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Development and Optimization of β-Cyclodextrin-Based Domperidone Mouth-Dissolving Films using a Quality by Design Framework

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A B S T R A C T

The present study was designed to formulate and optimize Domperidone mouth-dissolving films using β-cyclodextrin solid dispersion and a Quality by Design approach. Domperidone is a poorly water-soluble antiemetic drug; therefore, β-cyclodextrin was selected as a complexing agent to improve its apparent solubility and support rapid drug release from the oral film matrix. Domperidone is an antiemetic drug that is poorly water-soluble. Consequently, β-cyclodextrin was chosen as a complexing agent to enhance its apparent solubility and facilitate the rapid release of the drug from the oral film matrix. Hydroxypropyl methylcellulose E15 served as the film-forming polymer, polyethylene glycol 400 functioned as the plasticizer, Tween-80 acted as the surfactant/wetting agent, and citric acid was utilized as the saliva-stimulating ingredient. Factorial designs 3^2 were utilized, employing HPMC E15 concentration and PEG-400 concentration as independent formulation variables. The prepared films were evaluated for morphological appearance, film thickness, folding endurance, surface pH, disintegration time, drug content and in vitro drug release. Domperidone showed maximum absorbance at 286 nm in phosphate buffer pH 6.8, which was used for analytical estimation. The prepared films were soft, semi-transparent, and non-sticky that showed acceptable handling properties. Disintegration time ranged from 31 to 68 seconds, folding endurance from 162 to 376 folds, drug content from 96.8% to 99.1%, film thickness from 0.114 to 0.189 mm and drug release at 15 minutes from 79.5% to 98.2%. All formulations released more than 75% Domperidone within 15 minutes. Formulation F6, containing 750 mg HPMC E15 and 20% PEG-400 was selected as the optimized formulation because it showed rapid disintegration, maximum drug release, acceptable folding endurance, uniform drug content and suitable film thickness. The research demonstrates that β-cyclodextrin solid dispersion, in conjunction with factorial design optimization, is effective for the formulation of Domperidone mouth-dissolving films.

I. Introduction

Oral drug delivery remains one of the most preferred routes of administration because of convenience, patient acceptance, and ease of dosing. However, conventional tablets and capsules may be unsuitable for pediatric, geriatric, nauseated, bedridden, dysphagic, or non-cooperative patients. Mouth-dissolving films provide an alternative oral dosage form because they are thin polymeric films designed to disintegrate rapidly in the oral cavity, usually without the need for water [1-7].

Domperidone is an antiemetic and prokinetic drug used in the management of nausea and vomiting. However, its limited aqueous solubility may affect dissolution performance in rapidly disintegrating oral dosage forms. Previous work has shown that Domperidone mouth-dissolving films can be prepared using Domperidone–β-cyclodextrin solid dispersion, HPMC E15 as a film-forming polymer, and PEG-400 as a plasticizer [1]. Domperidone-loaded fast-dissolving buccal films have

also been investigated for improving patient acceptability and drug delivery performance [2].

Cyclodextrins are cyclic oligosaccharides capable of forming inclusion complexes with poorly water-soluble drugs. β-Cyclodextrin and its derivatives have been widely investigated as pharmaceutical solubilizers because they can improve apparent aqueous solubility, dissolution rate, and formulation performance of poorly soluble drugs [3–6]. Therefore, incorporation of Domperidone as a β-cyclodextrin solid dispersion is a rational formulation strategy for mouth-dissolving films [12-15].

Quality by Design is a systematic pharmaceutical development approach based on predefined product objectives, understanding of material and process variables, and control of critical quality attributes. ICH Q8(R2) emphasizes the role of pharmaceutical development in building product quality through scientific understanding rather than relying only on end-product testing [28]. The present study used a QbD-based factorial design to evaluate the effect of HPMC E15 and PEG-400 on important quality attributes of Domperidone mouth-dissolving films.

The objective of the present work was to formulate Domperidone mouth-dissolving films using β-cyclodextrin solid dispersion and optimize the formulation using a 3^2 full factorial design. The prepared films were evaluated for physical appearance, film thickness, folding endurance, in vitro disintegration time, drug content, and in vitro drug release[7-10].

