RESEARCH ARTICLE

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

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ABSTRACT

This experiment aimed to create a mouth dissolving film containing Olanzapine and basic adjuvants such as polymers, plasticizers, sweeteners, saliva stimulants, and flavorings were used. Solvent casting method was used created using to create films. HPMC E5 cps gave good thickness to the film. The films produced gave good tensile strength and folding endurance. The augmented formulation (F7) exhibited good mouth feel, folding endurance, immediate drug release, and strong mechanical properties. The F7 exhibited a disintegration time (DT) of 20 seconds and drug release of 99% within 10 minutes. Polynomial equations were derived for DT and percent drug dissolved 10 (PD_{10}) using Design Expert 7 software. Disintegration time (DT) and percent drug dissolved in 10min (PD_{10}) equations developed are as follows. $Y_1=36.00 +2.50 X_1-5.00 X_2+0.25X_1X_2-2.50X^2-5X_2^2$(DT); $Y_3=90.75-3.70X_1+2.50X_2-0.00 X_1X_2–1.95X^2+0.50 X^2$($PD_{10}$m).The positive sign for co-efficient of X1 in Y1 equations designates that as the concentration of HPMC rises, disintegrating time increases. The negative sign for co-efficient of X2 inY1equations indicates that as the enhancement in primojel concentration decreases the disintegrating time . To check the legitimacy of equation F10 was formulated with DT for 25 sec and PD10 for 90.00. The Final DT Values and PD10were found to be 25 sec and 90.64 % indicating the validity of equation. FTIR spectra indicated that API and adjuvants did not interact during the study. Thus Olanzapine mouth dissolving films could be successfully prepared using HPMC E5 and primojel using 3^2 Factorial Design.

Keywords: Olanzapine, 3^2 Factorial design, mouth dissolving film, FTIR spectra

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INTRODUCTION

Oral Films (OF's) are becoming more and more well-liked and accepted as cutting-edge ways to increase the efficacy and safety of therapeutic molecules. These dosage forms aim to enhance patient compliance by converting drugs into appropriate dosage forms for easier administration. Some companies have introduced advanced versions of OF's. For instance, Lavipharm Laboratories Inc. developed an exemplary fast-dissolving drug delivery system that effectively meets the market's previously unmet needs. Lavipharm has introduced a novel intraoral drug delivery system called Quick-DisTM, which is their registered patented technology. It consists of a thin, flexible film that dissolves rapidly. When placed on the tongue, the OF's disintegrates immediately, releasing the drug to dissolve in saliva. AS saliva descends into the stomach and absorbs some APIs from the mouth, throat, and esophagus. In these instances, the bioavailability of the APIs can be notably higher compared to conventional tablets.[1] The synthetic thienobenzo diazepine derivative Olanzapine is well-known for its antipsychotic, anti-nausea, and antiemetic effects. It functions as a selective antagonist at monoaminergic receptors, showing strong affinity for alpha-1-adrenergic, histamine H1, muscarinic M1-5, serotoninergic, and dopaminergic receptors. It exhibits reduced binding affinity for beta-adrenergic receptors, benzodiazepines, and gamma-aminobutyric acid type A. Olanzapine is known to start taking effect about one hour after it is administered orally, posing a challenge in achieving prompt relief from symptoms. Dysphagia is a widespread issue across all age groups, particularly among pediatric and elderly patients. Olanzapine has limited water solubility and undergoes significant first-pass metabolism, resulting in a low bioavailability of 40% following oral administration. Due to these challenges, it was envisioned that a mouth dissolving film incorporating a taste masking agent could be a viable solution. Such a formulation aims to achieve rapid onset of action of Olanzapine, thereby enhancing its therapeutic effectiveness.[2] Additionally, it seeks to improve compliance among geriatric, pediatric, and uncooperative patients.

