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Original Article

DESIGN AND OPTIMIZATION OF ESCITALOPRAM OXALATE ORAL DISSOLVING FILMS BY RESPONSE SURFACE METHODOLOGY

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ABSTRACT

Objective: To develop and optimise the oral dissolving films of escitalopram oxalate by response surface methodology.

Methods: Oral dissolving film compositions were optimized by central composite design. The films are prepared by solvent casting method. Initially, different polymers were screened and based on the results polyvinyl alcohol was selected as polymer, propylene glycol was selected as plasticizer. Concentration of polymer and concentration of plasticizer were fixed as independent variables; tensile strength, percent elongation, elastic modulus and amount dissolved up to 5 min ($\%D_{5\ min}$) were taken as responses.

Results: The prepared films exhibited good surface characteristics. The thickness, uniformity of weight, surface pH and drug content are within acceptable range. The mechanical properties like tensile strength, folding endurance, percent elongation and elastic modulus were determined. The statistical analysis showed that polymer concentration has a positive effect on disintegration time and the plasticizer concentration has a significant effect on folding endurance. The prepared film releases nearly 95% at the end of 5 min. The design space was used to optimize the quantities of polymer and plasticizer. The comparison of checkpoint experiment batch responses are corelating with the predicted responses.

Conclusion: Escitalopram oxalate oral dissolving films was successfully designed and optimized by response surface method. It was concluded that the prepared films exhibit good mechanical properties and maximum release within 10 min.

Keywords: Response surface method, Central composite design, Oral films, Optimization, Escitalopram oxalate

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INTRODUCTION

The trend towards novel drug delivery systems over the past few decades has significantly enhanced efforts to guarantee efficacy, safety, and patient acceptability [1]. The development of novel drug delivery methods for currently available medications is becoming more popular as the research and development of new chemical agents is a difficult, costly, and time-consuming process [2]. Orally disintegrating films (ODFs) are a prominent drug administration method in both pediatrics and geriatrics. These rapid disintegrating films are better than fast disintegrating tablets because the latter have choking and friability issues [3].

This oral film drug delivery has many advantages over traditional fast-dissolving tablets since it can be used for people with dysphasia and schizophrenia and because it can be taken without water because it dissolves in the mouth within a few seconds, releasing the medication [4]. ODFs are made using a variety of techniques, the most popular of which being solvent casting and spraying [5]. ODFs are often made using hydrophilic polymers and other excipients, which enable the films to dissolve and release the integrated active pharmaceutical ingredient, or API, within seconds [6]. Due to its numerous advantages over orally disintegrating tablets, orally disintegrating films have the potential to be commercially and commercially successful [7].

A selective serotonin reuptake inhibitor (SSRI), escitalopram oxalate (ESPO) is used to treat severe depression and anxiety disorders. This drug blocks human serotonin transport in a potent, dose-dependent, and highly selective manner. By blocking serotonin reuptake into presynaptic nerve terminals, this drug boosts serotonin activity in the central nervous system [8, 9].

Escitalopram oxalate is a class-II antidepressant medication. This medication is a first-line treatment for depression. It occurs as a fine white to slightly yellow powder. Its dose is 10 mg once daily, initially may increase to 20 mg per day after one to three weeks [10, 11].

The development of ODFs for this medication is necessary to improve patient compliance in the elderly and pediatric groups who have difficulty swallowing traditional solid oral medications. There are no commercial oral fast-dissolving films, despite the fact that this medication was commercially marketed as pills and solutions. The major objective of the study is to design and optimize the oral dissolving films of escitalopram oxalate by central composite design.

MATERIALS AND METHODS

Materials

Escitalopram oxalate was gift sample from Hetero drugs, Hyderabad, India. poly vinyl alcohol (PVA), propylene glycol (PG) was purchased from Fisher scientific, Mumbai. citric acid, Aspartame, was purchased from Loba Chemie Pvt Ltd, Mumbai. lemon oil was procured from Shiva exports India. All other chemicals and materials were of either analytical grade or pharmaceutical grade.

Methods

Construction of standard calibration curve for escitalopram oxalate in pH 6.8 phosphate buffer

The calibration curve for the estimation of ESPO was constructed in pH 6.8 phosphate buffer. The drug stock solution was prepared in pH 6.8 phosphate buffer. A series of dilutions were made to obtain different concentrations of 2 to 20 mg/ml using pH 6.8 phosphate buffer and the absorbance was measured in triplicate at 239 nm [12, 13].

Drug-excipient compatibility studies

Drug-excipient compatibility studies were performed using Attenuated Total Reflectance-Fourier transform infrared spectroscopy ATR-FTIR (Perkin-Elmer 100 FTIR). 10 mg of powder sample is placed onto the ATR crystal and pressure is evenly applied on the sample and analyzed at wave number range 4000-500 cm-1 at a resolution of 4 cm-1. FTIR spectra were obtained for pure drug and optimized formulations [14].

Design of experiment

Preliminary selection of formulation additives

The ODFs were prepared by using solvent casting method in petri plate. In the present investigation it was proposed to prepare film containing 10 mg of escitalopram oxalate in 2 cm^2 film. The amount of drug to be incorporated into the film was calculated with respect to size of the film area based on the following assumption and the calculations.

Calculation of drug for 80 cm^2 area

2 cm^2= 10 mg dose of ESPO (12.8 mg of ESPO is equivalent to 10 mg of escitalopram)

For 80 cm^2 = ?

80 X 10/4 = 200 mg (256 mg of ESPO)

Optimization of ODFs of escitalopram oxalate by face centred central composite design.