MATERIALS AND METHODS

Materials

Domperidone was used as the active pharmaceutical ingredient. β-Cyclodextrin was used as the solubility-enhancing complexing agent. Hydroxypropyl methylcellulose E15 was selected as the film-forming polymer. Polyethylene glycol 400 was used as the plasticizer. Citric acid was incorporated as a saliva-stimulating agent, while Tween-80 was used as a surfactant and wetting agent. Methanol and distilled water were used as solvents. Phosphate buffer pH 6.8 was used as the medium for in vitro disintegration and dissolution studies Domperidone mouth-dissolving films were prepared by the solvent casting method.

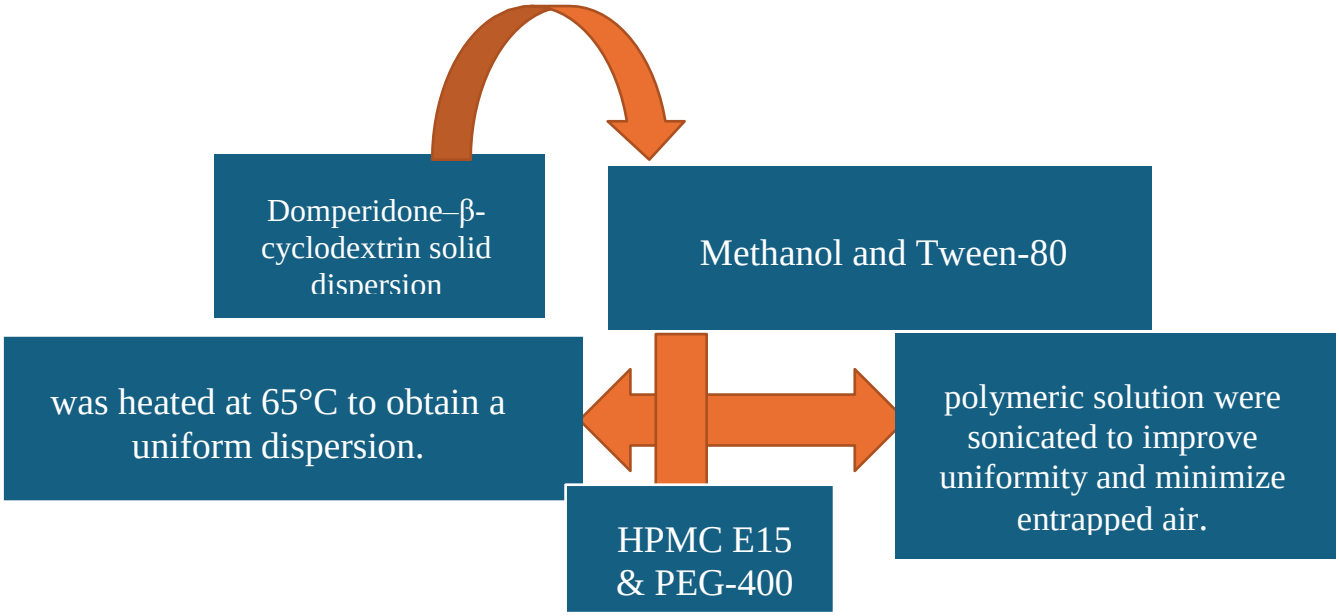


Fig: 1 Method of preparation

The drug dispersion was then mixed thoroughly with the polymeric solution. The final casting solution was poured into a 10 cm diameter Petri dish and dried in a hot air oven at 60°C for 5 hours. After drying, the films were carefully removed from the Petri dish and cut into 2 cm × 2 cm pieces. A 3^2 full factorial design was used to optimize the formulation. Two independent variables were selected: HPMC E15 concentration and PEG-400 concentration. Each factor was studied at three levels.