MATERIALS AND METHODS

Materials

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Table 1: Formulation trials

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Olanzapine (mg)	100	100	100	100	100	100	100	100	100	100
HPMCE5 (mg)	500	600	700	500	600	700	500	600	700	673.15
Primojel(mg)	30	30	30	40	40	40	50	50	50	50
Propylene glycol (ml)	2	2	2	2	2	2	2	2	2	2
Citric acid (g)	0.010	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Sugar (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Flavor (mg)	10	10	10	10	10	10	10	10	10	10
Ethanol (ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Table 2: Evaluation parameters

Formulations	Thickness (mm)	Folding endurance	*In-vitro DT* (sec)	Weight variation (mg)	Drug content (mg)	Assay (%)
F1	0.58	250	32	51	5.63	99.82
F2	0.55	280		54	5.62	99.64
F3	0.59	300	36	55.6	5.63	99.82
F4	0.51	250	31	53.5	5.61	99.46
F5	0.53	280	35	58	5.60	99.29
F6	0.52	300	37	50	5.59	99.11
F7	0.55	250	20	52	5.60	99.29
F8	0.57	280	28	55	5.61	99.46
F9	0.53	300	25	57	5.62	99.64
F10	0.55	250	25	52	5.60	99.29

Olanzapine was offered as a free sample by Seeko Biotics Pvt. Ltd. Loba Cheme Laboratories provided the hydroxypropyl methyl cellulose (HPMC E5), and all other compounds used were of analytical quality.[3]

Methods

Formulation of fast-dissolving films

In ethanol, the plasticizers and water-soluble polymers were dissolved. The solution was agitated for 2 hours using a magnetic stirrer and set aside to allow removal of any entrapped air bubbles. For half an hour, the medication and excipients were thoroughly mixed and dissolved thoroughly. After that, a film of the solution was cast onto an appropriate Petri plate. For twenty-four hours, the plates were allowed to air dry.[4] The film was cut to the appropriate sizes after being carefully removed from the glass plate when it had dried (Table 1).

Dose calculations

Glass plate length = 4.75cm

Glass plate width = 4.75 cm

Area of the plate = 70.84 cm^2

No. of 4 cm^2 films from whole plate = 70.4/4 = 17 films

Each film contains 5.64 mg of drug

Evaluation of Oral Film

Thickness

To ensure homogeneousness of the film thickness, measurements were taken at 5 different locations using a micrometer screw gauge. The criterion for uniformity specified that the thickness variation should be less than 5%. This means that the difference between the maximum and minimum measured thickness across the 5 locations should not exceed 5% of the average thickness of the film. If the thickness variation exceeds this threshold, it indicates non-uniformity in the film thickness, which may affect its performance or characteristics in applications such as drug delivery or barrier properties.[5]

Weight variation

Ten randomly chosen films were weighed individually, and the average weight of the films was ascertained in order to evaluate the weight uniformity of the films. Each film's weight was then compared to this average weight in order to calculate the deviation.

Folding endurance

A film is folded repeatedly at the same location until it cracks to determine folding endurance. This film's folding durability was between 300 and 450 folds.

Disintegrating time (DT)

The primary criterion of this study is rapid dissolution of the dosage form within a few seconds. This is accomplished by using a super disintegrating agent to reduce DT. A 4.0 cm^2 film (unit dose) was used in the experiment, and it was positioned on a petri dish with ten ml of distilled water. The *in-vitro* DT was determined by timing the breakup of the film.[6]

***In-vitro* dissolution test**

The LABINDIA dissolving apparatus II (Paddle) was used to perform the in-vitro dissolution test. The experimental conditions included a temperature of 37±0.5°C and a stirring speed of 50 rpm in 900 ml pH6.8 phosphate buffer. The film size used for dose delivery was 2.0×2.0 cm^2. During the dissolution study, 5 ml samples of the dissolution media were collected at every 2 minutes upto15 minutes. To maintain the dissolution volume, the same volume of phosphate buffer (pH 6.8) was replaced back after each sample collection. After passing the obtained samples through a 0.45 µm membrane filter, the amount of dissolved Olanzapine was measured at 260 nm wavelength with a UV-Visible spectrophotometer. Each reported concentration represents the average of three measurements.[7]

Drug content

This test involved dissolving a 4 cm² section of ODF in 50 milliliters of phosphate buffer (pH 6.8) while stirring. Following the dissolution process, the contents were filtered through Whatman filter paper to eliminate any remaining particles or film constituents. A UV spectrometer was used to to measure the concentration of the dissolved substance, at a specific wavelength of 260 nm.