Composition of ESPO oral dissolving films was optimized by central composite design [15]. The concentration of polymer and the concentration of plasticizer were selected as two independent variables and tensile strength, percent elongation, elastic modulus and the percent drug release at 5 min. were selected as dependent variables.

Based on the preliminary studies, amount of polymer (PVA) in between 250 to 350 mg and the concentration of plasticizer (PG) in between 45 to 75 mg was chosen for design space [16]. A total of 13 runs were generated by MINITAB 16. The list of independent variables and their levels are shown in table 1.

Table 1: Design space for central composite design

Independent variable	Level of variation		
	Low	Medium	High
PVA (mg)	250	300	350
PG (mg)	45	60	75

The details of design and the quantities of independent factors are shown in table 2.

Table 2: Central composite design for the formulated films containing different concentrations of PVA and PG for ESPO

Formulation code	Std order	Point type	Blocks	PVA (mg)	PG (mg)
CDE01	1	1	1	250	45
CDE02	2	1	1	350	45
CDE03	3	1	1	250	75
CDE04	4	1	1	350	75
CDE05	5	-1	1	250	60
CDE06	6	-1	1	350	60
CDE07	7	-1	1	300	45
CDE08	8	-1	1	300	75
CDE09	9	0	1	300	60
CDE10	10	0	1	300	60
CDE11	11	0	1	300	60
CDE12	12	0	1	300	60
CDE13	13	0	1	300	60

The formulae for preparation of ESPO ODFs was shown in table 3.

Table 3: Composition of ESPO ODFs used in factorial design experiments

Ingredient	Quantity
Escitalopram oxalate	128 mg (Equivalent to 100 mg of Escitalopram)
PVA	250-350 mg
PG	45-75 mg
Citric acid	60 mg
Aspartame	90 mg
Lemon oil	Q. S
Purified water	Q. S to 10 ml

The polymer dispersion was prepared by carefully transferring the required amount of PVA in a beaker containing 5 ml of distilled water. The dispersion was heated at 40 °C till PVA gets dissolved. In another beaker accurately weighed quantity of drug, propylene glycol, citric acid, aspartame and lemon oil were placed and dissolved in 5 ml of purified water. Both the solutions were mixed by continue stirring at 700 rpm for 2 h. Kept this casting solution aside for 2-3 h for complete deaeration. The resulting solution was then transferred into petri plate and evaporated in hot air oven maintained at 60 °C for 8 h. After evaporation, the films were removed with help of forceps. The obtained large film was cut into pieces with the area of 2 cm^2.

Evaluation of films

The prepared oral dissolving films were evaluated for the parameters like physical appearance, thickness, uniformity of weight, surface pH, uniformity of drug content disintegration time, moisture loss, moisture uptake, tensile strength, percent elongation, elastic modulus, folding endurance and dissolution [17].

Surface properties

The surface characters like surface texture, transparency and appearance were examined physically and reported.

Thickness

Thickness of the film was measured at five different points, including four corners and center point, using calibrated digital micrometer (Model: OCNEDMIC-25; Korea) and then mean average (n = 3) is calculated [18].

Uniformity of film weight

It was calculated by cutting the film in 2 cm length and 2 cm breadth (2 x 2 cm) for determining the weight of film [19].

Surface pH

The pH of an oral film was determined by placing the film in petri dish and film was made wet with distilled water and pH of the interface is measured by using a digital pH meter (Make: Systronics, Model: 335, Ahmedabad) [20].

Uniformity of drug content

This test was performed on 10 samples using UV spectrophotometric analytical technique as per the test procedures. According to USP 36, the contents should range from 90% to 110% [21]. A film of size 2 cm2 was cut and kept in 100 ml of a volumetric flask containing pH 6.8 phosphate buffer. This was then shaken in a mechanical shaker till it was dissolved to get a homogeneous solution and then filtered. The drug content was estimated spectroscopically after appropriate dilution. The absorbance was measured at 239 nm. After appropriate dilution.

Disintegration time

The disintegration time is the function of composition of film as it varies with the composition and generally ranges from 5 to 60 sec. There are no official guidelines available for determining disintegration time of oral fast disintegrating films. In this study a film was placed in petri plate containing 10 ml distilled water. Time taken by the film to dissolve completely is considered as the disintegrating time [22].

Moisture loss, moisture uptake

Moisture loss is determined by placing the pre-weighed film in the desiccator contains anhydrous $CaCl_2$ for three days. After three days, films were reweighed and the difference in weight of the film comparison with the initial weight was calculated as moisture loss by using the following formula as below.

$$\text{Percentage moisture loss} = \frac{[(\text{Inital weight} - \text{Final weight})]}{\text{Initial weight}} \text{ X } 100$$

Moisture uptake is determined by cutting the film with the dimension of 2 x 2 cm and initial weight was noted down. Then, these films were exposed to environment with a relative humidity 75% at room temperature for one week. Percentage moisture uptake is calculated as percent weight gain of the film as per below formula [23].

$$\text{Percentage moisture uptake} = \frac{[(\text{Final weight} - \text{Initial weight})]}{\text{Initial weight}} \text{ X } 100$$

Tensile strength

ODFs were placed and fixed between two clamps of tensile tester positioned at distance of 2 cm and load or force required to break the ODFs was measured by pulling the bottom clamp with 10 inch/minute. The force or load which causes the breaking of the ODFs can be calculated using following equation [24]:

$$\text{Tensile strength} = \left[\frac{\text{Load at failure}}{\text{Strip thickness X strip width}}\right] \text{X } 100$$

