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Effect of Cosolvent and Polymer HPMC P.603/PVA-based Lamotrigine Orodispersible Film: Optimization and Physicochemical Characterization

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ABSTRACT. Lamotrigine (LTG), classified as BCS class II, is dissolved in cosolvent ethanol (EtOH) or ethyl acetate (EA) to enhance solubility. The objectives of this study are to identify the appropriate formulation of LTG orodispersible film (OF) based on hydroxypropyl methylcellulose Pharmacoat® 603 and polyvinyl alcohol (HPMC P.603/PVA) polymer with EtOH or EA solvency using Central Composite Design in Response Surface Methodology (CCD-RSM). An experimental approach was utilized to investigate the effect of cosolvent amount and HPMC P.603/PVA ratios on the film disintegration time (DT) and folding endurance (FE). The optimized OF-EA composition was 0.46 HPMC P.603/PVA ratio and 3.66% EA with a desirability of 0.817. In comparison, the optimal OF-EtOH composition was 0.87 HPMC P.603/PVA ratio and 6.19% EtOH with a desirability of 0.843. The characteristic data for the optimal formulas include: OF-EtOH: weight variation 92.05±4.81 mg, thickness 0.15±0.01 mm, DT 36.11±1.48 sec, and FE 310.33±5.03; and OF-EA: weight variation 93.72±1.50 mg, thickness 0.16±0.00 mm, DT 26.73±3.32 sec, and FE 470.6±37.44. Based on the OF-EtOH FE, the HPMC P.603/PVA ratio had a greater effect compared to the amount of EtOH ($p<0.05$). The analysis of variance (ANOVA) demonstrated that the amount of EA had a greater impact compared to the HPMC P.603/PVA ratio, with statistical significance ($p<0.05$). The EtOH cosolvent was preferable to EA based on the LTG solubility and OF dissolution profile. LTG OF had favorable physicochemical properties and showed promise as a rapid-dissolving formulation for therapeutic purposes.

Keywords: Central composite design, cosolvency, disintegration time, folding endurance, oral film.

INTRODUCTION

LTG is an antiepileptic drug used to treat partial, generalized, and absence epilepsy in both children and adults. The drug selectively binds to and inhibits voltage-sensitive sodium channels, stabilizes pre-sympathetic neuronal membranes, and prevents excessive amino acid release, particularly aspartate and glutamate (Betchel et al., 2023). However, LTG is classified as BCS class II, with a low water solubility of 0.17 mg/mL at 25 °C and 0.57 mg/mL at 37 °C (Beattie et al., 2012; Singh et al., 2015). That impacts the drug's solubility and bioavailability. LTG is available in four doses: 25, 50, 100, and 200 mg. The dose often used in OF is 25 mg/film, while other researchers have reported up to 50 mg/6 cm^2. High drug loading can have devastating effects on the physical properties of OF, including thickness, DT, and mechanical properties (Abouhussein et al., 2022). Thus, a strategy is required to overcome the OF formulation's limitations, such as cosolvency, which several researchers have carried out (Abouhussein et al., 2022; Panraksa et al., 2020; Rodríguez-Pombo et al., 2024; Visser et al., 2015)

Cosolvents, such as EtOH and EA, are utilized as solvents to enhance lamotrigine solubility during the production process. Those cosolvents included class II solvents with low toxicity (ICH Expert Working Group, 2021). Using 55% EtOH as a cosolvent has enhanced LTG solubility by 26-fold (Jouyban-Gharamaleki et al., 2017). Meanwhile, adding EA can increase the solubility of LTG by 170-fold at 30°C (Youse & Haghtalab, 2016). The film-former is another component that influences the preparation's solubility and dissolution. The film's robustness is affected by the film-former and the OF production process (Senta-Loys et al., 2016). The HPMC/PVA combination produces a transparent, colorless, spotless film with fast disintegration, a pleasant mouthfeel, and good mechanical properties (Al-Nemrawi & Dave, 2014). HPMC, a hydrophilic polymer with low viscosity (LV), such as type P.603, is ideal because it is easy to pour (Al-Nemrawi & Dave, 2014; Rajvi et al., 2022).

Nevertheless, the mechanical properties of an individual HPMC LV film are comparatively feeble; hence, the combination with PVA results in better performance. PVA polymer possesses excellent tensile strength, flexibility, and oxygen barrier qualities (Rajvi et al., 2022). Combining HPMC with PVA produces physical, chemical, and mechanical qualities that fulfill the criteria (Al-Nemrawi & Dave, 2014).

According to the description above, the EtOH and EA as cosolvent and HPMC P.603/PVA ratios should be tuned utilizing response surface methodology (RSM) as the quality by design (QbD) approach. QbD is utilized in the pharmaceutical industry's formula design and development process to improve product quality and performance (Beg et al., 2019). RSM is used in response variable optimization to statistically assess the influence of the relationship between the variables (Nining et al., 2023). The controllable factor variables are the HPMC P.603/PVA ratio (A) and the amount of EtOH or EA (B), and the observed response variables are DT (Y_1) and FE (Y_2). This method produces mathematical modelling that connects the two variables and an optimal formula with expected product qualities. Several studies have shown positive results from employing the QbD approach to design and develop pharmaceutical formulations. So far, no investigation has been conducted to prepare the LTG OF by manipulating the solubility of LTG using cosolvency techniques and a mixture of HPMC P.603/PVA polymers.

EXPERIMENTAL SECTION

Materials and Equipment

Materials used were LTG USP (OM. Chem Distribution, Bogor, Indonesia), hypromellose (HPMC, Pharmacoat® 603, Shin-Etsu, Tokyo, Japan; substitution type 2910), PVA (Chang Chun Petrochemical, Miaoli, Taiwan; grade BP24), propylene glycol (MCosm Inc., Redmond, US), sucrose (Thermo Fischer Scientific, New Jersey, US), citric acid monohydrate (Fagron, Ladenburg, Germany), EtOH (Thermo Fischer Scientific, New Jersey, US), EA (Thermo Fischer Scientific, New Jersey, US), and distilled water.

The equipment utilized included analytical scales (Mettler Toledo, Switzerland), magnetic stirrer (Thermo Fisher Scientific, USA), oven (Memmert, Germany), digital caliper (Sata, Netherlands), pH meter (Hanna, USA), spectrophotometer (Shimadzu UV-1900i, Japan), ultimate tensile machine (Tinius Olsen, USA), micropipette 100-1000 μL (Ohaus, USA), shaker incubator (N-Biotek, South Korea), centrifuge (Centrurion C2 Series, England), and microscope (Trinocular Camera CS-T10 Series, Japan).

Design of Experiment

This work utilized the CCD-RSM approach to formulate the LTG OF. The DT and FE were initially screened using a 2-factor CCD-RSM design with two levels, namely high and low. The analysis of previous experiments and research materials determined the high and low variables. The statistical software tool Design-Expert® version 13 (Stat-Ease Inc., Minneapolis, MN) was used to examine the influence of the indicated parameters on the response variables to determine the optimal formulation for LTG OF. CCD designed and executed 13 experiments in a controlled environment, as designed in **Table 1**.

