized tablet formulation. A Formulation was stored at accelerated stability condition 40ºC ± 2ºC / 75 ± 5 %RH for 30 days. After 30 days samples were withdrawn and tested with regards to the disintegration time, wetting time, drug content and *in-vitro* drug release pattern and compared with the initial results.

## 3. RESULTS AND DISCUSSION

**Drug-Excipient Compatibility Study using FTIR**

Drug and excipient compatibility study was performed by using the FT-IR Spectrometer. Here, the peak of the pure Escitalopram oxalate correlates with drug in the presence of the other excipients (Figure 1). In all the FT-IR spectra, identical peak of the Escitalopram oxalate could not vary than of its original peak. So, it can be concluded that the drug is compatible with all excipients used in formulation.

**Pre-compression Evaluation of Batches S1 to S9**

The present study focused on the development of ODTs of Escitalopram oxalate that disintegrate within few seconds. Preliminary studies were carried to optimize the superdisintegrant, subliming agent and also their concentration in the formulation. The ODTs were prepared by sublimation method employing Kyron T-314 as superdisintegrants and camphor as subliming agent. Directly compressible agent microcrystalline cellulose was used as a diluent owing to its disintegrant property and pleasant mouth feel. Aspartame was used as a sweetening agent as unpleasant taste could be masked. The factorial formulations were evaluated for flow properties and all the formulations exhibited good flow properties. The various flow parameters are presented in Table 3.

**Post-compression Evaluation of Batches S1 to S9**

The result of post compression parameters (Table 4) specified that, all the formulated tablets were of uniform weight with acceptable weight variation and thickness. Hardness of all formulations was maintained between 2.50 ± 0.98 to 2.90 ± 0.68 kg/cm$^2$ and friability loss was less than 1%. The hardness and friability studies revealed that the tablets possessed good mechanical resistance. The sublimating agent increased the friability of tablets that may be attributed to increased porosity. The ODTs showed drug content in the range of98.13 ±2.23 to 99.86± 1.52%, which, was within acceptable limits.

The most important parameter that needs to be optimized in the development of orodispersible tablets and selection of optimized formulation is DT of tablets. DT was decreased with increasing concentration of superdisintegrant as shown in Figure 2. At low concentration of superdisintegrant tablets showed high DT that may be due to insufficient swelling of the tablet. But at higher concentration DT was decreased considerably (Table 5) due to optimum swelling of tablets required for effective disintegration and wicking action of superdisintegrant. Formulation S9was found promising with lowest DT of 17s.

The wetting time for all formulations was found between 15-29 s (Table 5 and Figure 2). This wide variation was observed due to developmental changes in the formulation to attain preliminary objectives. Formulations S3, S6 and S9 exhibited lowest wetting time, but the difference was not significant. However, wetting time was decreased with increasing concentration of camphor. The decrease in wetting time could be attributed to the increased number of pores on the tablet surface owing to the sublimation of camphor from the tablets. S9 formulation showed less wetting time compare to other batches (Table 5).

***In-vitro* Release Study of Batches S1 to S9**

The formulation S1-S9 containing different concentration of Camphor as sublimating agent and Kyron T-314 as superdisintegrant shows 92 to 100% drug release within 5 min. In vitro drug of all batches are shown in Figure 3 and revealed that Batch S9 containing higher concentration of superdisintegrant and sublimating agent has shown faster drug release. Higher dissolution rate was resulted due to faster breakdown and rapid dispersion of tablet; it may be due to rapid diffusion or the porous nature of the tablet. So, batch S9 which shows maximum drug release within 5min. and less disintegration time considered as optimized batch.

**Statistical Analysis**

The $3^2$ full factorial design was applied to study the effect of independent variables such as concentration of camphor ($X_1$) & Kyron T-314 ($X_2$) on dependent variables such as disintegration time ($Y_1$), wetting time ($Y_2$) and %CDR at 5min. ($Y_3$). Various models, such as linear, 2FI, quadratic and cubic, were fitted to the data for these responses simultaneously using the Design Expert software and adequacy and good fit of the model was tested using analysis of variance (ANOVA). Results of Analysis of variance (ANOVA) for disintegration time, wetting time and % CDR at 5min are tabulated in Table 6 to 8.