Percent elongation

Percent elongation is determined by calculating the ratio of ultimate length and initial length of the film with the application of stress before the point of breakage. Then, percent elongation was calculated by using following equation.

$$\text{Percentage elongation} = \left[\frac{\text{Increase in length at breaking point (cm)}}{\text{Original length (cm)}}\right] \text{X } 100$$

Elastic modulus (Young's modulus)

It is a measurement of stiffness of the films against the applied force up to the elastic limit. It was determined by measuring the applied force over the film to cause stiffness of the film using the following formula [25].

$$\text{Young's modulus} = \left[\frac{\text{Slope}}{\text{Strip thickness X Cross head speed}}\right] \text{X } 100$$

Folding endurance

Folding endurance is used to determine mechanical properties of film and was noticed by repeatedly folding of the film at the same place until the film ruptured [26].

Dissolution

The *in vitro* dissolution studies were carried out using USP paddle-type dissolution testing apparatus (Electro lab, Mumbai, India) set at 37±0.5 °C and 50 rpm for 15 min using 300 ml pH 6.8 phosphate buffer solution served as medium for ESPO ODFs. Dissolution study is performed by placing the film (2 cm^2 film containing the equivalent of 10 mg of drug) attached with the metal wire to prevent the floating of the film in the dissolution apparatus. Samples were withdrawn at 0, 2,3,4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 min and 1 ml of the fresh dissolution medium was added to the vessel to maintain volume of dissolution medium. The absorbance was measured at 239 nm and cumulative drug release was calculated [27].

Surface texture

The surface morphology of pure ESPO and optimized films of ESPO was observed by scanning electron microscope at an accelerating voltage of 0.5-30kv, resolution of 3.5 nm and magnification of 500X-2000X [28].

RESULTS AND DISCUSSION

Standard calibration curve

The absorbance values against concentration are constructed as standard curve as shown in fig. 1. The present method obeyed Beer's law in the concentration range of 2-16 mg/ml suitable in pH 6.8 phosphate buffer. The correlation coefficient (r) value was found to be 0.9997 indicating a positive correlation between the concentration and corresponding absorbance readings (Y = 0.0611x+0.014).

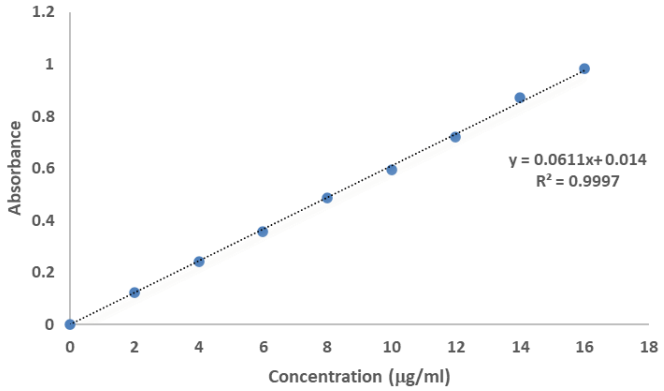
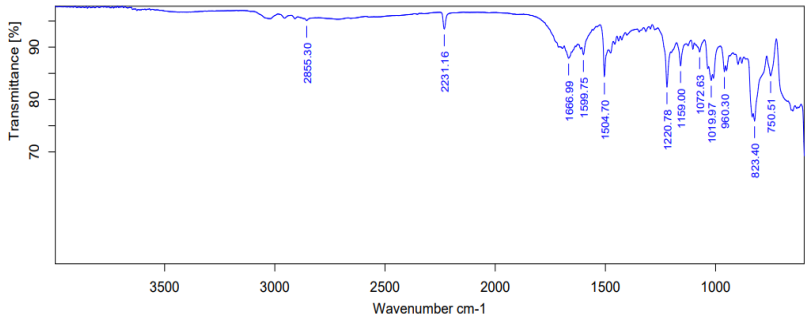


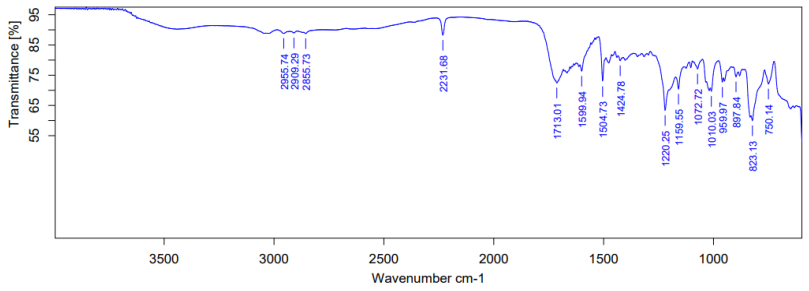
Fig. 1: Calibration curve of ESPO

Drug excipient compatibility studies

The FTIR of ESPO and ESPO optimized formulation are shown in fig. 2. The sharp peak obtained at 2855.30 cm^{-1} represents C-H stretching, a sharp peak at 2231.16 cm^{-1} was due to C≡ N stretching vibration, a broad peak at 1599.75 cm^{-1} represents C=O stretch, peak at 1220.78 cm^{-1} represents C-F stretching and a peak obtained at 1159.75 cm^{-1} was due to C-N stretching. The same characteristic bands were observed in the ESPO film composition indicating that there was no physical incompatibility in between the ingredients used to develop the films.