Preparation of Casting Solution and OFs

The solvent casting method is used. PVA is dispersed with a magnetic stirrer at 300 rpm at 60°C until homogeneous. Then, HPMC P.603 is added and stirred for 15 min. Other excipients (10% propylene glycol, 1% citric acid, 2% sugar) are added with constant stirring speed and temperature. In the end, 25 mg LTG is dispersed until homogeneous. The liquid is poured into a petri dish (Ø 9 cm) and heated at 50 °C for 2-4 hours. Then, the film is removed from the dish and cut into 2x2 cm^2. The film is packed in plastic clips and stored in a desiccator (Bala et al., 2013).

Disintegration Time (DT)

Three films were put on each petri dish and transferred to a shaker incubator set at 37 °C and a speed of 50 rpm. The test utilized 25 mL of water at 37 °C. The recorded time corresponds to when the film started to degrade and become destroyed (Mazumder et al., 2017).

Folding Endurance (FE)

This test is conducted by repetitively folding the film at the exact location until it breaks. The FE scoring is derived from the film's ability to endure repeated folding until it reaches its breaking point (Senta-Loys et al., 2016).

Table 1. Level of factors and constraints of responses for CCD-RSM

Variable	Code	Level					Unit
		-α	-1	0	+1	+α	
Factor variables							
HPMC P.603/PVA ratio	A	0.2	0.46	1.1	1.74	2	-
EtOH or EA	B	0	0.79	1.5	2.20	2.5	% $^{w}/_{w}$
Response variables		Constraints					
Disintegrating time (DT)	Y_1	Minimize					Second
Folding endurance (FE)	Y_2	Target 300					-

Weight Variation and Thickness

Three films were taken and weighed using a digital scale. Subsequently, the mean weight and standard deviation were measured (Abouhussein et al., 2022). The thickness was determined by employing a digital caliper with a precision of 0.01 mm at five distinct locations. The data represent the mean value derived from five measurements (Nining et al., 2021).

Determination of pH

The experiment involved immersing a single film in 4 mL of distilled water, which was then placed in a glass container for 1 hour at room temperature. Subsequently, the solution pH was determined using a pH meter (Abouhussein et al., 2022).

Drug Content Uniformity

The film was dissolved with 50 mL of phosphate buffer, pH 6.8, which determined the LTG content in OF. The solution was diluted to 25 μg/mL and homogenized for 1 hour with a shaker incubator. Furthermore, the solution was analyzed with a UV Spectrophotometer at λmax 305.4 nm (Rajendraprasad et al., 2012; Salama et al., 2021).

Moisture Content

The film was weighed, and its initial weight (W_1) was recorded. It was then heated at 100 – 120 °C until it attained a stable weight. The final weight (W_2) of the desiccated sample was measured. The equation provided is utilized to compute the moisture content in the film, represented as follows (Karki et al., 2016).

$$\text{Moisture Content (\%)} = \frac{W_1 - W_2}{W_1} \times 100$$

Moisture Uptake

This test measures a film's ability to absorb moisture from its environment. The experiment includes weighing a single film (W_1) and putting it in a desiccator for seven days at ambient temperature. The dry film's moisture absorption is assessed by exposing it to 75% relative humidity and 200 mL of saturated KCl solution at ambient temperature (20-25 °C) for seven days. The film strip is periodically weighed (W_2), and the percentage of weight increase caused by water absorption is subsequently estimated by the equation below (El-Bary et al., 2019).

$$\text{Moisture Uptake (\%)} = \frac{W_2 - W_1}{W_1} \times 100$$

Solubility

LTG was dissolved in 6.8 phosphate buffer solvent and cosolvent in saturated conditions of 2 mL each. Saturation was conditioned by stirring with a magnetic stirrer for 1 hour at 150 rpm at 25 °C. Then, the sample was centrifuged, and the supernatant was pipetted 1 mL and diluted in a 10 mL flask (Abouhussein et al., 2022). Subsequently, the spectrophotometer UV was used to measure the absorbance of the sample at λ_{max} 305.4 nm.

In-Vitro Dissolution

The test used an orbital stirrer at 60 rpm and phosphate buffer pH 6.8 as a dissolving medium at 37 °C. The sample was introduced into 10 mL of dissolution medium. Medium samples were obtained at different time intervals (1, 3, 5, and 10 min) and quantified using spectrophotometry at λmax 305.4 nm. The absorbance measurement was then incorporated into a linear equation based on the LTG calibration curve in phosphate buffer pH 6.8. The test was conducted in triplicate, and the average result was calculated (Alhayali et al., 2019).

Tensile Strength and Elongation at Break

The films' tensile strength and % elongation were measured to evaluate their strength. The film's tensile strength was determined using an Ultimate Testing Machine. The film's tensile strength was determined by progressively applying tension until it reached the fracture point. The tensile strength was calculated by employing the cross-sectional area of the film, as outlined in the equation provided below. The mean value was derived from three replicated measurements.

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross-sectional area of film (cm}^2\text{)}}$$

The percentage elongation was determined by measuring the distance reached at the maximum length before the film reached its breaking point on the scale, using the calculation below. Percentage elongation is a useful indicator for assessing the elasticity and strength of a film (Haque & Sheela, 2015).

$$\text{Elongation (\%)} = \frac{\text{Increase in length}}{\text{Initial length}} \times 100$$

Statistical Analysis

The response data was analyzed and optimized using the CCD-RSM model by Design-Expert® statistical program software version 13 (Stat-Ease Inc., Minneapolis, MN). The significance of each phrase was determined using an F-test with a p-value less than 0.05 ($p<0.05$) or 0.01 ($p<0.01$). The percentage errors are determined by comparing the actual response data with the predictions in order to validate the suggested equation model (Nining et al., 2024).

RESULTS AND DISCUSSION

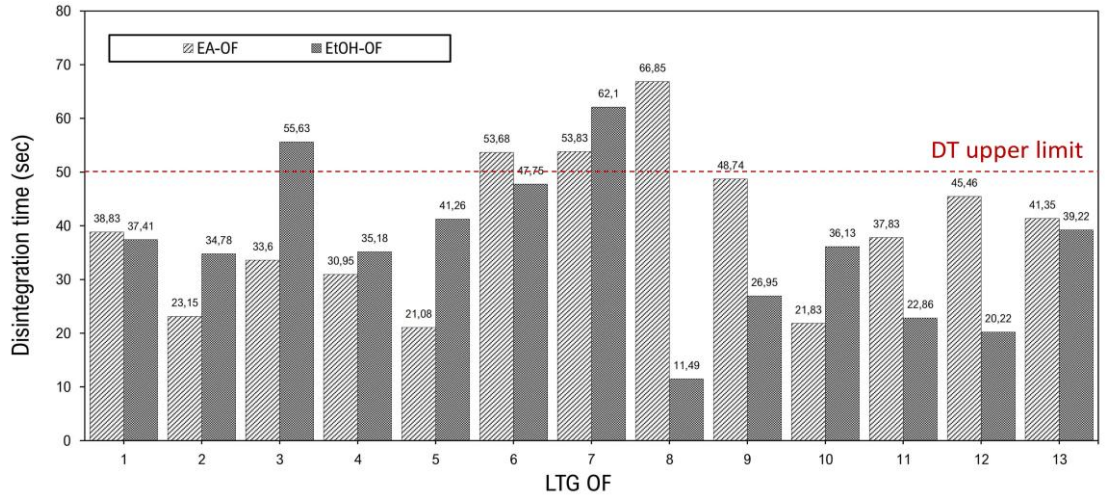
The data was collected from 26 formulations with varying HPMC P.603/PVA ratios, ranging from 0.2 to 2. The total polymer content in each OF was 6%, and the amount of EtOH or EA used ranged from 0.0 to 25.0% (from total casting solution weight). The films were found to be white, opaque, and spotless and were evaluated for their physical and mechanical properties, as shown in **Table 2**. The comparison of DT and FE of both OFs with EtOH and EA as cosolvents is shown in **Figure 1**. The average weights of OF-EtOH and OF-EA ranged from 68.35 to 121.08 mg and 56.14 to 154.17 mg, respectively. In the same formulation, the measurement results showed that OF-EtOH had a shorter film weight range than OF-EA. Overall, the amount of LTG (i.e., 25 mg) and total HPMC P.603/PVA polymer (i.e., 6%) significantly

