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Original Article

Formulation and Evaluation of Escitalopram Oxalate Oral Films by 3^2 Factorial Design

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ABSTRACT

Background: The aim of this work was to develop a mouth dissolving film containing Escitalopram oxalate, utilizing basic ingredients such as polymers, plasticizers, sweeteners, saliva-stimulating agents, and flavors, to achieve rapid drug release with good mechanical properties. **Materials and Methods:** The films were prepared using the solvent casting method. Hydroxy Propyl Methyl Cellulose (HPMC) E5 cps was used as the polymer to provide uniform film thickness, while propylene glycol was employed as a plasticizer to enhance folding endurance, tensile strength, and percent elongation. A 3^2 Factorial Design was utilized to optimize the formulations and assess the influence of variables on film properties. **Results and Discussion:** The optimized formulation (F7) exhibited excellent properties, including good mouth feel, folding endurance, and rapid disintegration. The disintegration time was as short as 20 sec, and 99% of the drug was released within 10 min. These results demonstrated the formulation's potential for immediate drug delivery. Mouth dissolving films of Escitalopram oxalate were successfully developed using HPMC E5 cps and primojel. **Conclusion:** The optimized Formulation (F7) showed promising attributes, such as rapid drug release, satisfactory mechanical properties, and a short disintegration time, making it a suitable candidate for pharmaceutical applications requiring a rapid onset of action.

Keywords: Escitalopram oxalate, HPMC E5, 3^2 Factorial Design.

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IINTRODUCTION

The oral form of administration of drugs ranks as one among the most popular. Latest dosage forms are being developed with the goal to improve therapeutic effectiveness and safety. Rapid disintegrating dosage forms, which are designed to induce more rapid drug absorption than conventional oral dosage forms that include sublingual tablets, have gained popularity in the pharmaceutical sector during the last ten years. Fast Dissolving Oral Films (FDOF) manufacture requires active medicinal substances, polymers, plasticising agents, saliva simulators, surfactants as well sweeteners, and flavours. Rapid dissolving oral films breakdown instantly after being placed on the tongue, releasing the drug into the saliva and require no additional swallowing (Kundu *et al.*, 2013). The active pharmaceutical components are taken in orally with saliva, facilitating absorption in the GI system or from the vascular area in the oral cavity, enabling the drug to reach the circulation more quickly. Thus, as much as at least 90% of the medicine is effectively transported into the body. The rate of release of drugs can be altered by altering the concentration of polymers and plasticisers.

Systemic drug administration can be used to achieve drugs with shorter half-lives, the small intestine as the primary site of absorption, and the maintenance of sufficient plasma levels. For active therapeutic agents with high solubility and low permeability, results in low bioavailability, this dosage form may be preferred (Patel *et al.*, 2011). After formulating the fast-dissolving oral films, they need to pass a number of evaluations, including tensile strength, percentage elongation, thickness, folding endurance, unit surface area, average weight, drug content, and content uniformity by assay technique, disintegration time, and drug release. FDOF will continue to progress in the pharmaceutical market alongside other pharmaceutical developments simply because it offers certain benefits such as self-medication and easy administration, plus moreover avoiding pain present in parenteral route of administration (Madhav *et al.*, 2009).

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MATERIALS AND METHODS

API was sent as a gift from SeekoBiotics Pvt. Ltd., HPMC E5 was sourced from LobaCheme Laboratories, while all other chemicals utilized were of analytical grade (Koland *et al.*, 2010).

Procedure

Scientists used ethanol solution to mix with both plasticizing elements and polymers which dissolve in water. The magnetic stirrer continues operating for 2 hr to remove trapped air bubbles from the solution after which the solution receives rest. During the mixing period the drugs and excipients absorbed into solution under vigorous stirring for 30 min. After the stirring was finished the two solutions were combined. The film formation requires casting the solution onto the right petri dish. The petri plates remained in a hot air oven with temperature control at 60°C for the duration of 60 min. A drying process concludes then the filmistéams off the dish followed by cutting it to the required measurement (Shankar *et al.*, 2024).

The Dose Calculations

Glass plate Length = 9 cm.

Area covered by plate = 63.58 cm^2.

The number of 6.35 cm^2 films on the full plate is 10 films.

Each film contains 10 mg of API.

Standard Graph of Escitalopram oxalate

50 mg of Escitalopram oxalate was mixed with 100 mL of water to make a stock solution. From this stock solution, 10 mL of this stock solution was extracted and diluted with water (H_20) to achieve 100 mL. To develop a calibration curve, stock solution was diluted at various concentrations (2 µg/mL-10 µg/mL). The absorbance was determined at 239 nm (Chatwal and Anand, 2007).