(a)



(b)

Fig. 2: FTIR spectra of a) Escitoporam oxalate Pure API b) Escitoporam oxalate ODF

Evaluation of ODFs of ESPO

Surface texture of film

The surface texture of ESPO film was found to be smooth. Fig. 3 and fig. 4 shows the scanning electron microscopy (SEM) images of both ESPO pure API and ESPO optimized film formulation at different scales. The crystals obtained in fig. 3 represents the Escitalopram oxalate pure API. The SEM image of ESPO optimized film did not contain any crystals and a smooth surface indicates the drug was in amorphous form and it results in faster drug release rate.

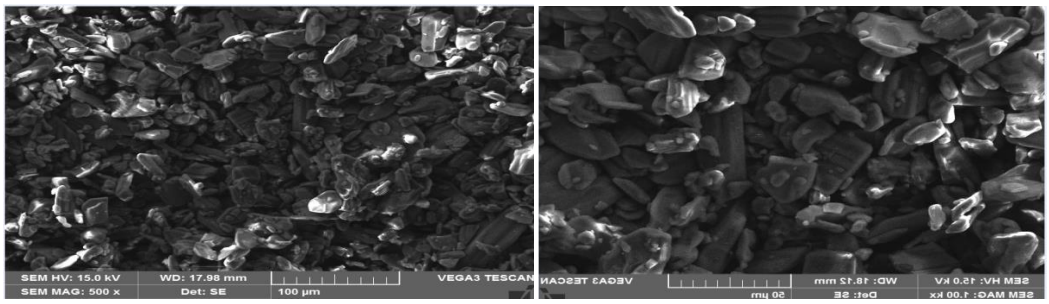
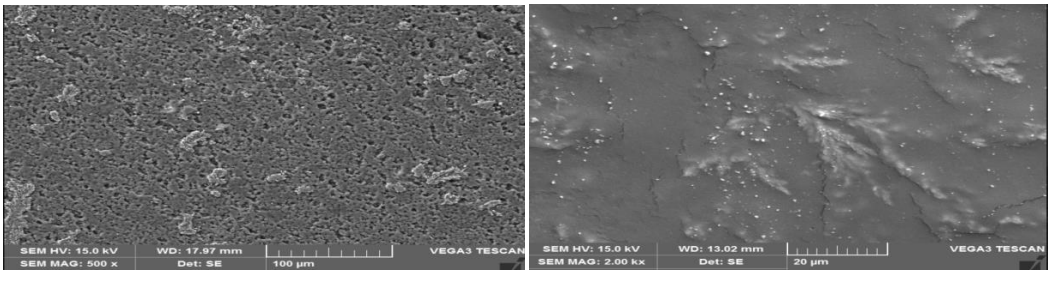


Fig. 3: SEM images of escitalopram oxalate pure API



(a) **(b)**

Fig. 4: SEM images of a) Escitalopram oxalate placebo film(PVA) b) Optimized film formulation

The physical characteristics of ESPO ODFs was shown in table 4. All experimental batches were clear, transparent, non-sticky with a smooth surface in physical appearance. The thickness of the films was measured at five different locations of the film and found that in the range of 0.123 to 0.178 mm with±0.09 standard deviation, which indicates the thickness of the film were uniform. It can also conclude that the prepared drug-polymer dispersion had the optimum viscosity to spread on petri plate uniformly. The weight of the prepared films was in the range of 56-64 mg. The results show the lack of any significant weight variations. The thickness and weights of different films were observed that with increase in polymers concentration the thickness and weights were increased.

The polymer used to for formulation of ODFs are expected to affect the moisture absorption properties. The moisture absorption of the films is important because it influence the mechanical properties, disintegration time and dissolution behavior of the film. The percentage moisture uptake varies in the range of 9.4-15.5%, with an overall trend of increase in moisture uptake with an increase in both plasticizer and polymer levels. The moisture loss was in the range of 4.9-7.9%. The pH of the film indicates the non-irritability of the films in oral mucosa. The pH of the films was found to be in the range of 6.34-6.66. The results were close to the neutral pH for all the batches, it means they are non-irritative in oral cavity.

The drug content of the films was found to be more than 98%, which indicate that the drug was distributed homogeneously in the polymer matrix. The drug content of all the films was found to be in the acceptable pharmacopeial range for standard oral solids. Disintegration time of film varied due to different concentrations of polymer. Disintegration time of all the batches was in the range of 27-43 sec. It is evident from the results that as the concentration of polymer increases the disintegration time for the film was also increases.

The mechanical properties of the films were shown in table 5. The mechanical strength of films is estimated by determining the folding endurance, tensile strength, percent elongation and elastic modulus. An ideal ODF should exhibit high tensile strength, in order to with stand normal handling [29]. The prepared films have tensile strength values in range of 15.430-31.065 gm/cm^2. It was noticed that increasing the polymer concentration significantly increases the tensile strength, because of the formation of a densely packed network of the polymer chains at higher concentration, leading to formation of strong matrix. These findings are good agreement with that detected by Tayel SA *et al.* who found that increase in the polymer concentration of polymer had significant effect on tensile strength [30].

ODFs should have large percentage elongation values, in order to exhibit the desired stretchability and flexibility.

The percentage elongation values of the all prepared films were found to be in range of 33.25-76.85%. Here the percentage elongation of ODFs was significantly affected by plasticizer concentration. The increase in the percentage elongation can be attributed by the replacement of intermolecular bonds in polymer matrix with plasticizer. This disruption and reconstruction of polymer molecular chains allows greater chain mobility, resulting in the decrease of rigidity and providing flexibility and stretching of the film. These findings are in accordance with those given by Shah KA *et al.*, who stated that PG was best plasticizer [31].