affected the weight of OF with different ratios. The measurement of film thickness was directly correlated with the amount of drug in OF and the comfort of use (Irfan et al., 2015; Karki et al., 2016). The thickness of OF-EtOH and OF-EA ranged from 0.10 to 0.23 mm and 0.11 to 0.26 mm, respectively. Both showed characteristics with a thickness suitable for oral use without causing discomfort. The film thickness varied depending on the polymer type and concentration (Abouhussein et al., 2022).

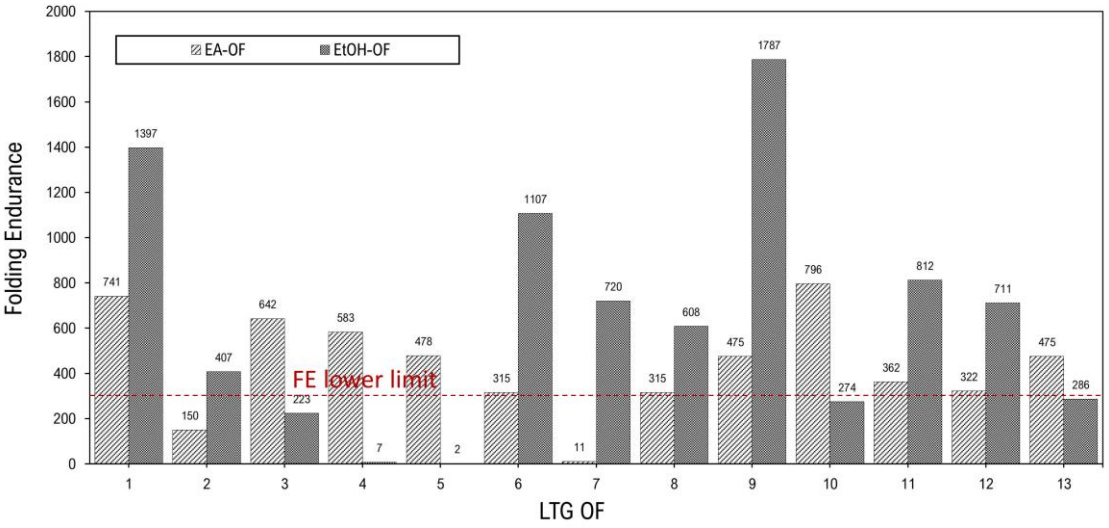
HPMC and PVA were chosen as the film-forming materials to obtain rapid disintegration, good mouthfeel, and good mechanical properties (Al-Nemrawi & Dave, 2014). Mechanical properties, such as FE, will facilitate handling and, on the other hand, must exhibit rapid disintegration. DT is an essential parameter for OF characterization, although there is no official method for its determination (Abouhussein et al., 2022). OF must rapidly disintegrate upon contact with saliva in the oral cavity. The quick breakdown of a substance is an important quality and safety standard to prevent choking and ensure patient compliance (Senta-Loys et al., 2016). The US FDA has set a threshold of 30 seconds for orodispersible tablets. This size can be a reference in ensuring rapid disintegration, including in OF, which represents the preparation's quality and safety (Abouhussein et al., 2022). According to another study, an OF with a size of 4 cm^2 that dissolved in less than 50 seconds under simulated saliva conditions at 37°C was classified as "fast disintegration" (Senta-Loys et al., 2016). **Table 2** and **Figure 1a** compare DT between OF-EtOH and OF-EA. The disintegration process lasted for more than 50 seconds and was seen in OF 3 (EtOH), 6 and 8 (EA), and 7 (both).

Table 2. Characteristics of OF-EtOH and OF-EA designed experiment by using CCD-RSM

Run	HPMC P.603/ PVA ratio	Cosolvent (%)	Weight variation (mg)	Thickness (mm)	DT (sec) Y_1	FE Y_2
OF-EtOH 1	1.10	12.50	91.74	0.13	36.13	274
OF-EtOH 2	1.10	12.50	115.37	0.18	55.63	223
OF-EtOH 3	1.10	12.50	69.2	0.10	39.22	286
OF-EtOH 4	1.74	3.66	94.15	0.19	26.95	1787
OF-EtOH 5	1.10	0.00	78.96	0.13	34.78	407
OF-EtOH 6	1.74	21.34	68.35	0.12	11.49	608
OF-EtOH 7	1.10	12.50	121.08	0.23	62.1	720
OF-EtOH 8	1.10	12.50	72.36	0.12	20.22	711
OF-EtOH 9	2.00	12.50	102.11	0.14	37.41	1397
OF-EtOH 10	0.46	21.34	96.19	0.17	47.75	1107
OF-EtOH 11	0.46	3.66	79.48	0.13	41.26	2
OF-EtOH 12	0.20	12.50	100.28	0.13	35.18	7
OF-EtOH 13	1.10	25.00	86.32	0.21	22.86	812
OF-EA 1	1.10	12.50	80.53	0.12	38.83	741
OF-EA 2	1.10	12.50	56.14	0.11	23.15	150
OF-EA 3	1.10	12.50	102.91	0.21	33.6	642
OF-EA 4	1.74	3.66	104.33	0.17	30.95	583
OF-EA 5	1.10	0.00	102.59	0.17	21.08	478
OF-EA 6	1.74	21.34	91.19	0.27	53.68	315
OF-EA 7	1.10	12.50	97.27	0.16	53.83	11
OF-EA 8	1.10	12.50	118.88	0.23	66.85	315
OF-EA 9	2.00	12.50	154.17	0.19	48.74	475
OF-EA 10	0.46	21.34	93.56	0.17	21.83	796
OF-EA 11	0.46	3.66	100.24	0.17	37.83	362
OF-EA 12	0.20	12.50	109.51	0.26	45.46	322
OF-EA 13	1.10	25.00	90.3	0.15	41.35	475



a. DT of OF-EtOH and OF-EA



b. FE of OF-EtOH and OF-EA

Figure 1. Comparison of DT (**a**) and FE (**b**) of OF-EtOH and OF-EA in the designed experiment using CCD-RSM

FE could rapidly determine the mechanical properties of the film. High FE describes high mechanical strength (Irfan et al., 2015). Furthermore, FE is a physical indicator of the film's flexibility, an important parameter considering that the film can be adjusted without damage (Karki et al., 2016; Mazumder et al., 2017). The correlation between mechanical strength and FE enables FE to estimate the mechanical strength of OF from both cosolvents. **Table 2** and **Figure 1b** show the comparison of FE between OF-EtOH and OF-EA. Films with an FE greater than 300 are classified as having excellent flexibility (Karki et al., 2016). OFs that have FE less than 300 are shown in OF 2 and 7 (EA), 3, 4, 5, 10, and 13 (EtOH).