Assay

In this test, a 4 cm² section of thin film was dissolved while being stirred in 50 milliliters of pH 6.8 phosphate buffer. A Whatman filter paper was used to filter the

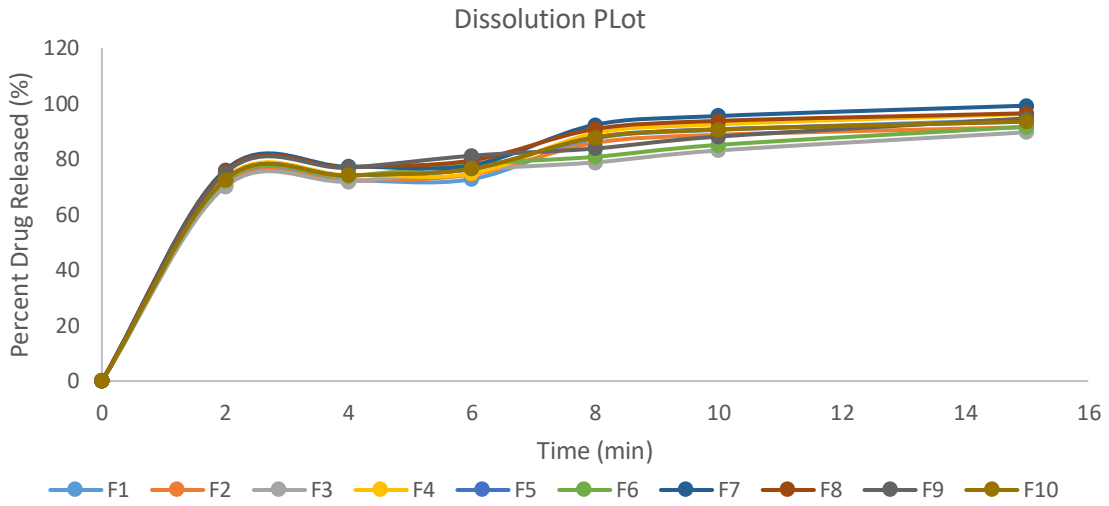

Figure 1: Dissolution profile of Olanzapine oral films

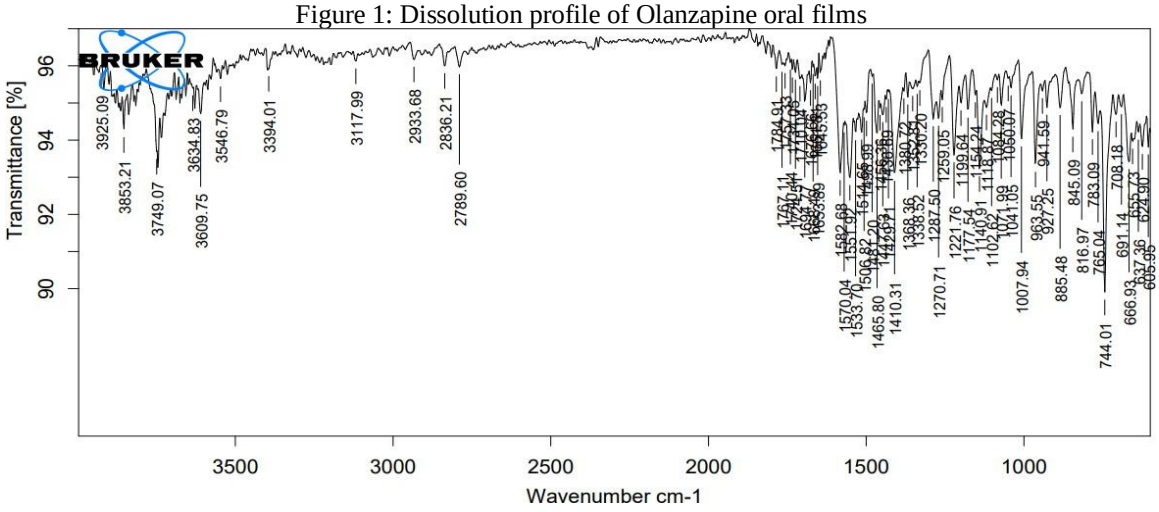

Figure 2: FTIR spectrum of Olanzapine

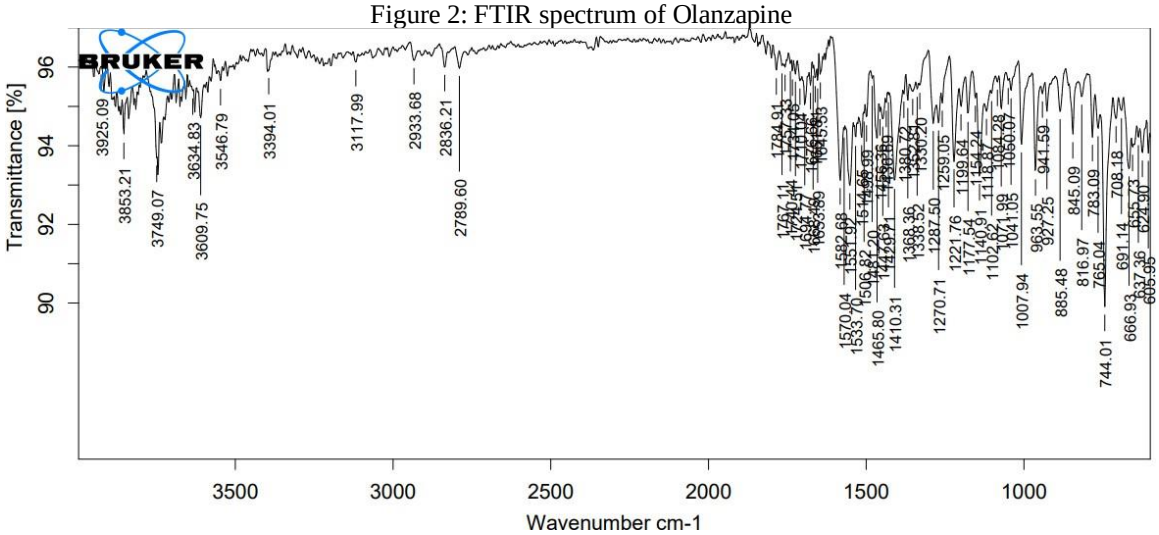

Figure 3: FTIR spectrum of Olanzapine film

Table3:Dissolution parameters

Formulation	PD4	DT	K1
F1	72.25	32	0.172
F2	72.07	35	0.147
F3	71.9	36	0.123
F4	74.69	31	0.200
F5	78.1	35	0.164
F6	73.1	37	0.135
F7	74.85	20	0.298
F8	72.67	28	0.204
F9	71.6	25	0.161
F10	74.85	25	0.296

mixture.8. A UV spectrophotometer set to 260 nm was used to evaluate the filtrate after it had been diluted with the same buffer in a volumetric flask (Table 2).

RESULTS AND DISCUSSION

The goal of the current study was to develop Olanzapine oral films for the treatment of mania. ODF's were prepared using HPMC E5 as polymer, saccharin as sweetener, citric acid as saliva enhancer, primojel as disintegrating agent, propylene glycol as plasticizer and menthol as flavouring agent. ODF's were prepared using 3^2 factorial design using HPMC E5 and Primojel as disntegrant.