Evaluation of Oral Film

Thickness

The test determined uniformity of film thickness through measurements conducted at five separate points utilizing a micrometer screw gauge. The test standard states that any film thickness variation should not exceed 5%. The difference between maximum and minimum determined thickness values across five testing areas should remain below five percent of the average film thickness. The threshold indicates non-uniformity in film thickness beyond which performance or characteristics might be impacted in drug delivery and barrier properties applications (Pavia *et al.*, 2011).

Weight variation

Ten randomly chosen films were weighed individually to evaluate their weight uniformity. The mean weight of the films was calculated, and the variance was assessed by examining the differences between each film's weight and the calculated mean.

Folding endurance

Folding endurance can be assessed by constantly folding the film in exactly the same location unless it cracks. For this film, the folding endurance ranged from 300 to 450 folds.

Disintegrating time

The major requirement for this investigation involves attaining fast formulation dissolution that occurs within mere seconds. A super disintegrating agent served as an addition to shorten the disintegration period of the formulation. A single 4.0 cm^2 film acted as the unit dosage for the experiment which researchers placed on a petri dish with 10 mL of distilled water. Scientists determined the *in vitro* time for disintegration by measuring the amount of time the film required to separate into pieces.

In vitro dissolution studies

The drug release study used the LABINDIA Disso equipment II (Paddle) to conduct an *in vitro* investigation under 37±0.5°C and 50 rpm with 900 mL of 6.8 phosphate buffer. The LABINDIA Disso equipment II (Paddle) operates at 50 rpm within 900 mL 6.8 phosphate buffer that maintains temperature levels between 37±0.5°C. The selected size will be useful for preparing an effective dosage form. The measured size of the delivery film was set at 2.0×2.0 cm^2. The dissolution study required the collection of 5 mL dissolution medium samples at 2 min intervals up to 15 min. The maintenance of dissolution volume occurred through replacement of phosphate buffer solution at pH 6.8 after every sample collection. The analysis of dissolved API in filtered samples used an Ultraviolet visible spectrophotometer at 239 nm wavelength. Researchers calculated concentrations through measuring samples three times as the basic number for each concentration value (Pavia *et al.*, 2011).

Drug content

The experiment used a 4 cm^2 surface area of the Oral D is integrating Films (ODF) which dissolved in 50 mL of phosphate buffer solution at pH 6.8 while the mixture received stirring. The dissolution mixture was filtered through Whatman filter paper in order to eliminate remaining particles and film components. The spectrophotometer measured dissolved substance concentration at a wavelength of 239 nm.

Assay

Dissolve a 4 cm^2 portion of the thin film in 50 mL of pH 6.8 phosphate buffer, stirring well. The resultant solution undergone filtration by aid of Whatman filter paper. Dilution was performed to the filtrate by employing the similar buffer in a volumetric flask and investigated with aid of UV-visible spectrophotometer at 239 nm (Sharma *et al.*, 2010).

RESULTS AND DISCUSSION

This research was envisioned to develop Escitalopram oxalate oral films for the medical management of mania. oral dissolving films were formulated using HPMC E5 as the polymer, sugar as the sweetening agent, citric acid as the saliva enhancer, Primojel as the disintegrant, propylene glycol as the plasticizer, and menthol as the flavoring agent. The films were formulated using a 3^2 factorial design, incorporating HPMC E5 and Primojel as the key disintegrant components.

Films, each containing 100 mg of Escitalopram oxalate, were formulated using HPMC E5 and Primojel according to the formulas provided in Table 1.

For preparation of films solvent casting method was employed. Films were found to be clear and transparent. They exhibited uniform thickness and good flexibility, along with favorable mechanical attributes. The assay findings revealed that the drug was effectively placed around the films. Each of the prepared films was tested for various properties including folding endurance, thickness, weight variation, drug content, disintegration time, and dissolution rate. The films showed a folding endurance exceeding 200-300 folds, reflecting their excellent mechanical strength (Table 2).

The Escitalopram oxalate content found in the produced films remained between 100±2%. Drug disintegration time decreased when adding higher amounts of super disintegrants to the drug formulations because both factors had a negative correlation. The dissolution experiments of different film types occurred under a pH 6.8 phosphate buffer solution (Kalyan and Bansal, 2012).