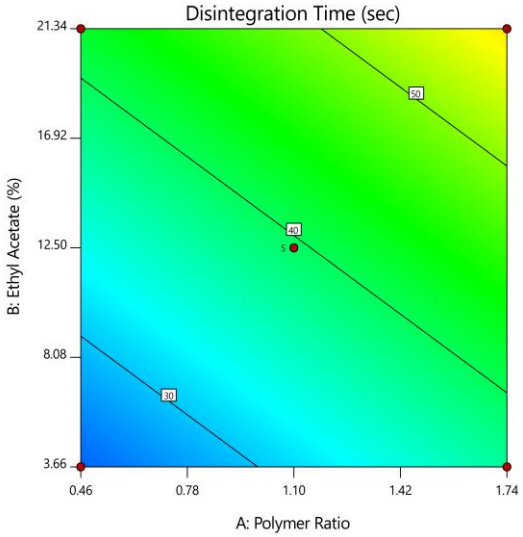
CCD-RSM optimized LTG OF by determining the optimal concentration of HPMC P.603/PVA ratio (A) and cosolvent (B) as critical parameters affecting the response. The optimization process with an effective two-level design can describe the possible curvature of the response and a predictable factorial axial design (Ye et al., 2021). Prediction of the influence of significant factors on the response is significant in process optimization (Nining et al., 2023). Based on the literature, two responses, namely DT and FE, were selected because they provided sufficient information on OF quality at the beginning of the study.

Prediction and model determination are obtained from statistical data analysis. **Table 3** presents the statistical analysis of the linear model for DT and 2FI for FE. This table shows the significant factors with p-values less than 0.01 and 0.05, corresponding to the 99 and 95% confidence levels, respectively. In addition, a considerable F value and lack of fit (lack of fit not significant) will minimize errors in the model (Abdallah et al., 2021; Nining et al., 2023). Both responses show distinct models determined by the highest R-squared value and the lowest residual predictive sum of squares. The chosen model exhibits a lack of fit that is not statistically significant. The residual test plot on the regression model validates model validity, which is further supported by supplementary information for both replies.

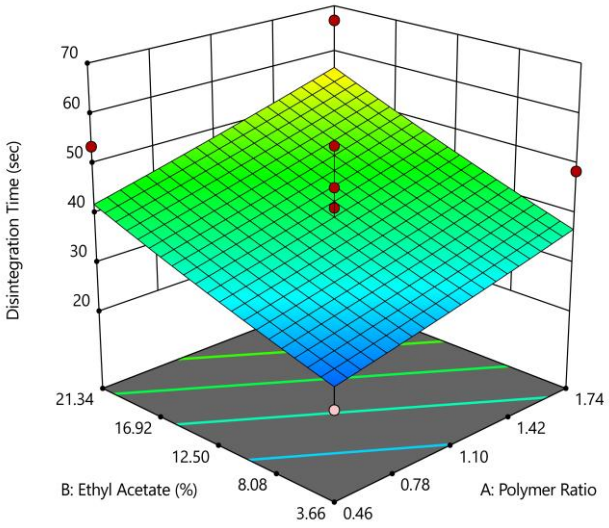
Table 3. Statistical analysis of DT (Y_1) and FE (Y_2) LTG-OF on CCD-RSM.

Factors		OF-EA		OF-EtOH	
		DT (Y_1)	FE (Y_2)	DT (Y_1)	FE (Y_2)
A	Coefficient	0.5231	No model	No model	406.47
	p-value	0.1377			0.0037**
B	Coefficient	0.7280			406.47
	p-value	0.0485*			0.5656
AB	Coefficient				-571.00
	p-value				0.0038**
Intercept	Coefficient	6.22	19.88	36.23	641.62
Sum of squares		6.43	0.00	0.00	2,657E+06
df		2	0	0	3
Mean square		3.21	-	-	8,857E+05
F-value		3.82	-	-	10.13
p-value		0.0584		-	0.0030**
R-Squared		0.4334	0	0	0.7715

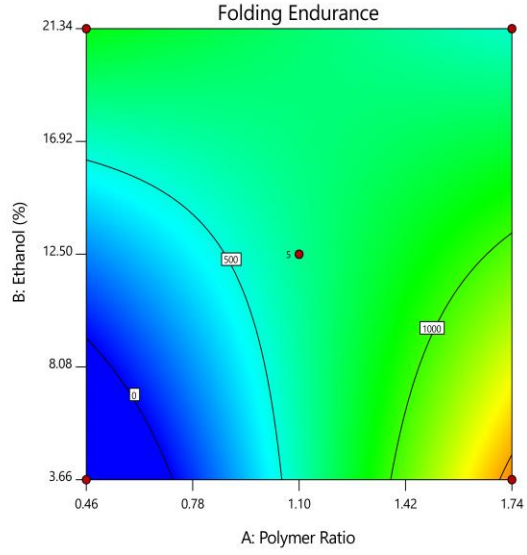
A: HPMC P.603/PVA ratio; B: cosolvent concentration; * p-value < 0.05; ** p-value < 0.01



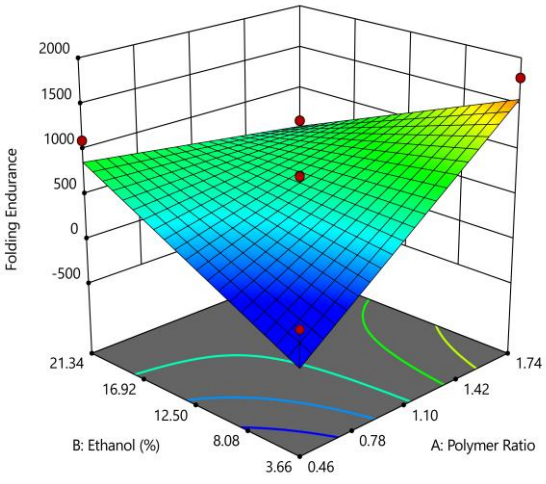
2a. Contour plot of DT OF-EA by A and B



2b. 3D graph of DT OF-EA by A and B



2c. Contour plot of FE OF-EtOH by A and B



2d. 3D graph of FE OF-EtOH by A and B

Figure 2. Contour plots (a, c) and response surface (3D graphs) (b, d) showing the effects of HPMC/PVA ratio and cosolvent concentration on DT (a, b) and FE (c,d) of LTG-OF

According to **Table 3**, the DT response exhibits a linear model that is not statistically significant, as indicated by an F-value of 3.82 (p-value 0.0584 > 0.05). The proposed equation for the linear model was as follows:

$$Y_1 = 6.22 + 0.5231A + 0.7280B$$

The equation demonstrates that the variable DT OF-EA is significantly influenced by the EA quantity (B), with both factors having positive coefficients. That indicates a synergistic effect on the response. A p-value of less than 0.05 supports the significance of this relationship. Hence, the contour plot and 3D response surface (**Figures 2a** and **2b**) may depict the collective impact of components A and B, demonstrating that Y1 exhibits a linear variation with the quantity of both factors. **Figure 2b** demonstrates that component B's gradient is greater than factor A's, as indicated by the comparison representation of the response surface. From this reasoning, the value of DT can be modified by choosing a suitable factor level.