Films each containing 100 mg of olanzapine was formulated employing using HPMCE 5 and primojel as given in formulae Table 1. The ODFs were uniformly thick, clear, and transparent after being formed using the solvent casting procedure. They have good mechanical and flexible qualities.[9] According to assay results, the API was appropriately incorporated in the films. All the prepared films were assessed for folding endurance, thickness, weight variation, drug content, DT, and dissolution rate characteristics. The physical parameters of the films are shown in Table 2. The films demonstrated excellent mechanical strength, with a folding endurance between 250 and 300. The Olanzapine drug content in the films was within 100±2%. DT ranged from 25 to 37 seconds, with shorter DT times observed at higher concentrations of super disintegrants. The dissolution rate of the various films was studied in a 6.8 phosphate buffer. The dissolution profiles of various films prepared are shown in Figure 1. FTIR spectra of pure drug and formulation gave similar peaks gave in FTIR spectra indicating that there is no interaction between API's and excipients employed in the experiment. The FTIR Spectra was shown in figure 2 and 3. The dissolution of Olanzapine was found to follow first order kinetics, as evidenced by the higher correlation coefficient (r) values in the first order model compared to the zero order model. Specifically, the r values in the first order model ranged from 0.918 to 0.998. The dissolution parameters of various Olanzapine films are summarized in Table3. Factorial design is a technique used to identify and evaluate the significance of various factors in a process, as well as any interactions between those factors. Constructing a factorial design involves selecting the parameters to be studied and choosing the responses to measure.[10] A three-level, two-factor experimental design (3^2 factorial design) was employed to ascertain the proportions of the independent variables HPMC E5 and Primojel in the formulation of Olanzapine oral dissolving films. DT and PD10 were selected as the dependent variables. For the final equations, significant terms were found at a 95% confidence interval ($p<0.05$). Polynomial equations were created to describe the relationships for both DT and PD10.The 3 levels of factor X1 (HPMC) at concentrations of 500 mg, 600 mg, and 700 mg, and the three levels of factor X2 (Primojel) at concentrations of 30 mg, 40 mg, and 50 mg, were used as the basis for designing the formulation of Olanzapine fast dissolving films.[11] A total of nine Olanzapine mouth dissolving films were developed using chosen pairings of the two variables, X1 (HPMC) and X2 (Primojel), as per the 3^2 factorial design. In order to find the optimal combination and concentration necessary to produce the desired quick release and dissolution of the drug, these films were assessed to assess the relevance of the combined effects of X1 and X2. The concentration of HPMC E5 was divided into three levels, which were coded as follows: +1 = 700 mg, 0 = 600 mg, and -1 = 500 mg. Similarly, three levels for the concentration of Primojel were selected and coded as: -1 = 30 mg, 0 = 40 mg, and +1 = 50 mg. The formulas of ODF are provided in Table 1. Polynomial equations for DT and percent drug dissolved in 10 minutes (PD10) were formulated using Design Expert 7 software. Figure 4 depicts the response surface plot for D.T. and response surface plot for PD10. The impacts of X1 and X2, indicated on the corresponding axes, are displayed in this figures.[12]

F10 formulation was used to check the Validity of derived equations

The equations for DT and percent drug dissolved in 10 min (PD10) developed as follows.[13]

$$Y_1 = 36.00 + 2.50\ X_1 - 5.00\ X_2 + 0.25\ X_1X_2 - 2.50X^2 - 5X_2^2 \text{ (DT)}$$

$$Y_3 = 90.75 - 3.70X_1 + 2.50X_2 - 0.00\ X_1X_2 - 1.95X^2 + 0.50\ X^2 \text{ (PD10m)}$$

The co-efficient of X1 in the Y1 equations has a positive sign, meaning that the DT with HPMC concentration. The DT reduces with increasing primojel concentration, as indicated by the negative sign for the co-efficient of X2 in the Y1 equations. Based on the data, it can be established that increasing the amount of the super disntegrant (X2) decreases the D.T. of the dosage form. Furthermore, the olanzapine release pattern can be changed by selecting appropriate levels of X1 (HPMC E5) and X2 (Primojel). The response surface plots exemplified the effects of X1 and X2 on D.T. and PD10, confirming the validity of the resultant equations for these dependent variables.[14] To further validate the equations, formulation F10 was prepared with a target DT of 25 seconds and PD10 of 90.00%. The final experimental values obtained were DT of 25 seconds and PD10 of 90.64%, which closely