A mathematical relationship in the form of polynomial equation for disintegration time, wetting time and %CDR at 5min. are as follows:

$Y_1=29.11 - 4.17X_1 - 3.50X_2 - 0.75X_1X_2 - 2.17X_1^2 - 1.17X_2^2$, $R^2= 0.9955$

$Y_2=25 - 4.50X_1 - 2.67X_2 - 0.50X_1X_2 - 1.50X_1^2 - X_2^2$, $R^2= 0.9981$

$Y_3=95.39 + 1.83X_1 + 2.12X_2 + 0.7050X_1X_2 - 0.5233X_1^2 + 0.7017X_2^2$, $R^2= 0.9955$

The high $r^2$ value indicating the adequate fitting of the linear model. The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries; i.e. positive or negative. The negative coefficient of variable $X_1$ i.e. concentration of Camphor and $X_2$ i.e. concentration of Kyron T-314 for responses disintegration time ($Y_1$) and wetting time ($Y_2$) indicates that, as the concentration was increased, the disintegration and wetting time were decreased. Similarly, the positive coefficient of variable $X_1$ i.e. concentration of Camphor and $X_2$ i.e. concentration of Kyron T-314 for response % CDR at 5min. ($Y_3$) indicates that, as the concentration was increased, the drug release was decreased. The data clearly indicate that the dependent variables are strongly dependent on the independent variables. The relationship between the variables was further elucidated by using the response surface plot (Figure 4 to 6).

**Check Point Analysis**

Three check point batches were prepared and evaluated for disintegration time, wetting time and %CDR at 5 min. Results indicated that measured values match well with expected values. When measured disintegration time, wetting time and %CDR at 5 min values were compared to predicted disintegration time, wetting time and %CDR at 5 min values, the values were found significant (Table 9). Thus, it can be concluded that the obtained mathematical equation is valid for predicting values.

**Optimization of Formulation**

An optimization technique using desirable approach to develop a new formulation with the desired responses. The optimum formulation was selected based on the criteria of attaining minimum disintegration time, wetting time and maximum drug release in less time. Upon "trading off" various response variables, constraints like minimizing the disintegration and wetting time were set at appropriate limits and importance. The composition with 17 mg of camphor and 10 mg of Kyron T-314 fulfilled maximum requisites of an optimum formulation because of less disintegration time and wetting time (Figure 7).

**Stability Study of the Optimized Formulation**

Stability studies were carried out on optimized tablet formulation (Batch S9) as per ICH guidelines Q1C. A formulation was stored at accelerated stability condition 40ºC ± 2ºC / 75 ± 5% RH for 30 days. After 30 days sample was taken and examine with regards to the parameter, i.e. appearance, disintegration time, wetting time, drug content and *in-vitro* drug release pattern and compared with the initial results. After 30 days storage the results showed no more change in appearance, disintegration time, wetting time and *in-vitro* drug release pattern (Table 10).

**Table 1: Selection of Levels for Independent Variables and Coding of Variable**

| Levels | Coded value | Independent variables | |
|---|---|---|---|
| | | Concentration of Camphor (mg)$X_1$ | Concentration of Kyron T-314 (mg)$X_2$ |
| **Low** | -1 | 13 | 6 |
| **Intermediate** | 0 | 15 | 8 |
| **High** | +1 | 17 | 10 |
| **Dependent variables** | | $Y_1$ = Disintegration Time(sec)<br>$Y_2$ = Wetting Time (sec)<br>$Y_3$ = % CDR at 5 (min) | |