The statistical analysis of the FE response in **Table 3** indicates a highly significant 2FI model, with an F-value of 10.13 (p-value 0.0030 <0.01). The proposed equation for the 2FI model ~~is~~ as follows:

$$Y_2 = 641.62 + 406.47A + 406.47B – 571.00AB$$

The equation demonstrated that the FE OF-EtOH was statistically significant (p-value < 0.01) and was influenced by both the HPMC P.603/PVA ratio (A) and the HPMC P.603/PVA ratio-cosolvent amount (AB). Factors A and B have positive coefficients, which means there is a synergistic effect on the response, while factor AB is the opposite. Negative coefficients indicate antagonistic effects, which result in an inverse relationship between factors and response (Ye et al., 2021). Hence, the contour plot and 3D response surface (**Figure 2c** and **2d**) can depict the collective impact of factors A, B, and AB, demonstrating that Y_2 varies by changes in these parameters. The response surface plot demonstrates that factor AB exhibits a more pronounced reduction in gradient than the other two factors, as depicted in **Figure 2d**. The conclusion asserts that selecting the suitable factor level can modify the functional equation.

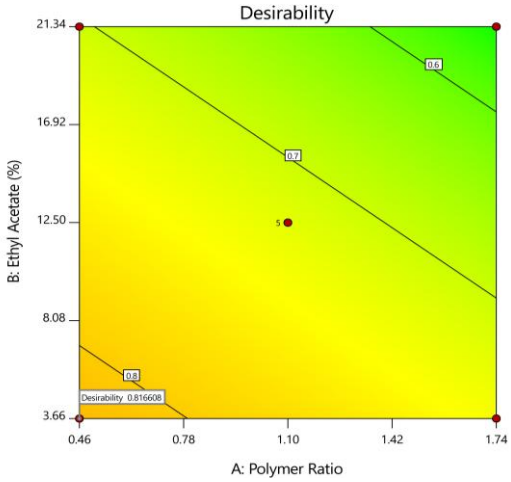
OF formula optimization was performed using Design-Expert software version 13 with minimum DT constraints and an FE target of 300 folds (**Table 1**). The variable composition for the optimized OF-EA was 0.46 HPMC P.603/PVA ratio and 3.66% EA with a desirability of 0.817. The optimal OF-EtOH composition was 0.87 HPMC P.603/PVA ratio and 6.19% EtOH with a desirability of 0.843. The optimal formulation produced from the optimization stage of the program has the maximum desirability, reaching a value of 1 (Badwaik et al., 2012; Nining et al., 2024).

Figures 3a and **3c** depict the outcomes of the optimization process through 2D contour plots. A contour visual represents a two-dimensional image created using a predictive model of DT and FE response values. The contour graph displays the highest level of desirability at points 0.817 and 0.843, which are the closest values to 1 compared to other points. **Figures 3b** and **3d** depict the 3D surface forecast, where lower regions represent lower popularity, while higher regions suggest more desire, nearing a value of 1. The software predicts the response at this phase, as illustrated in **Table 4**. Three validation runs were performed to confirm the optimization (Amalia et al., 2023; Mohtashamian et al., 2018). The equation model and response prediction were validated by observing the actual response of the optimal OF, which showed acceptable variations from the predicted values (**Table 4**). The two optimal OFs were further evaluated in terms of pH, drug content, moisture content, moisture uptake, tensile strength, elongation at break, and in-vitro dissolution.

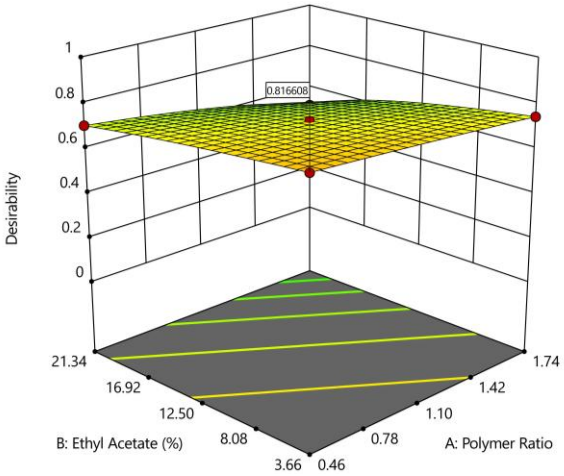
Table 5 shows the results of the optimal OF evaluation of both cosolvents. OF-EtOH pH is slightly lower than OF-EA pH. However, both produce a film pH suitable for the oral environment, as pH ranges from 5.8 to 7.4 (Abouhussein et al., 2022). The oral cavity has a protective buffering mechanism against irritation caused by pH changes. Saliva, consisting of bicarbonate buffers and other buffer systems (mucin, protein, and phosphate), acts as a buffer system that also protects against dental caries. However, OF is recommended to be in that range to avoid irritation to the oral mucosa (Janigova et al., 2022).

OF should show good dosage uniformity for weight variation and content uniformity (Ouda et al., 2020). According to USP 27, drug content should range from 85-115% with a standard deviation less than or equal to 6% (Irfan et al., 2015). Drug content is calculated based on a predetermined calibration curve, namely $Y = 0.0201358X + 0.135855$, with an r^2 of 0.99667. **Tables 4** and **5** summarize the results of weight variation and drug content uniformity by showing the expected characteristics.