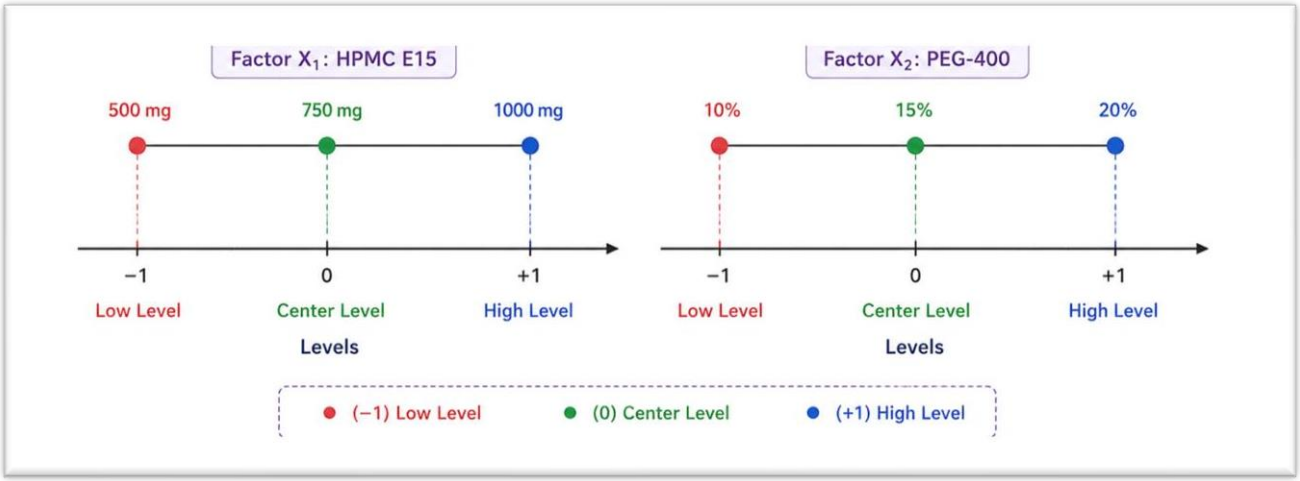


Fig 2: Independent Variables and Factor Levels Used in the 3^2 Full Factorial Designs PEG-400 concentration was calculated as a percentage with respect to polymer concentration, and the same calculation basis was maintained for all formulations.

2.1.1 Dependent Variables

Table. 1 Dependent Variables Selected for Optimization of Domperidone Mouth-Dissolving Films

Response	Code	Optimization Goal
Disintegration time	Y_1	Minimize
Folding endurance	Y_2	Maximize
Drug release at 15 minutes	Y_3	Maximize
Drug content	Y_4	Close to theoretical value
Film thickness	Y_5	Uniform and acceptable
Surface PH	Y_6	Approximately 6.8–7.2

2.1.2 Preparation of Domperidone–β-Cyclodextrin Solid Dispersion

Domperidone–β-cyclodextrin solid dispersions were prepared using different drug-to-carrier ratios to identify the most suitable ratio for film incorporation. Four batches were prepared using Domperidone:β-cyclodextrin ratios of 1:1, 1:2, 1:3, and 1:4.

Table. 2 Domperidone–β-Cyclodextrin Solid Dispersion Batches

Batch	Domperidone:β-Cyclodextrin Ratio
SD1	1:1
SD2	1:2
SD3	1:3
SD4	1:4

The 1:4 w/w Domperidone:β-cyclodextrin ratio was selected because it showed the highest solubility among the prepared solid dispersions. In the selected solid dispersion, 1 g Domperidone was mixed with 4 g β-cyclodextrin, producing 5 g of total solid dispersion. Thus, the selected solid dispersion contained 20% w/w Domperidone and 80% w/w β-cyclodextrin.

For each formulation batch, 500 mg Domperidone–β-cyclodextrin solid dispersion was used, equivalent to 100 mg Domperidone and 400 mg β-cyclodextrin.