**Table 2: Composition of $3^2$ Full Factorial Design Batches S1to S9**

| Ingredient | S1 | S2 | S3 | S4 | S5 | S6 | S7 | S8 | S9 |
|---|---|---|---|---|---|---|---|---|---|
| Escitalopram Oxalate | 12.8 | 12.8 | 12.8 | 12.8 | 12.8 | 12.8 | 12.8 | 12.8 | 12.8 |
| Microcrystalline cellulose | 160.2 | 158.2 | 156.2 | 158.2 | 156.2 | 154.2 | 156.2 | 154.2 | 152.2 |
| Camphor | 13 | 15 | 17 | 13 | 15 | 17 | 13 | 15 | 17 |
| Kyron T-314 | 6 | 6 | 6 | 8 | 8 | 8 | 10 | 10 | 10 |
| Aspartame | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Talc | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Magnesium Stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Total Weight (mg/tablet) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

**Table 3: Pre-compression parameter of Full Factorial Design Batches**

| Batch Code | Bulk density (g/ml) | Tapped density (g/ml) | Compressibility index (%) | Hausner's ratio | Angle of repose (Θ) |
|---|---|---|---|---|---|
| **S1** | 0.459 ±0.041 | 0.578 ± 0.036 | 11.26 ±1.27 | 1.12 ± 0.35 | 24.69 ± 0.52 |
| **S2** | 0.470 ± 0.032 | 0.539 ±0.028 | 10.35 ±1.20 | 1.11 ±0.15 | 25.25 ± 0.15 |
| **S3** | 0.449 ± 0.025 | 0.510 ±0.021 | 11.91 ±1.26 | 1.13 ± 0.57 | 24.20 ± 0.15 |
| **S4** | 0.439 ± 0.053 | 0.506 ± 0.049 | 13.29 ±1.27 | 1.15 ±0.15 | 23.68 ± 0.25 |
| **S5** | 0.470 ± 0.045 | 0.536 ± 0.042 | 12.35 ±1.25 | 1.14 ± 0.27 | 24.84 ± 0.45 |
| **S6** | 0.451 ± 0.031 | 0.530 ± 0.028 | 14.89 ±1.34 | 1.17 ± 0.71 | 26.50 ± 0.78 |
| **S7** | 0.458 ± 0.039 | 0.530 ±0.031 | 13.63 ±1.31 | 1.15 ± 0.25 | 25.73 ± 0.43 |
| **S8** | 0.453 ± 0.032 | 0.531 ± 0.280 | 14.73 ±1.18 | 1.17 ± 0.25 | 25.20 ± 0.31 |
| **S9** | 0.457 ±0.044 | 0.528 ± 0.380 | 13.38 ± 1.85 | 1.15 ± 0.11 | 24.34 ± 0.27 |

All values are expressed as mean ± standard deviation, n=3

**Table 4: Post-Compression Evaluation Parameters of Full Factorial Design Batches**

| Batch Code | Weight variation (n=20) | Diameter (n=5) | Thickness (mm) (n=3) | Hardness ($kg/cm^2$) (n=5) | % Friability (n=5) | % Drug Content (n=10) |
|---|---|---|---|---|---|---|
| **S1** | Pass | 7.99 ± 0.002 | 4.20 ± 0.037 | 2.76 ± 0.18 | 0.61 ±0.13 | 99.40 ± 0.36 |
| **S2** | Pass | 7.98 ± 0.003 | 4.45 ± 0.047 | 2.76 ± 0.58 | 0.43 ± 0.15 | 99.45 ± 1.18 |
| **S3** | Pass | 7.99 ± 0.004 | 4.60 ± 0.041 | 2.88 ±0.30 | 0.63 ± 0.19 | 99.86± 1.52 |
| **S4** | Pass | 7.99 ± 0.003 | 4.30 ±0.050 | 2.50 ± 0.98 | 0.50 ± 0.15 | 99.33 ± 1.52 |
| **S5** | Pass | 7.98 ± 0.002 | 4.28 ± 0.075 | 2.73 ± 0.55 | 0.53± 0.23 | 98.13 ±2.23 |
| **S6** | Pass | 7.98 ± 0.002 | 4.41 ± 0.095 | 2.54 ± 0.36 | 0.41 ± 0.17 | 99.26 ± 1.32 |
| **S7** | Pass | 7.98 ± 0.004 | 4.42 ±0.020 | 2.75 ± 0.15 | 0.47 ±0.16 | 98.60 ± 1.87 |
| **S8** | Pass | 7.99 ± 0.004 | 4.47 ±0.015 | 2.61 ± 0.23 | 0.57± 0.45 | 99.05 ± 0.71 |
| **S9** | Pass | 7.99 ± 0.001 | 4.53 ±0.320 | 2.90 ± 0.68 | 0.61± 0.45 | 99.50 ± 1.47 |