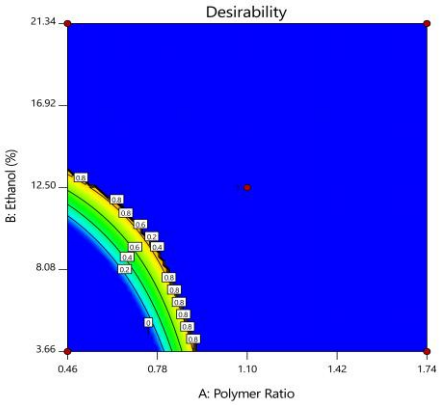
Moisture content in OF is very important because it affects the stability of the film related to microbial contamination, degradation, and unwanted reactions of the drug and the determination of storage conditions (Janigova et al., 2022; Turkovi et al., 2022). Furthermore, other factors affect the fragility, adhesive qualities, and mechanical strength of films (Karki et al., 2016). As seen in **Table 5**, the moisture content of both LTG-OFs is in the range of > 10% which is quite high. The literature states that moisture content generally does not exceed 15%, but Takeuchi et al. (2020) reported a moisture content higher than 30% for HPMC-based OF with a large glycerol load (Turkovi et al., 2022). Increasing moisture content can cause film stiffness, negatively impacting product handling. Several factors that play a role in high water content are polymers, drug hygroscopicity, manufacturing techniques, and the solvent system used (Karki et al., 2016). Moisture uptake studies



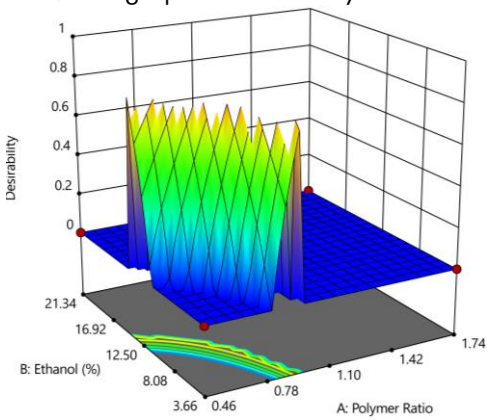
a. Contour plot of desirability OF-EA



b. 3D graph of desirability OF-EA



c. Contour plot of desirability OF-EtOH



d. 3D graph of desirability OF-EtOH

Figure 3. Contour plots (**a**, **c**) and response surface (3D graphs) (**b**, **d**) showing the desirability of LTG-OF

Table 4. Predicted and actual responses of optimal OF

Responses	OF-EtOH			OF-EA		
	Prediction	Actual[a]	Error (%)[b]	Prediction	Actual[a]	Error (%)[b]
Weight variation (mg)	90.43	92.05±4.81	1.76	100.22	93.72±1.50	32.76
Thickness (mm)	0.15	0.15±0.01	0	0.16	0.16±0,00	0
DT (sec)	36.23	36.11±1.48	0.33	25.74	26.73±3.32	3.84
FE	300	310.33±5.03	3.33	454.3	470.6±37.44	8.73

a Data presented is the mean ± standart deviation (n=3)
b Erorr (%) = [(Actual value – Predicted value)/Predicted value]*100%

Table 5. Optimal LTG OF characterization

Parameters	OF-EtOH	OF-EA
pH	6.56 ± 0.06	6.61 ± 0.14
Drug content uniformity (%)	99.54 ± 0.91	99.48 ± 0.94
Moisture content (%)	22.48 ± 1.38	18.01 ± 7.82
Moisture uptake (%)	5.15 ± 2.44	29.24 ± 19.50
Tensile strength (Mpa)	4.73 ± 1.24	2.35 ± 0.12
Elongation break (%)	41.5 ± 16.14	17.37 ± 3.25
In-vitro dissolution[a]		
D_1 (%)	24.98 ± 9.64	23.53 ± 7.14
D_3 (%)	53.33 ± 4.08	41.25 ± 11.98
D_5 (%)	80.97 ± 8.12	70.49 ± 11.90
D_{10} (%)	108.99 ± 12.49	98.17 ± 14.75

a The numbers 1, 3, 5, and 10 indicate the sampling time during dissolution in minutes

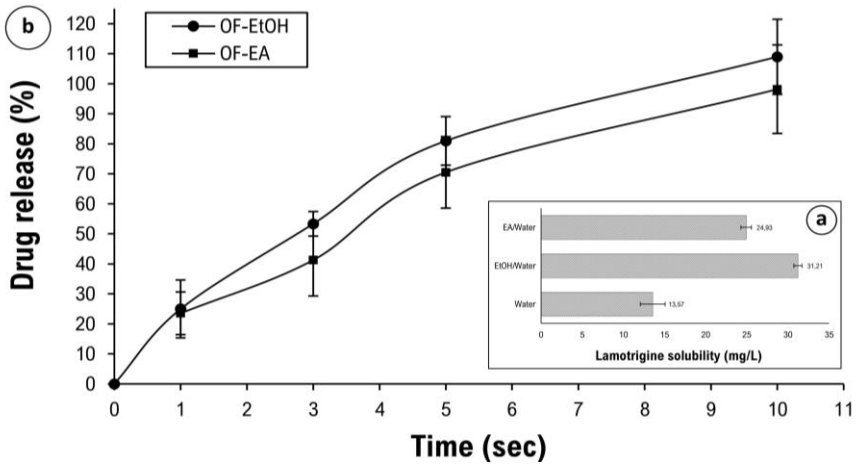


Figure 4. LTG solubility in water and cosolvent (**a**) LTG-OF dissolution profile graph (**b**)

determine the film's ability to absorb water from its environment, which is reflected as the hygroscopicity of the film, and to regulate the most appropriate packaging and storage conditions (El-Bary et al., 2019). **Table 5** shows that the moisture uptake of OF-EA is much greater than that of OF-EtOH. High moisture uptake, ranging from 13-18%, was also found in LTG-OF with pre-gelatinized starch and sorbitol as film formers and plasticizers (Mazumder et al., 2017).

The OF material should possess adequate tensile strength to aid in its removal from the container, rolling after casting, and peeling from the release liner. However, it should not be excessively flexible as this might lead to increased elongation during cutting and packaging, which in turn can cause variations and inconsistencies in the drug content (Karki et al., 2016). Furthermore, apart from the concept of FE, the film's mechanical properties can be precisely determined by considering its tensile strength and elongation at break (Preis et al., 2014). OF is expected to be flexible, stable, and easy to handle so that the targeted mechanical properties include high tensile strength and low elongation at break (Turkovi et al., 2022). Based on **Table 5**, the tensile strength of both OFs is 2.35 MPa to 4.73 MPa and the elongation at break is in the range of 17.37% to 41.5%. Similar results were found in another study using a combination of HPMC/HPC and HPMC/Carbomer 974P with tensile strength of 2.80 MPa to 4.44 MPa and elongation at break of 13.20% to 29.17%. These results include moderate tensile strength with high elongation at break (Visser et al., 2015). It is estimated that film-forming polymers, plasticizers, and drug substances play the main role in mechanical properties. Depending on its grade, HPMC is a polymer with good physical integrity as a film former. HPMC P.603, which is included in the low viscosity polymer, allows the formation of thin, brittle, and unpeelable films. Adding PVA improves film-forming properties and mechanical strength (Al-Nemrawi & Dave, 2014; Borges et al., 2016).