Table. 3 Dose Calculation per Formulation Batch

Component	Amount per Batch
Domperidone	100 mg
β-Cyclodextrin	400 mg
Domperidone–β-CD solid dispersion	500 mg

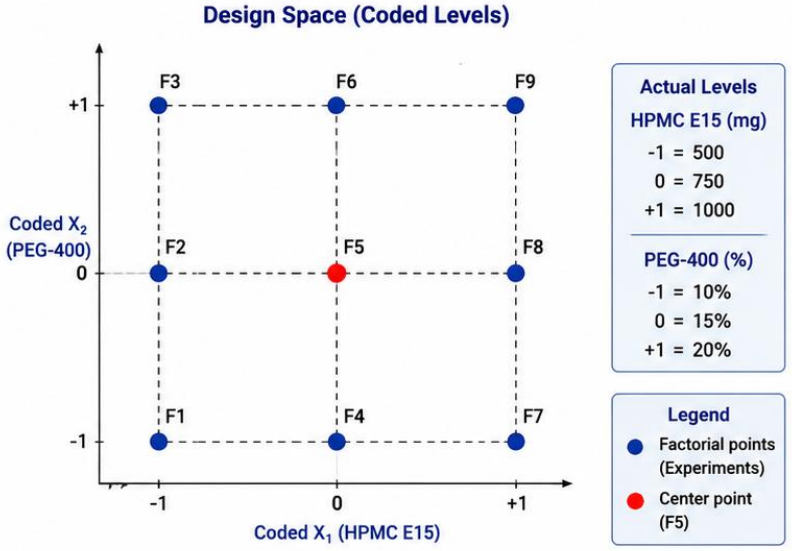
2.1.3 Coded Factorial Design Matrix

Table 4 Coded Design Matrixes for the 3² Full Factorial Designs

3^2 Full Factorial Design

Formulation	HPMC E15 (mg)	PEG-400 (%)	Coded X_1 (HPMC E15)	Coded X_2 (PEG-400)
F1	500	10	-1	-1
F2	500	15	-1	0
F3	500	20	-1	+1
F4	750	10	0	-1
F5	750	15	0	0
F6	750	20	0	+1
F7	1000	10	+1	-1
F8	1000	15	+1	0
F9	1000	20	+1	+1

- X_1 (HPMC E15): -1 = 500 mg, 0 = 750 mg, +1 = 1000 mg
- X_2 (PEG-400) : -1 = 10%, 0 = 15%, +1 = 20%



3. Evaluation of Domperidone Mouth-Dissolving Films

The prepared films were evaluated for morphological characteristics, film mass, film thickness, folding endurance, surface pH, in vitro disintegration time, drug content, and in vitro dissolution behavior.

3.1 Morphological Evaluation

The films were visually examined for homogeneity, color, transparency, smoothness, surface texture, cracks, and air bubbles. Films showing uniform appearance, smooth texture, and absence of visible defects were considered acceptable.

3.2 Film Mass

Three films from each formulation were selected randomly and weighed individually using an analytical balance. The mean film mass and standard deviation should be calculated for each formulation.

3.3 Film Thickness

Film thickness was measured using a digital Vernier caliper. Each film was measured at five different positions, and the average thickness was calculated.

3.4 Folding Endurance

Folding endurance was determined by repeatedly folding each film at the same position until it broke. The number of folds required to break the film was recorded as the folding endurance value.

3.5 Surface pH

The surface pH of the films was determined to assess compatibility with the oral mucosa. A film was placed in contact with a small quantity of phosphate buffer pH 6.8 to allow surface wetting. The pH was measured using a calibrated pH meter or pH paper, depending on laboratory availability. A surface pH close to neutral was considered acceptable.

3.6 In Vitro Disintegration Time

In vitro disintegration time was determined by placing the film on a stainless-steel wire mesh in a Petri dish containing 10 mL phosphate buffer pH 6.8. The time required for complete disintegration was recorded in seconds.

3.7 Drug Content

Drug content was determined by UV spectrophotometric analysis. Each film was dissolved or dispersed in a suitable quantity of phosphate buffer pH 6.8 and diluted appropriately. Absorbance was measured at 286.5 nm, and drug content was calculated using the calibration curve.