All values are expressed as mean ± standard deviation

**Table 5: Disintegration Time and Wetting Time of Full Factorial Design Batches**

| Batch Code | Disintegration Time (Sec) (n=3) | Wetting Time (Sec) (n=3) |
|---|---|---|
| S1 | 33 ± 0.18 | 29 ± 0.11 |
| S2 | 31 ± 0.20 | 27 ± 0.14 |
| S3 | 26 ± 0.13 | 21 ± 0.08 |
| S4 | 31 ± 0.09 | 28 ± 0.10 |
| S5 | 29 ± 0.11 | 25 ± 0.07 |
| S6 | 23 ± 0.17 | 19 ± 0.19 |
| S7 | 27 ± 0.23 | 25 ± 0.13 |
| S8 | 25 ± 0.16 | 21 ± 0.15 |
| S9 | 17 ± 0.18 | 15 ± 0.12 |

All values are expressed as mean ± standard deviation, n=3

**Table 6: ANOVA for Response of Disintegration time ($Y_1$)**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 192.03 | 5 | 38.41 | 133.80 | 0.0010 | Significant |
| **$X_1$** | 104.17 | 1 | 104.17 | 362.90 | 0.0003 | |
| **$X_2$** | 73.50 | 1 | 73.50 | 256.06 | 0.0005 | |
| **$X_1X_2$** | 2.25 | 1 | 2.25 | 7.84 | 0.0679 | |
| **$X_1^2$** | 9.39 | 1 | 9.39 | 32.71 | 0.0106 | |
| **$X_2^2$** | 2.72 | 1 | 2.72 | 9.48 | 0.0542 | |
| **Residual** | 0.8611 | 3 | 0.2870 | - | - | |
| **Cor Total** | 192.89 | 8 | - | - | - | |

**Table 7: ANOVA for Response of Wetting time ($Y_2$)**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | Significant |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| **Model** | 171.67 | 5 | 34.33 | 309.00 | 0.0003 | |
| **$X_1$** | 121.50 | 1 | 121.50 | 1093.50 | < 0.0001 | |
| **$X_2$** | 42.67 | 1 | 42.67 | 384.00 | 0.0003 | |
| **$X_1X_2$** | 1.0000 | 1 | 1.0000 | 9.00 | 0.0577 | |
| **$X_1^2$** | 4.50 | 1 | 4.50 | 40.50 | 0.0079 | |
| **$X_2^2$** | 2.00 | 1 | 2.00 | 18.00 | 0.0240 | |
| **Residual** | 0.3333 | 3 | 0.1111 | - | - | |
| **Cor Total** | 172.00 | 8 | - | - | - | |

**Table 8: ANOVA for Response of %CDR at 5 min. ($Y_3$)**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 50.55 | 5 | 10.11 | 133.41 | 0.0010 | |
| $X_1$ | 20.02 | 1 | 20.02 | 264.18 | 0.0005 | |
| $X_2$ | 27.01 | 1 | 27.01 | 356.40 | 0.0003 | Significant |
| $X_1X_2$ | 1.99 | 1 | 1.99 | 26.23 | 0.0144 | |
| $X_1^2$ | 0.5478 | 1 | 0.5478 | 7.23 | 0.0745 | |
| $X_2^2$ | 0.9847 | 1 | 0.9847 | 12.99 | 0.0366 | |
| **Residual** | 0.2273 | 3 | 0.0758 | - | - | |
| **Cor Total** | 50.78 | 8 | - | - | - | |