The prepared ODFs should have low elastic modulus to exhibit desired elasticity. Higher values of elastic modulus lead to formation of brittle and stiff films. The elastic modulus of all prepared films was in the range of 12.45-53.75 kg/m^2. The ODFs should have satisfactory folding endurance. Here, these values were in the range of 210-259. Higher folding endurance was indicative of high mechanical strength of the films. It was observed that as the plasticizer and polymer concentrations increase, the folding endurance also increased. The results of all evaluated parameters of experimental batches were within acceptable range.

Table 4: Physical characteristics for ESPO ODFs

Formulation code	Surface texture	Transparency	Thickness[a] (mm)	Weight[b] (mg)	Surface pH[a]	Drug content[b] (%)	D. T[c] (sec)	Moisture loss[d] (%)	Moisture uptake[d] (%)
CDE01	Smooth	Transparent	0.123±0.04	56.32±1.24	6.58±0.04	99.45±0.54	28±1	5.357±0.38	6.547±0.35
CDE02	Smooth	Transparent	0.132±0.07	60.24±2.23	6.44±0.06	98.99±0.62	41±3	4.91±0.54	9.456±0.24
CDE03	Smooth	Transparent	0.147±0.09	58.56±1.32	6.52±0.05	99.45±0.66	27±2	5.783±0.47	10.451±0.68
CDE04	Smooth	Transparent	0.129±0.05	60.21±3.11	6.46±0.02	98.93±0.28	43±4	7.455±0.64	7.411±0.65
CDE05	Smooth	Transparent	0.155±0.01	57.45±.08	6.59±0.02	100.4±0.27	27±3	6.652±0.34	9.532±0.18
CDE06	Smooth	Transparent	0.146±0.08	61.25±1.22	6.66±0.06	99.88±0.34	42±2	5.358±0.53	10.421±0.54
CDE07	Smooth	Transparent	0.175±0.06	59.42±2.45	6.34±0.01	98.40±0.28	37±3	7.953±0.46	15.485±0.66
CDE08	Smooth	Transparent	0.155±0.05	64.22±1.56	6.64±0.01	99.25±0.64	40±2	7.453±0.57	10.14±±0.81
CDE09	Smooth	Transparent	0.164±0.08	61.54±2.70	6.55±0.05	99.87±0.29	37±3	6.334±0.29	9.136±0.48
CDE10	Smooth	Transparent	0.154±0.08	62.61±3.12	6.41±0.08	98.14±0.46	39±3	6.538±0.41	9.44±0.64
CDE11	Smooth	Transparent	0.178±0.02	60.65±1.18	6.55±0.02	98.94±0.25	34±4	7.334±0.52	8.432±0.45
CDE12	Smooth	Transparent	0.166±0.07	60.45±2.43	6.48±0.06	99.58±0.64	39±2	6.712±0.29	10.21±0.37
CDE13	Smooth	Transparent	0.143±0.04	61.32±1.18	6.37±0.02	99.76±0.54	38±2	6.450±0.35	8.475±0.51

a: mean±SD (n = 3); b: mean±SD (n = 10); c: mean±No. of sec (n = 5); d: mean±SD (n = 5)

Table 5: Mechanical properties for ESPO ODFs

Formulation code	Mechanical properties			
	Tensile strength* (gm/cm^2)	% Elongation*	Elastic modulus* (kg/m^2)	Folding endurance*
CDE01	15.430±0.49	33.25±0.48	34.56±0.36	250±7.57
CDE02	29.000±0.35	55.45±0.24	53.44±0.15	224±6.44
CDE03	16.420±0.54	51.68±0.28	13.54±0.16	231±8.21
CDE04	30.044±0.12	68.46±0.26	12.45±0.35	228±6.45
CDE05	15.950±0.31	47.65±0.34	21.46±0.25	239±8.4
CDE06	31.065±0.43	71.65±0.24	53.75±0.11	210±5.54
CDE07	23.010±0.12	68.45±0.28	32.46±0.25	228±9.21
CDE08	25.320±0.24	70.94±0.18	19.54±0.42	261±8.45
CDE09	26.1±0.34	74.56±0.22	37.87±0.34	240±6.2
CDE10	25.018±0.26	75.64±0.46	39.13±0.18	254±11.54
CDE11	26.224±0.45	74.32±0.34	38.47±0.45	259±9.58
CDE12	26.050±0.26	76.85±0.57	39.12±0.22	242±5.4
CDE13	25.045±0.25	75.24±0.51	38.96±0.19	257±8.68

*All the results are given as mean±SD, n = 3

In vitro dissolution studies

In vitro dissolution data of the prepared films was shown in table 6, table 7, fig. 2 and fig. 3. All the formulations follow first-order release. The results shows that all the independent variables had significant impact on the percentage of drug released. All the formulations show more than 90% of drug released within 5 min.