3.8 In Vitro Dissolution Study

In vitro dissolution was carried out using a USP Type II

paddle apparatus. The dissolution medium consisted of 900 mL phosphate buffer pH 6.8 maintained at 37 ± 0.5°C. Paddle speed was set at 50 rpm. Samples were withdrawn at predetermined time intervals and analyzed by UV-visible spectrophotometry at 286 nm. Cumulative percentage drug release was calculated using the calibration curve.

3.9 Optimization and Data Analysis

The responses obtained from the 3^2 factorial design were analyzed using coded model equations. The general equation used was:

$$Y = b_0 + b_1X_1 + b_2X_2$$

where Y represents the measured response, X_1 represents the coded concentration of HPMC E15, X_2 represents the coded concentration of PEG-400, b_0 is the intercept, and b_1 and b_2 represent the effect coefficients of formulation variables.

The optimized formulation was selected based on minimum disintegration time, maximum drug release, acceptable folding endurance, uniform drug content, and suitable film thickness.

4. RESULTS AND DISCUSSION

4.1 Drug Characterization

Domperidone was characterized before formulation development to confirm its suitability for incorporation into mouth-dissolving films. The characterization studies included physical examination, UV spectrophotometric characterization, calibration curve preparation, and solubility-based selection of Domperidone–β-cyclodextrin solid dispersion.Domperidone has limited aqueous solubility; therefore, β-cyclodextrin was used as a complexing agent to improve apparent solubility and support rapid drug release from the mouth-dissolving film matrix. The formulation strategy was based on incorporation of Domperidone as a β-cyclodextrin solid dispersion into a polymeric film containing HPMC E15 and PEG-400.

4.2 Physical Characterization

The Domperidone sample was visually examined for physical appearance, color, texture, aggregation, discoloration, and visible foreign particles. Visual examination is an important preliminary test because changes in appearance may indicate poor storage conditions, contamination, or possible degradation.

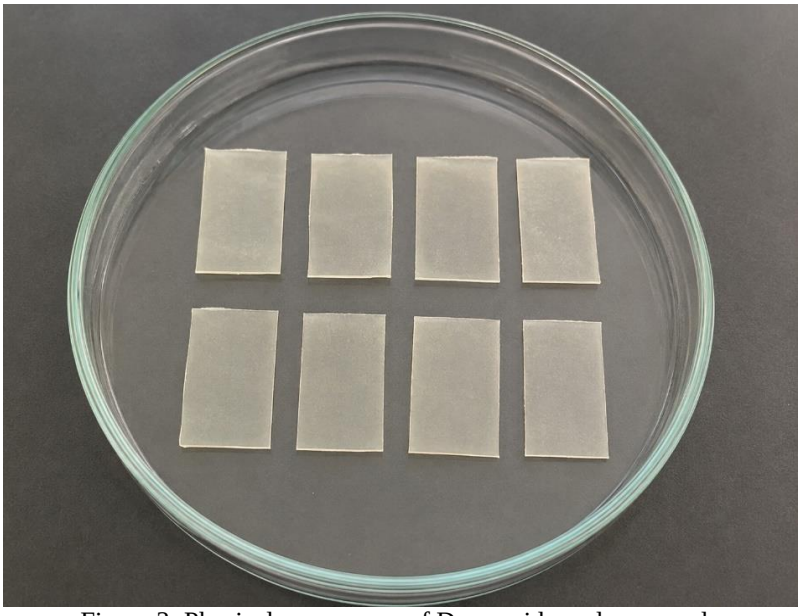


Figure 3: Physical appearance of Domperidone drug sample

These observations indicate that solvent casting was suitable for preparing Domperidone mouth-dissolving films. Minor differences in surface appearance may occur due to variation in polymer concentration, plasticizer level, casting uniformity, and drying behavior.

4.3 Evaluation of Formulation Batches

The prepared formulations were evaluated for critical quality attributes, including disintegration time, folding endurance, drug release at 15 minutes, drug content, and film thickness.