The solubility of LTG in both cosolvents was assessed and presented in **Figure 4a**. LTG showed saturated solubility in water, EtOH/water, and EA/water of 13.57±1.51 mg/L, 31.21±0.49 mg/L, and 24.93±0.64 mg/L, respectively. The solubility of LTG was enhanced by 2.3-fold and 1.8-fold when 4.91% EtOH and 3.66% EA were added, respectively, compared to its solubility in water. This outcome was achievable due to the variation in the quantity of cosolvent applied. **Figure 4b** demonstrates that the proportion of dissolved LTG was higher in OF-EtOH than in OF-EA. Therefore, its rate of dissolution also changed. The variation in the preparation process of the OF may be attributed to the utilization of diverse cosolvents. The higher concentration of dissolved drug molecules in OF-EtOH enables them to distribute more readily in the water-soluble polymer matrix. That leads to faster release and dissolution in the dissolution media. The use of cosolvents in drug dissolution can induce a transformation in the drug's crystal structure, resulting in a more amorphous form (Panraksa et al., 2020). At the beginning, during the first minute, the release of LTG from both OFs was equal. However, as time progressed, the drug release in OF-EtOH was higher compared to OF-EA, specifically at minutes 3, 5, and 10. The dissolving profile demonstrates that the solubility of pharmaceuticals with low water solubility, such as LTG, in the form of OF, can be enhanced by choosing a suitable cosolvent. In general, the solubility of a substance is determined by the formation of intermolecular hydrogen bonds between the molecules of the solvent and the molecules of the solute. The crystalline form has greater stability than the amorphous form and possesses lower molecular energy, characterized by stronger intermolecular interactions that necessitate a higher energy input for their disruption (Hassan et al., 2019). The study discovered comparable outcomes when examining the formulation of phenytoin in OF using PEG and EtOH cosolvents. The drugs exhibited an accelerated release when the formulation incorporated cosolvents as compared to the formulation without cosolvents due to a transformation in the crystal structure to amorphous

form (Panraksa et al., 2020). Furthermore, the release of the drug from the OF matrix can also be influenced by the specific polymer used and its quantity. OF-EtOH has a higher HPMC P.603 polymer concentration than OF-EA, with HPMC P.603/PVA ratios of 0.87 and 0.46, respectively.

CONCLUSIONS

The optimal film formulations of OF-EtOH and OF-EA were achieved with desirability values of 0.843 and 0.817, respectively. The variable composition for OF-EtOH was 0.87 HPMC P.603/PVA ratio and 6.19% EtOH, while for OF-EA it was 0.46 HPMC P.603/PVA ratio and 3.66% EA. Based on the OF-EtOH FE, the HPMC P.603/PVA ratio showed a greater effect compared to the amount of EtOH ($p<0.05$). In contrast, ANOVA demonstrated that the amount of EA had a greater impact compared to the HPMC P.603/PVA ratio ($p<0.05$). The EtOH cosolvent was preferable to EA based on LTG solubility and OF dissolution profile. The LTG OF exhibited favorable physicochemical properties and showed promise as a rapid-dissolving formulation. The characteristics of the optimal formulas were as follows: OF-EtOH — weight variation 92.05±4.81 mg, thickness 0.15±0.01 mm, DT 36.11±1.48 sec, and FE 310.33±5.03; OF-EA — weight variation 93.72±1.50 mg, thickness 0.16±0.00 mm, DT 26.73±3.32 sec, and FE 470.6±37.44. These results indicate that both cosolvents can be used to achieve rapid disintegration and high mechanical strength, with OF-EA showing the fastest DT and highest FE, while OF-EtOH offers better solubility performance.

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REFERENCES

Abdallah, M. H., Elsewedy, H. S., Abulila, A. S., Almansour, K., Unissa, R., Elghamry, H. A., & Soliman, M. S. (2021). Quality by design for optimizing a novel liposomal jojoba oil-based emulgel to ameliorate the anti-inflammatory effect of brucine. *Gels*, *7*(219), 1–18. https://doi.org/10.3390/gels7040219

Abouhussein, D., El Nabarawi, M. A., Shalaby, S. H., & El-Bary, A. A. (2022). Development and optimization of cosolvent-based blended sertraline orodispersible films - a step to personalized medicine. *Brazillian Journal of Pharmaceutical Sciences*, *58*, 1–16. https://doi.org/10.1590/s2175-97902022e20584

Al-Nemrawi, N. K., & Dave, R. H. (2014). Formulation and characterization of acetaminophen nanoparticles in orally disintegrating films. *Drug Delivery*, 1–10. https://doi.org/10.3109/10717544.2014.936987

Alhayali, A., Rao, P., & Velaga, S. (2019). Silodosin oral films: development, physico-mechanical properties and in vitro dissolution studies in simulated saliva. *Journal of Drug Delivery Science and Technology*, *53*(December 2018), 101122. https://doi.org/10.1016/j.jddst.2019.06.019

Amalia, A., Nining, N., & Dandi, M. (2023). Characterization of modified sorghum starch and its use as a film-forming polymer in orally dissolving film formulations with glycerol as a plasticizer. *Journal of Research in Pharmacy*, *27*(05), 1855–1865. https://doi.org/10.29228/jrp.469

Badwaik, L. S., Prasad, K., & Deka, S. C. (2012). Optimization of extraction conditions by response surface methodology for preparing partially defatted peanut. *International Food Research Journal*, *19*(1), 341–346.

Bala, R., Khanna, S., Pawar, P., & Arora, S. (2013). Orally dissolving strips: a new approach to oral drug delivery system. *International Journal of Pharmaceutical Investigation*, *3*(2), 67. https://doi.org/10.4103/2230-973x.114897

Beattie, K., Phadke, G., & Novakovic, J. (2012). Lamotrigine. In *Profiles of Drug Substances, Excipients, and Related Methodology* (Vol. 37, pp. 245–285). Elsevier Inc. https://doi.org/10.1016/B978-0-12-397220-0.00006-4

Beg, S., Rahman, M., & Kohli, K. (2019). Quality-by-design approach as a systematic tool for the development of nanopharmaceutical products. *Drug Discovery Today*, *24*(3), 717–725. https://doi.org/10.1016/j.drudis.2018.12.002

Betchel, N. T., Fariba, K. A., & Saadabadi, A. (2023). Lamotrigine. In *NCBI Bookshelf* (pp. 1–5). StatPearls Publishing.

Borges, A. F., Silva, C., Coelho, J. F. J., & Simões, S. (2016). Outlining critical quality attributes (CQAs) as guidance for the development of orodispersible films. *Pharmaceutical Development and Technology*, *July*, 1–9. https://doi.org/10.1080/10837450.2016.1199567

El-Bary, A. A., Al Sharabi, I., & Haza'a, B. S. (2019). Effect of casting solvent, film-forming agent and solubilizer on orodispersible films of a polymorphic poorly soluble drug: an in vitro/in silico study. *Drug Development and Industrial Pharmacy*, *45*(11),1751–1769. https://doi.org/10.1080/03639045.2019.1656733

Haque, S. E., & Sheela, A. (2015). Development of polymer-bound fast-dissolving metformin buccal film with disintegrants. *International Journal of Nanomedicine*, *10*(Suppl I: Challenges in biomaterials research), 199–205. https://doi.org/10.2147%2FIJN.S80052

Hassan, S., Adam, F., Bakar, M. A., & Mudalip, S. A. (2019). Evaluation of solvents' effect on solubility, intermolecular interaction energies and habit of ascorbic acid crystals. *Journal of Saudi Chemical Society*, *23*, 239–248. https://doi.org/10.1016/j.jscs.2018.07.002

ICH Expert Working Group. (2021). Impurities: guideline for residual solvents Q3C (R8). In *ICH Harmonised Guideline* (Issue April).