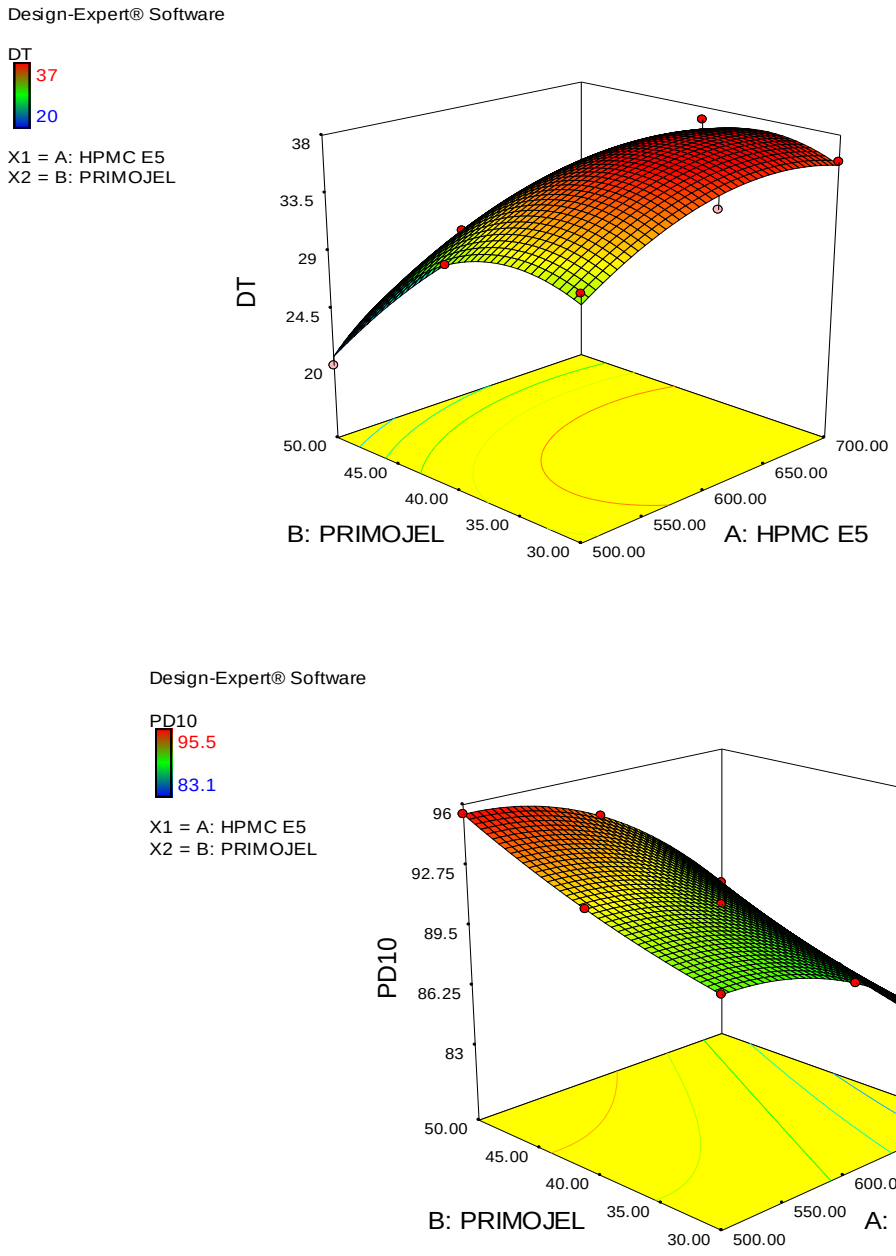

Figure 4: 3D Surface Plots for DT and PD_{10}

matched the predicted values, indicating the validity and accuracy of the equations.[15] In summary, the study demonstrates that adjusting the levels of HPMC E5 (X1) and Primojel (X2) effectively controls time for disintegration and drug release characteristics in Olanzapine ODF, as predicted by the derived polynomial equations. Thus olanzapine oral dissolving films could be successfully prepared using HPMC E5 and primojel using 3^2 Factorial Design

CONCLUSION

In this study, the development and evaluation of Olanzapine oral dissolving films (ODFs) were successfully carried out using a 3² factorial design. The optimized formulation, specifically formulation F7, demonstrated superior mechanical properties, rapid disintegration, and immediate drug release. The DT of the optimized film was found to be 20 seconds, with a drug release of 99% within 10 minutes. The factorial design approach provided valuable insights into the effects of the independent variables, HPMC E5 and Primojel, on the disintegration time and drug release profile. The derived polynomial equations effectively predicted the relationship between these variables and the response outcomes, confirming the validity of the model. Additionally, FTIR spectra analysis indicated no significant interaction between the active pharmaceutical ingredient (API) and the excipients, ensuring the stability of the formulation. The dissolution studies revealed that the release kinetics of Olanzapine from the ODFs followed first-order kinetics, further validating the efficacy of the formulation. Overall, the study concludes that Olanzapine mouth dissolving

films can be successfully formulated using HPMC E5 and Primojel. The rapid disintegration and high drug release rate of the ODFs make them a promising dosage form for enhancing the therapeutic effectiveness and patient compliance, particularly in populations with dysphagia or those requiring rapid onset of action.

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