Table. 5 Evaluation Parameters of Domperidone Mouth-Dissolving Films F1–F9

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC E15 (mg)	500	500	500	750	750	750	1000	1000	1000
PEG-400(%)	10	15	20	10	15	20	10	15	20
Disintegration time (s)	55	44	31	68	47	32	66	39	52
Folding endurance	376	298	204	297	269	218	356	162	237
Drug release at 15 min (%)	88.25	94.17	93.14	79.24	90.41	98.12	86.71	91.18	86.39
Drug content (%)	98.18	99.14	98.10	97.54	98.16	98.24	98.21	97.1	96.18
Film thickness (mm)	0.189	0.156	0.119	0.178	0.152	0.121	0.175	0.114	0.135

All formulations released more than 75% Domperidone within 15 minutes, satisfying the predefined QTPP criterion. Disintegration time ranged from 31 to 68 seconds. Most formulations showed disintegration time below 60 seconds, except F4 and F7, which showed disintegration times of 68 seconds and 66 seconds, respectively.

4.4 Film Thickness

Film thickness is an important quality attribute because it can affect dose uniformity, mechanical strength, packaging suitability, and disintegration behavior. The thickness of the prepared films ranged from 0.114 to 0.189 mm. The maximum thickness was observed in F1, while the minimum thickness was observed in F8.

The thickness pattern was not strictly proportional to HPMC E15 concentration. This indicates that film thickness was influenced not only by polymer amount but also by plasticizer concentration, casting uniformity, drying shrinkage, and polymer–plasticizer interaction.

4.5 Folding Endurance

Folding endurance was evaluated as an indicator of film flexibility and resistance to mechanical breakage. Folding endurance values ranged from 162 to 376 folds. The highest folding endurance was observed in F1, followed by F7 and F2. The lowest value was observed in F8.

Although PEG-400 is commonly used as a plasticizer to improve flexibility, the present data showed that increasing PEG-400 concentration from 10% to 20% reduced folding endurance at each HPMC E15 level. This suggests that excessive PEG-400 may have produced softer but mechanically weaker films within the studied formulation range. Excess plasticizer may reduce cohesive strength within the polymeric matrix, resulting in lower resistance to repeated folding.

4.5 In Vitro Disintegration Time

In vitro disintegration time is a critical quality attribute for mouth-dissolving films because rapid film breakup is necessary for patient acceptability and prompt drug release. Disintegration time ranged from 31 to 68 seconds. The fastest disintegration was observed in F3, followed closely by F6. F3 contained 500 mg HPMC E15 and 20% PEG-400, while F6 contained 750 mg HPMC E15 and 20% PEG-400. These results indicate that higher PEG-400 concentration promoted faster disintegration. PEG-400 may increase hydrophilicity and facilitate faster penetration of dissolution medium into the film matrix, thereby accelerating film hydration and breakup.

4.6 Drug Content

Drug content ranged from 96.8% to 99.1%. The highest drug content was observed in F2, while the lowest value was observed in F9. All formulations showed drug content close to the theoretical value, indicating satisfactory distribution of Domperidone–β-cyclodextrin solid dispersion within the polymeric film matrix.

The narrow variation in drug content suggests that the solvent casting method provided acceptable uniformity of drug loading. Minor variation may be attributed to casting uniformity, film cutting, drying behavior, and possible redistribution of dispersed solid during solvent evaporation.

4.7 In Vitro Drug Release

The in vitro dissolution study was carried out in phosphate buffer pH 6.8 using a USP Type II paddle apparatus. Drug release at 15 minutes ranged from 79.5% to 98.2%. All formulations released more than 75% Domperidone within 15 minutes, meeting the predefined release criterion.

The highest drug release at 15 minutes was observed in F6, containing 750 mg HPMC E15 and 20% PEG-400.

The lowest release was observed in F4, containing 750 mg HPMC E15 and 10% PEG-400. At 750 mg HPMC E15, increasing PEG-400 concentration from 10% to 20% increased drug release from 79.5% to 98.2%.

This indicates that PEG-400 had a favorable effect on drug release, probably due to improved wetting, increased hydration of the film matrix, and faster diffusion of drug from the polymeric network. Higher HPMC E15 concentration tended to reduce drug release in some formulations, possibly because of increased matrix viscosity and diffusion resistance.