The dissolution data went through an analysis of zero-order and first-order kinetics models throughout all scenarios. The first-order model demonstrated better correlation coefficient (r) values than the zero-order model thus indicating Escitalopram disintegration followed first-order kinetics. In the first order model the correlation coefficient (r) maintained values from 0.928 up to 0.996. The slopes of the first order linear regressions were used to estimate the associated first order dissolution rates (K1) for the individual products. The Dissolution Efficiency (DE30) values were computed using the Khan technique (Yellanki *et al.*, 2010).

The Fourier Transform Infrared Spectroscopy (FTIR) analysis provided valuable evidence of the compatibility between Escitalopram oxalate and the excipients used, supporting the suitability of the formulation for potential pharmaceutical applications (Figure 1).

Factorial design, a methodology that enables an investigation of variables impacting a process and analyses their relative relevance. It also enables the detection of interactions between the selected factors. Constructing a factorial design entails specifying parameters and determining the corresponding responses.

A 3-level, 2-factor experimental design (3^2 factorial design) was employed for determining the optimal proportion of the independent variables HPMC E5 and Primojel in the formulation of Escitalopram oxalate fast dissolving oral films (Shankar *et al.*, 2024). The dependent variables selected were Disintegration Time (DT) and percent drug dissolved at 10 min. Significance was assessed for resultant equations that were evaluated using a 95% confidence interval ($p<0.05$). Polynomial equations have been generated for the DT and the % of drug dissolved (10 min).

The experimental design for formulating Escitalopram oxalate fast dissolving oral films involved three levels of factor X1 (HPMC): 500 mg, 600 mg, and 700 mg, and three levels of factor X2 (Primojel): 30 mg, 40 mg, and 50 mg. Nine Escitalopram oxalate fast dissolving oral films developed by combining both of these components (X1, X2) using a 3^2 factorial approach. The films were assessed to discover the combined impacts of X1 and X2, as well as the optimal combination and concentrations. To achieve the desired rate of medication release and disintegration, the concentration levels of HPMC E5 were coded as -1 = 500 mg, 0 = 600 mg, +1 = 700 mg. The concentration levels of Primojel were coded as -1 = 30 mg, 0 = 40 mg, +1 = 50 mg.

Polynomial equations were derived for DT and percent drug dissolved 10 min (PD10) using Design Expert 7 software.

Table 1: Formulation of Ecitolopramoxalate Oral Film.

Formulation	HPMC	SSG	Propylene glycol	Citric Acid	Mannitol	Methanol	Drug
F1	500	30	2 mL	10	100	10	100
F2	600	30	2 mL	10	100	10	100
F3	700	30	2 mL	10	100	10	100
F4	500	40	2 mL	10	100	10	100
F5	600	40	2 mL	10	100	10	100
F6	700	40	2 mL	10	100	10	100
F7	500	50	2 mL	10	100	10	100
F8	600	50	2 mL	10	100	10	100
F9	700	50	2 mL	10	100	10	100

Table 2: Evaluation parameters.

Formulations	Thickness (mm)	Folding endurance	Tensile strength (g/cm²)	*In vitro* disintegration time (sec)	Drug content (mg)	Assay (%)
F1	0.59	355	48.41	25	20	100
F2	0.54	365	51.18	28	19.86	99.30
F3	0.55	375	62.04	20	19.94	99.70
F4	0.53	385	54.25	31	19.89	99.475
F5	0.51	355	53.68	35	19.99	99.95
F6	0.51	357	52.33	27	19.89	99.45
F7	0.56	387	56.45	36	19.86	99.30
F8	0.60	396	57.62	32	19.75	98.75
F9	0.62	398	48.63	35	19.89	99.45
F10	0.60	396	57.62	32	19.92	99.60