Table 6: Dissolution data observed from ESPO ODFs (CDE01-CDE07)

Time	Formulation code and percent drug dissolved (mean±SD, n=6)						
(Min)	CDE01	CDE02	CDE03	CDE04	CDE05	CDE06	CDE07
0	0	0	0	0	0	0	0
2	50.54±2.57	41.21±1.92	43.15±1.28	48.46±3.45	51.22±1.93	39.77±4.35	44.84±3.42
3	75.44±1.25	68.55±1.88	69.55±1.54	65.58±2.43	77.13±1.24	58.21±3.55	69.55±2.45
4	87.78±1.27	75.78±1.45	79.49±2.46	73.54±3.12	84.23±1.54	77.85±2.84	81.48±2.54
5	98.42±0.95	93.17±1.1	95.22±1.84	92.23±1.9	97.44±0.94	92.14±1.9	95.78±0.89
6	99.24±0.98	95.61±0.94	96.54±1.92	93.47±0.75	98.45±0.57	94.22±0.88	96.78±0.95
7	-	96.45±0.99	97.66±0.87	94.55±0.84	99.45±0.56	96.45±0.75	98.54±0.72
8	-	98.88±0.84	98.74±0.57	96.04±0.94	100.04±	97.58±0.85	99.43±0.58
9	-	99.86±0.53	99.87±0.94	97.54±0.54	-	98.44±0.64	-
10	-	-	-	98.55±0.62	-	100.21±0.46	-
11	-	-	-	99.892	-	-	-

All the results are given as mean±SD, n = 6

Table 7: Dissolution data observed from ESPO ODFs (CDE08-CDE13)

Time	Formulation code and percent drug dissolved (mean±SD, n=6)					
(Min)	CDE08	CDE09	CDE10	CDE11	CDE12	CDE13
0	0	0	0	0	0	0
2	47.65±2.42	40.45±2.54	44.98±3.45	47.45±2.84	50.88±2.45	42.54±1.97
3	67.25±3.45	65.22±3.14	71.24±3.21	70.44±3.45	71.45±1.94	67.54±2.48
4	82.56±1.98	80.70±1.92	84.74±1.54	82.97±1.95	84.78±2.55	79.88±2.66
5	95.62±1.55	96.45±1.44	95.55±1.75	96.79±0.87	96.51±1.23	95.20±1.54
6	96.99±0.75	97.87±0.57	96.12±0.92	97.99±0.55	97.54±0.88	96.48±0.57
7	97.73±0.94	98.55±0.82	97.56±1.25	98.56±0.84	98.45±0.75	97.55±0.85
8	99.14±0.57	99.79±0.47	98.57±0.54	99.84±0.76	99.12±0.82	98.89±0.94
9	-	-	99.54±0.86	-	100.14±0.46	99.84±0.68
10	-	-	-	-	-	-
11	-	-	-	-	-	-

All the results are given as mean±SD, n = 6

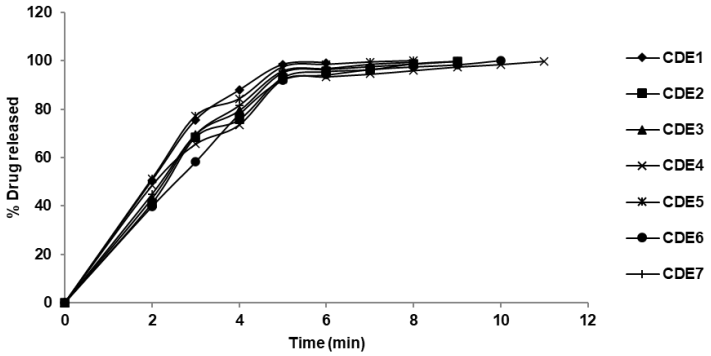


Fig. 3: *In vitro* drug dissolution profile of ESPO ODFs (CDE01-CDE07)

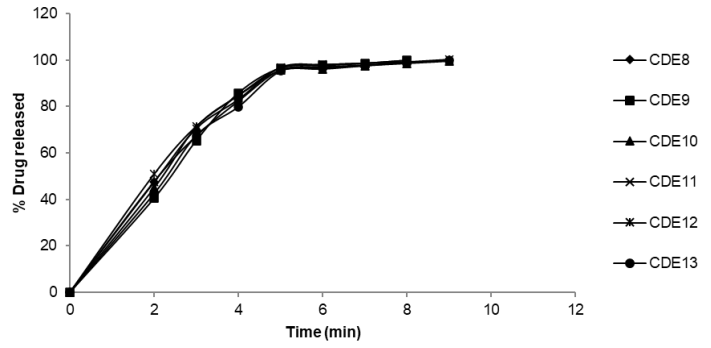
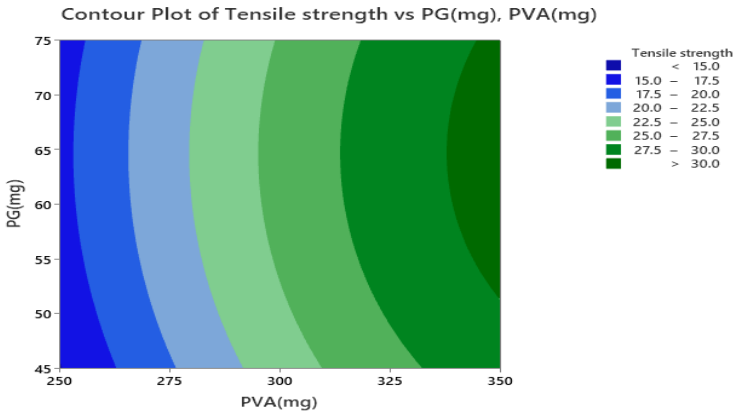
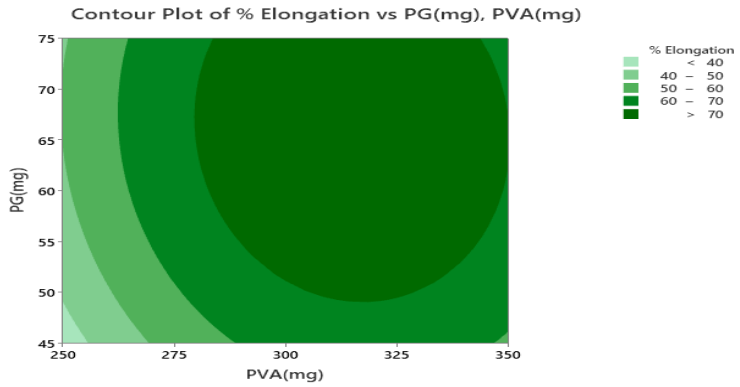