**Table 9: Checkpoint Batches with Predicted and Measured Value Disintegration time, Wetting time and %CDR at 5 min.**

| Batch Code | $X_1$ | $X_2$ | Disintegration time ($Y_1$) | | Wetting time ($Y_2$) | | %CDR at 5 min. ($Y_3$) | |
|---|---|---|---|---|---|---|---|---|
| | | | Measured | Predicted | Measured | Predicted | Measured | Predicted |
| S10 | 0 | 0.5 | 27.16 | 27.07 | 23.48 | 23.42 | 96.53 | 96.62 |
| S11 | 0.5 | 1 | 21.37 | 21.44 | 18.13 | 18.08 | 99.42 | 99.35 |
| S12 | 1 | 0.5 | 20.39 | 20.35 | 17.09 | 17.17 | 98.34 | 98.28 |

**Table 10: Results of Stability Study of Optimized Batch (S9)**

| Batch Code | Parameter | Storage Time | |
|---|---|---|---|
| | | **0 Month** | **1 Month** |
| **S9** | Appearance | White colored, round shaped, plain on both side of the uncoated tablets | White colored, round shaped, plain on both side of the uncoated tablets |
| | Disintegration Time (Sec) | 17±0.18 | 17±0.25 |
| | Wetting Time (Sec) | 15±0.12 | 15±0.17 |
| | Drug content(%) | 99.50±1.47 | 99.83±1.24 |
| | % Drug release at 5min. | 100.23 ± 0.22 | 100.40 ± 0.16 |