Irfan, M., Rabel, S., Bukhtar, Q., Qadir, M. I., Jabeen, F., & Khan, A. (2015). Orally disintegrating films: a modern expansion in drug delivery system. *Saudi Pharmaceutical Journal*. https://doi.org/10.1016/j.jsps.2015.02.024

Janigova, N., Elbi, J., Pavlokova, S., & Gajdziok, J. (2022). Effects of various drying times on the properties of 3D printed orodispersible films. *Pharmaceutics*, *250*(14), 1–12. https://doi.org/10.3390/pharmaceutics14020250

Jouyban-Gharamaleki, V., Soleymani, J., Jouyban-Gharamaleki, K., Suleymanov, T. A., & Jouyban, A. (2017). Solubilization of celecoxib, lamotrigine and phenytoin using ethanol and a nonionic surfactant. *Journal of Molecular Liquids*, *243*, 715–719. https://doi.org/10.1016/j.molliq.2017.08.080

Karki, S., Kim, H., Na, S.-J., Shin, D., Jo, K., & Lee, J. (2016). Thin films as an emerging platform for drug delivery. *Asian Journal of Pharmaceutical Sciences*, *11*(5), 559–574. https://doi.org/10.1016/j.ajps.2016.05.004

Mazumder, S., Pavurala, N., Manda, P., Xu, X., Cruz, C. N., & Krishnaiah, Y. S. R. (2017). Quality by design approach for studying the impact of formulation and process variables on product quality of oral disintegrating films. *International Journal of Pharmaceutics*, *527*(1–2), 151–160. https://doi.org/10.1016/j.ijpharm.2017.05.048

Mohtashamian, S., Boddohi, S., & Hosseinkhani, S. (2018). Preparation and optimization of self-assembled chondroitin sulfate-nisin nanogel based on quality by design concept. *International Journal of Biological Macromolecules*, *107*, 2730–2739. https://doi.org/10.1016/j.ijbiomac.2017.10.156

Nining, N., Amalia, A., & Rahmatullah, R. (2024). Optimization of oral thin film cetirizine HCl by response surface methodology: disintegration and mechanical properties. *Indonesian Journal of Pharmaceutical Science and Technology*, *11*(2), 163–173. https://doi.org/10.24198/ijpst.v11i2.44098

Nining, N., Amalia, A., & Zahrok, F. (2023). Response surface methodology for optimization of turmeric essential oil-loaded nanoemulgel. *Journal in Research in Pharmacy*, *27*(4), 1499–1512. https://doi.org/10.29228/jrp.436

Nining, N., Elfiyani, R., & Wulandari, E. (2021). Comparison eugenol and oleic acid as a plasticizer on characteristic of dextromethorphan hydrobromide film by solvent casting method. *Pharmaceutical Sciences Asia*, *48*(2), 139–146. https://doi.org/10.29090/psa.2021.02.20.023

Ouda, G. I., Dahmash, E. Z., Alyami, H., & Iyire, A. (2020). A novel technique to improve drug loading capacity of fast/extended release orally dissolving films with potential for paediatric and geriatric drug delivery. *AAPS PharmSciTech*, *21*(4), 1–14. https://doi.org/10.1208/s12249-020-01665-5

Panraksa, P., Tipduangta, P., Jantanasakulwong, K., & Jantrawut, P. (2020). Formulation of orally disintegrating films as an amorphous solid solution of a poorly water-soluble drug. *Membranes*, *10*(376), 1–17.

Preis, M., Knop, K., & Breitkreutz, J. (2014). Mechanical strength test for orodispersible and buccal films. *International Journal of Pharmaceutics*, *461*(1–2), 22–29. https://doi.org/10.1016/j.ijpharm.2013.11.033

Rajendraprasad, N., Basavaiah, K., Vinay, K., & Ramesh, P. (2012). Simple and sensitive spectrophotmetric determination of lamotrigine in pure form and in dosage forms pharmaceutica analytica acta. *Pharmaceutica Analytica Acta*, *3*(9), 1–5. https://doi.org/10.4172/2153-2435. 1000188

Rajvi, Y., Bhadoriya, A., & Patani, P. (2022). Polymers use in mouth dissolving formulation: a review article. *Journal of Pharmaceutical Negative Results*, *13*(Special issue 5), 2579–2586. https://doi.org/10.47750/pnr.2022.13.S05.398

Rodríguez-Pombo, L., Carou-Senra, P., Rodríguez-Martínez, E., Januskaite, P., Rial, C., Paulo, F., Alvarez-Lorenzo, C., Basit, A. W., & Goyanes, A. (2024). Customizable orodispersible films: inkjet printing and data matrix encoding for personalized hydrocortisone dosing. *International Journal of Pharmaceutics*, *655*(March), 29–39. https://doi.org/10.1016/j.ijpharm.2024.124005

Salama, A. H., Basha, M., & Salama, A. A. (2021). Micellar buccal film for safe and effective control of seizures: preparation, in vitro characterization, ex vivo permeation studies and in vivo assessment. *European Journal of Pharmaceutical Sciences*, *166*(August), 105978. https://doi.org/10.1016/j.ejps.2021.105978

Senta-Loys, Z., Bourgeois, S., Pailler-Mattei, C., Agusti, G., Briancon, S., & Fessi, H. (2016).

Formulation of orodispersible films for paediatric therapy: investigation of feasibility and stability for tetrabenazine as drug model. *Journal of Pharmacy and Pharmacology*, *69*(5), 582–592. https://doi.org/10.1111/jphp.12627

Singh, J., Garg, R., & Gupta, G. Das. (2015). Enhancement of solubility of lamotrigine by solid dispersion and development of orally disintegrating tablets using 32 full factorial design. *Journal of Pharmaceutics*, *2015*, 1–8. https://doi.org/10.1155/2015/828453

Turkovi, E., Vasiljevic, I., Draskovic, M., & Parojcic, J. (2022). Orodispersible films — pharmaceutical development for improved performance: a review. *Journal of Drug Delivery Science and Technology*, *75*(June), 103708. https://doi.org/10.1016/j.jddst.2022.103708

Visser, J. C., Woerdenbag, H. J., Crediet, S., Gerrits, E., Lesschen, M. A., Hinrichs, W. L. J., Breitkreutz, J., & Frijlink, H. W. (2015). Orodispersible films in individualized pharmacotherapy: the development of a formulation for pharmacy preparations. *International Journal of Pharmaceutics*, *478*(1), 155–163. https://doi.org/10.1016/j.ijpharm.2014.11.013

Ye, Q., Li, J., Li, T., Ruan, J., Wang, H., Wang, F., & Zhang, X. (2021). Development and evaluation of puerarin-loaded controlled release nanostructured lipid carries by central composite design. *Drug Development and Industrial Pharmacy*, *47*(1), 113–125. https://doi.org/10.1080/03639045.2020.1862170

Youse, J., & Haghtalab, A. (2016). Measurement and thermodynamic modeling of the solubility of lamotrigine, deferiprone, cefixime trihydrate, and cephalexin monohydrate in different pure solvents from 283.1 to 323.1 K. *Journal of Chemical & Engineering Data*, *61*(6), 2170–2178. https://doi.org/10.1021/acs.jced.6b00163