Fig. 4: *In vitro* drug dissolution profile of ESPO ODFs (CDE08-CDE13)



(a)



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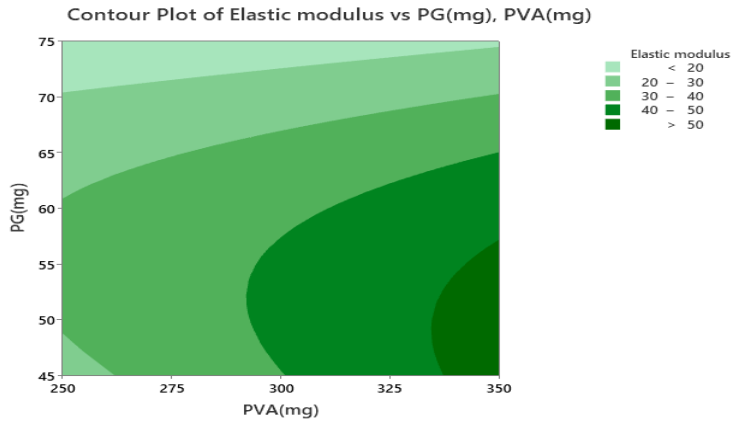
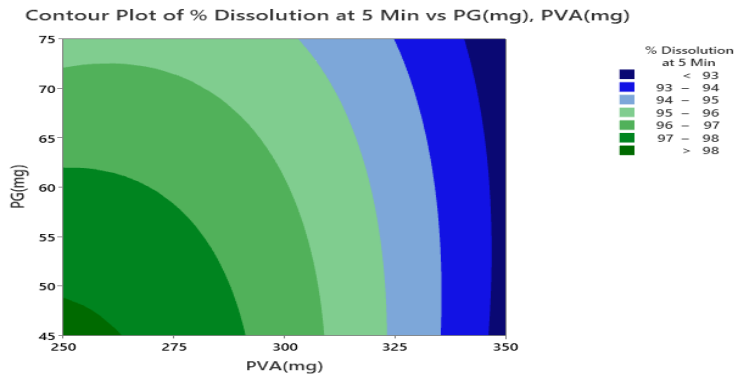


(c)



(d)

Fig. 5: Contour plots of a) Tensile strength b) Percent elongation c) elastic modulus d) Percent dissolved at the end of 5 min (% $D_{5\ min}$)

Optimization and data analysis

Linear, interaction and quadratic regression models were generated for all the responses such as tensile strength, Percent elongation, elastic modulus and percent dissolved at the end of 5 min (% $D_{5\ min}$). The following equations were generated to evaluate the responses using central composite design [32].

Y_1= Tensile strength = 25.5856+7.0515(PVA)+0.742(PG)-1.8234$(PVA)^2$-1.1659$(PG)^2$

Y_2= Percent elongation = 75.572+10.497(PVA)+5.655(PG)-16.547$(PVA)^2$-6.502$(PG)^2$

Y_3= elastic modulus = 38.2131+8.3467(PVA)-12.4883(PG-10.9706$(PG)^2$

Y_4=(%$D_{5\ min}$) = 6.0488-2.2575(PVA)-0.7158(PG)-1.1308$(PVA)^2$

Quadratic model was suggested to tensile strength, Percent elongation, elastic modulus and percent dissolved at the end of 5 min (% $D_{5\ min}$). All the responses were fitted to quadratic model. In case of tensile strength and percent elongation, two squared effects and two linear effects were observed. In case of elastic modulus two linear effects and one squared effect (PG*PG) were identified as significant, so reduced model equation was generated. Similarly, in case of % $D_{5\ min}$, two linear effects and one squared effect (PVA*PVA) were identified as significant, so a reduced model equation was generated. In all the responses interaction effects are not significant.

The F-values for tensile strength, percent elongation, elastic modulus and percent dissolved at the end of 5 min (% $D_{5\ min}$) responses were 142.96, 42.07, 8.48 and 15.28, respectively, showing significant models. The model equations R^2 values were close to 1, indicating good models. The summary of responses for the models generated by central composite design was shown in table 8.