All values are expressed as mean ± standard deviation

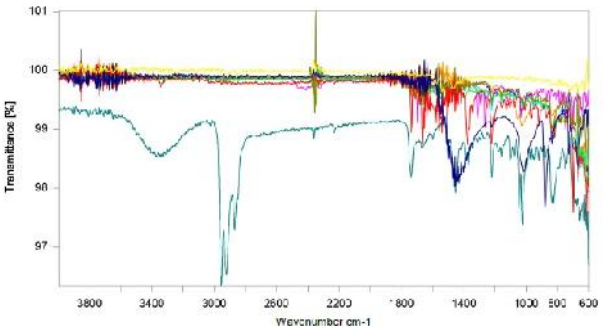


**Fig 1: FTIR of Escitalopram oxalate and all ingredients**

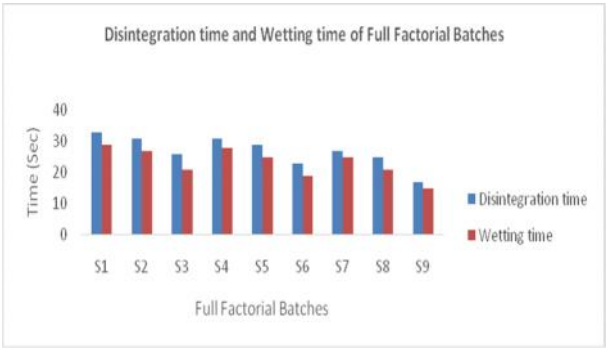


**Fig 2: Disintegration Time and Wetting Time of Full Factorial Design Batches**

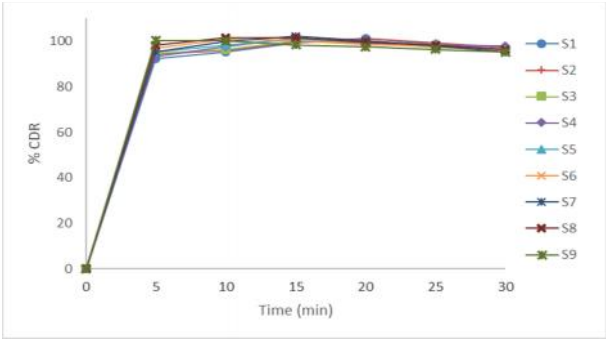


**Fig 3: *In vitro* drug release Study of batches S1-S9 in 0.1N HCl**

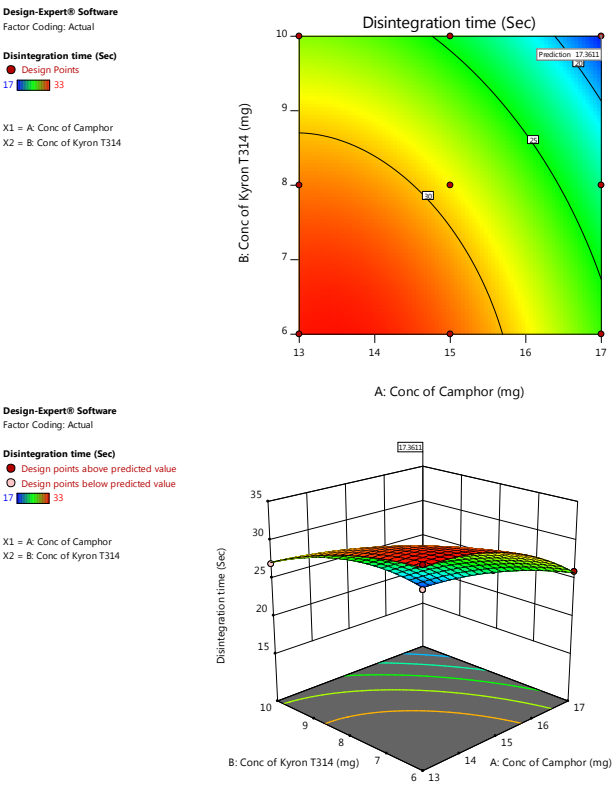


**Fig 4: 2D and 3D Curve of Concentration of Camphor ($X_1$) & Concentration of Kyron T-314 ($X_2$) for Disintegration time ($Y_1$)**