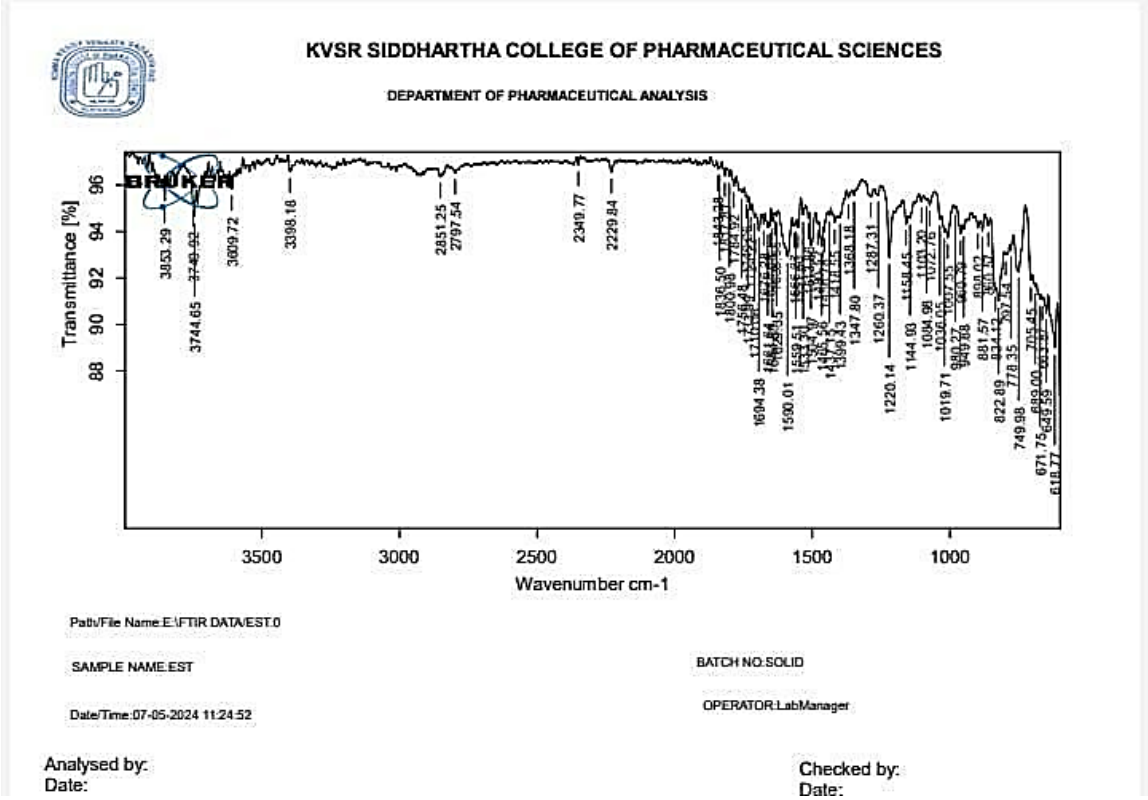

Figure 1: FTIR spectrum of Escitalopram oxalate.

Figure 2 shows the response surface plots for disintegration time and PD10 using X1 and X2 on both axes.

The reliability of the derived equations was confirmed by preparing two intermediate concentration formulations (F10) as reference point.

The equations for DT and PD10 developed as follows (Cilurzo *et al.*, 2011).

$$Y1=36.00+ 2.30X1-4.00X2+1.25X1X2-3.50X12-5X22(DT)$$

$$Y3=95.75-2.70X1+3.55X2-1.50X1X2–2.95X12 +0.50X22(PD10m)$$

In the equations for Y1, a positive coefficient for X1 illustrates the fact that concentration of HPMC increases, disintegration time increases. Conversely, a negative coefficient for X2 indicates that as the concentration of Primojel increases, disintegration time decreases.

Increasing super disintegrant dosage shortens disintegration times of the films while drug release patterns can be modified