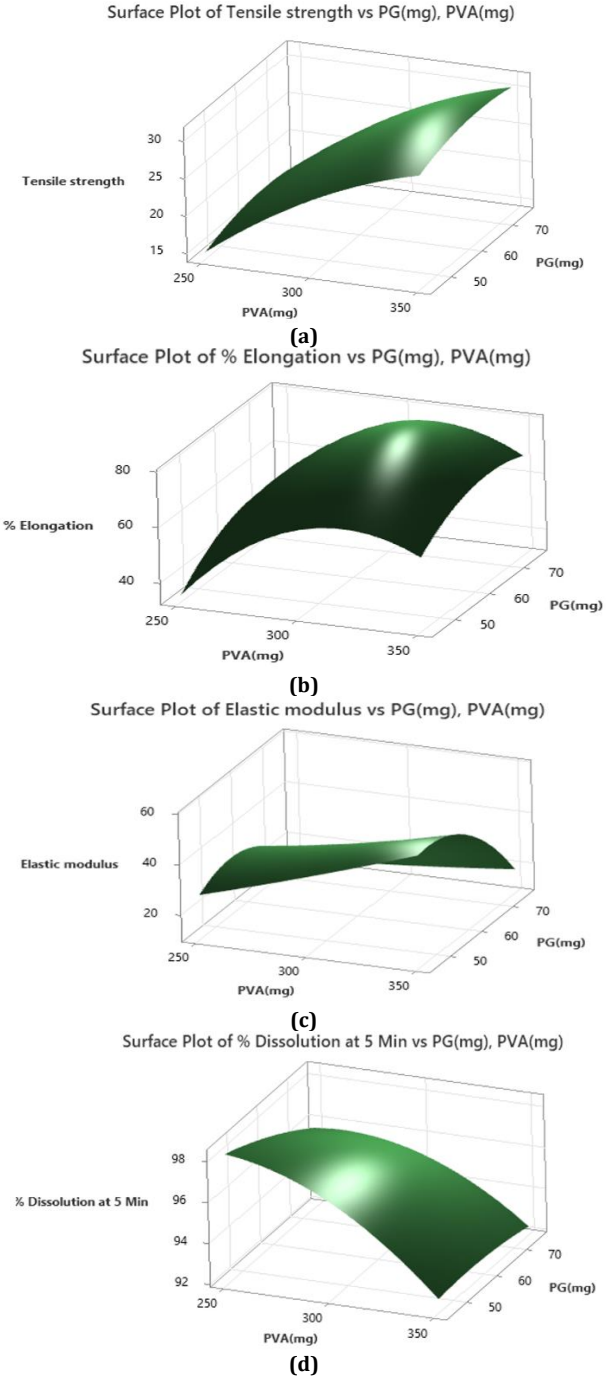


Fig. 6: Response surface plots of a) Tensile strength b) Percent elongation c) elastic modulus d) Percent dissolved at the end of 5 min (% $D_{5\ min}$)

Table 8: Summary of responses for generated models

Response	F	P	R^2	R^2 (Pred)	R^2 (Adj)
Tensile strength,	142.96	<0.005	99.03	94.41	98.34
Percent elongation,	42.07	<0.005	96.78	69.14	94.48
Elastic modulus	8.48	<0.005	85.83	72.15	75.71
% $D_{5\ min}$	15.28	<0.005	91.61	52.97	85.61

The 2D-contour plots and 3D-surface plots for the responses are shown in fig. 5 and fig. 6.

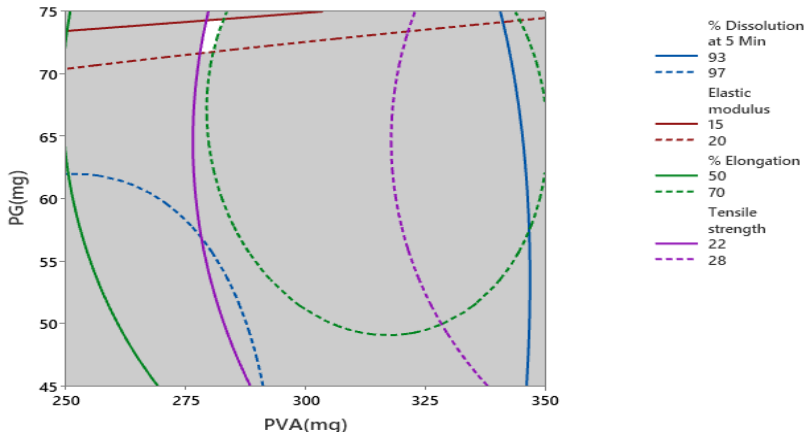


Fig. 7: Overlay plot of the optimized responses by CCD

The overlay contour plot for optimized parameters is shown in fig. 7.

The optimized values of variables were used to fix the limits on dependent variables and possible solutions are generated with help of MINITAB software. From the generated predicted solutions, the optimal values of variables are 304.80 mg of PVA and 74.16 mg of PG for getting maximum desirability (closer to 1) for the responses. In order to check the validity of the predicted values, the optimized checkpoint batches were made and responses were measured. The comparison of predicted responses and observed responses were shown in table 9. The values of predicted responses and observed responses are close to each other with<5% relative error.

Table 9: Comparison of predicted and observed responses

Response	Predicted	Observed	% Relative error
Tensile strength	25	25.072	0.288
Percent elongation	75	75.320	0.427
Elastic modulus	18.035	18.421	2.410
% $D_{5\ min}$	95.3	94.47	-0.871

CONCLUSION

The main objective of the study is succeeded by developing and optimizing the ESPO oral films. The Central composite design of response surface method was applied in the present study. This method significantly helped to understand the effect of polymer concentration and plasticizer concentration on the tensile strength, percent elongation, elastic modulus and amount dissolved up to 5 min. The selected models helped in the identification of design space. The quantities of polymer and plasticizer was checked within the design space to meet the optimum desirability. The responses of checkpoint experiments were compared with predicted values and we conclude that escitalopram oxalate oral dissolving films were successfully developed by quality by design approach.

ABBREVIATIONS

SSRI-Selective serotonin reuptake inhibitor, ESPO-Escitalopram oxalate, ODFs-Oral dissolving films, ATR-FTIR-Attenuated total reflectance-fourier transform infrared spectroscopy, PVA-Poly vinyl alcohol, PG-Propylene glycol, SEM-Scanning electron microscope, CCD-Central composite design, DT-Disintegration time, ANOVA-Analysis of variance.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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