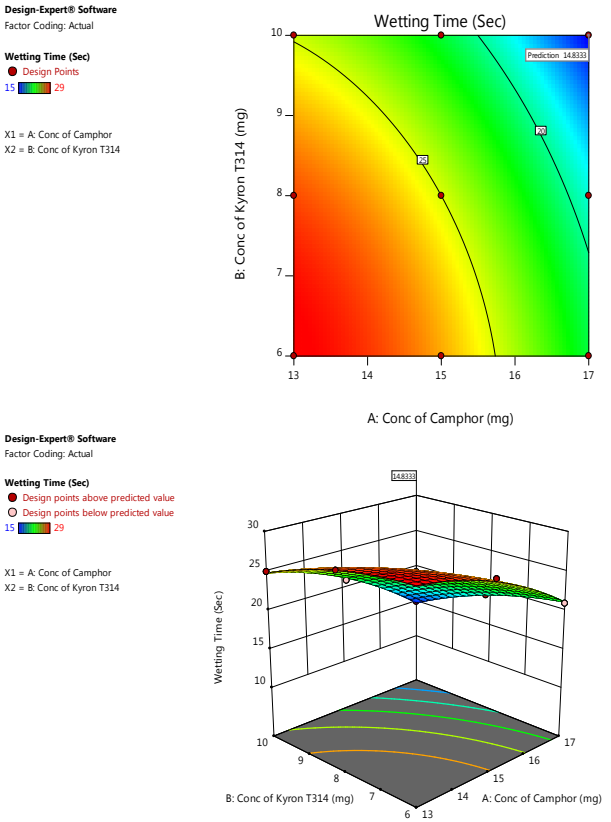


**Fig 5: 2D and 3D Curve of Camphor ($X_1$) & Concentration of Kyron T-314 ($X_2$) for Wetting time ($Y_2$)**

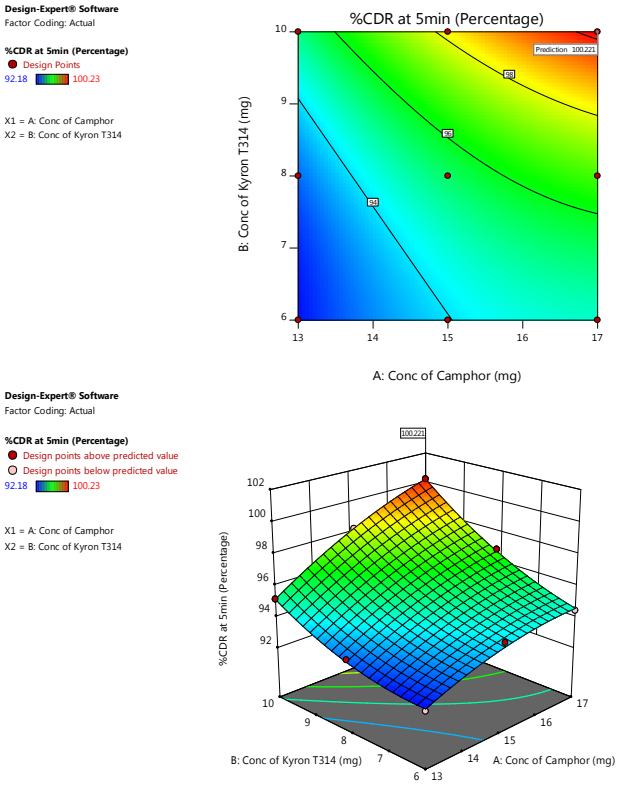


**Fig 6: 2D and 3D Curve of Camphor ($X_1$) & Concentration of Kyron T-314 ($X_2$) for %CDR at 5 min. ($Y_3$)**

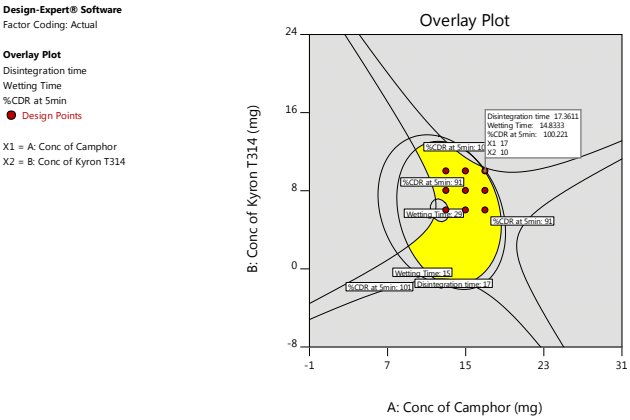


**Fig 7: Optimization of statistical Model by Overlay Plot**

## 4. CONCLUSION

An attempt was made to formulate and evaluate orodispersible tablets of Escitalopram oxalate for the treatment of major depressive disorder and generalized anxiety disorder. Tablets were prepared by sublimation technique to enhance the dissolution rate. Drug excipient compatibility study checked by FTIR showed no interaction between drug and excipients. A $3^2$ full factorial design was applied to investigate the combined effect of two independent variables like amount of Camphor and Kyron T-314. The disintegration time, wetting time and %CDR at 5 min. were selected as dependent variables. The results indicate that the concentration of Camphor ($X_1$) and Kyron T-314 ($X_2$) significantly affect the disintegration time ($Y_1$), wetting time ($Y_2$) and %CDR at 5 min. ($Y_3$). Multiple regression analysis was performed to identify the best batch. The optimized batch S9 containing Camphor (17 mg) and Kyron T-314 (10 mg) shows less disintegration time (17 sec.), less wetting time (15 sec.) and good drug release (100.23%) at 5 min. compared to other batches. Stability study conducted as per ICH guidelines and optimized batch S9 was found to be stable. In conclusion, formulation of orodispersible tablets of Escitalopram oxalate using sublimation method is able to enhance the dissolution rate. This approach is effective, economical and industrially feasible.

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