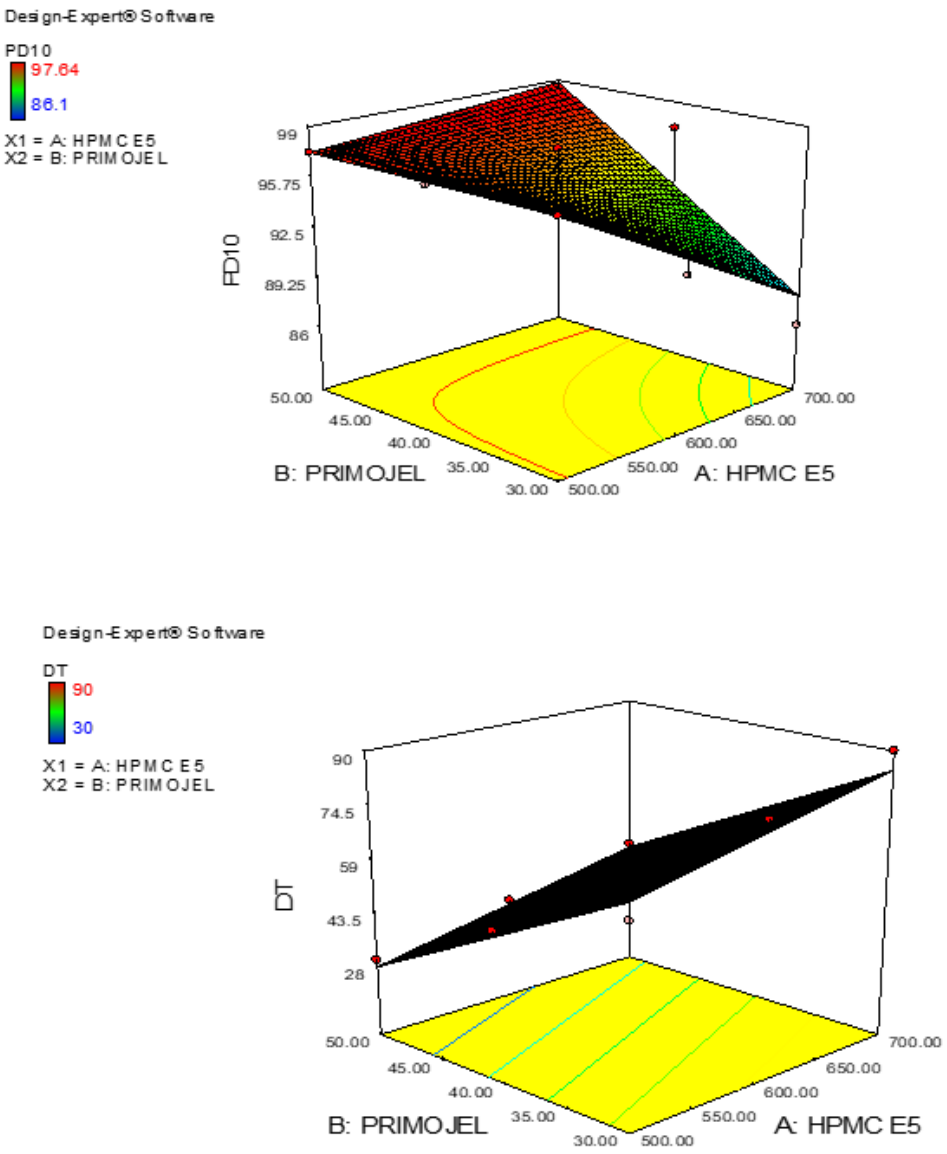

Figure 2: 3D Surface plot for % DD in 10 min.

through optimized X1 and X2 concentrations. Experimental results demonstrate the relationship between X1 and X2 factors with DT and PD10 through response surface graphs which confirm the mathematical equations designed for these response variables. F10 formulation was developed for validating equation by using 32 sec as the DT target together with a PD10 target of 95.00%. The recorded PD10 value of 95.64% and DT value of 32 sec verified the correctness of the mathematical equation. Research data proved that Escitalopram mouth dissolving films could be successfully developed through the combination of HPMC E5 and Primojel using a 3^2 factorial design approach (Chauhan *et al*., 2012).

CONCLUSION

As the core aim of this research was the development of a mouth dissolving film containing Escitalopram oxalate while using basic components including polymers, plasticizers, sweetener, saliva stimulating agent and flavor. Production of films occurred through solvent casting technique. The film obtained its required thickness from HPMC E5 cps. The use of propylene glycol yielded excellent results for folding endurance and tensile strength as well as percent elongation. The produced formulation F7 demonstrated both desirable mechanical qualities and drug-release timing and instant drug release features along with acceptable mouth feel and folding resilience. F7 experienced a disintegration time of 20 sec while releasing 99% of its drug content in 10 min. The preparation of Escitalopram mouth dissolving films was successful through the combination of HPMC E5 along with primojel using 3^2 Factorial Design.

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ABBREVIATIONS

HPMC: Hydroxy Propyl Methyl Cellulose; **FDOF:** Fast Dissolving Oral Films, **ODF:** oral disintegrating films; **DE30:** Dissolution Efficiency; **DT:** Disintegration time; **FTIR:** Fourier Transform Infrared Spectroscopy; **PD10:** Percent drug dissolved 10.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL STATEMENT

The study titled Formulation and Evaluation of Escitalopram Oxalate Oral Films by 3^2 Factorial Design does not involve human participants, animals, or clinical trials. All experimental procedures were conducted in compliance with institutional and regulatory guidelines for pharmaceutical formulation and evaluation. No ethical approval was required for this study as it focused solely on the development and *in vitro* characterization of drug delivery formulations.

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