Table 6 In Vitro Cumulative Drug Release Profile of Domperidone Mouth-Dissolving Films F1–F9

Time Interval	**F1 (%)**	**F2 (%)**	**F3 (%)**	**F4 (%)**	**F5 (%)**	**F6 (%)**	**F7 (%)**	**F8 (%)**	**F9 (%)**
2 min	11.78	12.61	12.5	10.60	12.00	13.10	11.59	12.21	11.60
4 min	23.159	25.13	24.9	21.20	24.12	26.12	23.11	24.50	23.20
6 min	35.14	37.19	37.40	31.80	36.00	39.30	34.70	36.70	34.80
8 min	47.12	50.50	49.90	42.23	48.87	52.12	46.20	49.04	46.23
10 min	59.02	63.10	62.30	53.01	60.10	65.50	57.80	61.20	57.18
15 min	88.50	94.70	93.50	79.50	90.21	98.20	86.70	91.80	86.190
20 min	92.30	96.50	95.70	86.30	93.40	98.45	91.12	94.57	91.34
25 min	94.17	98.20	97.87	93.11	95.94	98.50	95.61	96.83	94.35
30 min	94.16	98.13	99.52	93.11	95.94	98.30	96.90	96.83	94.35

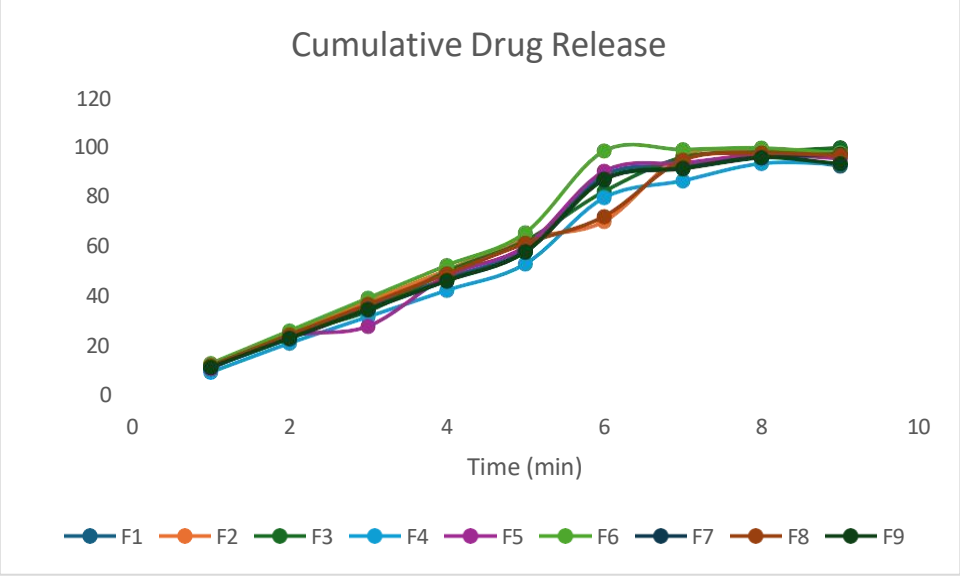


Figure 4: In vitro cumulative drug release profile of Domperidone mouth-dissolving films F1–F9

4.8 Effect of Formulation Variables Based on QbD Analysis

The QbD approach was applied to evaluate the effect of HPMC E15 and PEG-400 on selected response variables. HPMC E15 was selected as factor X_1, and PEG-400 was selected as factor X_2.

Table.7 Coded regression equations for the optimization responses of Domperidone oral film formulations

Response	Coded Model Equation
Disintegration time	$Y_1 = 48.22 + 4.50X_1 - 12.33X_2$
Folding endurance	$Y_2 = 268.56 - 20.50X_1 - 61.67X_2$
Drug release at 15 min	$Y_3 = 89.99 - 1.88X_1 + 3.98X_2$
Drug content	$Y_4 = 98.04 - 0.63X_1 - 0.20X_2$
Film thickness	$Y_5 = 0.1488 - 0.0067X_1 - 0.0278X_2$

Film thickness $Y_5 = 0.1488 - 0.0067X_1 - 0.0278X_2$
X_1: HPMC E15concentration; X_2: PEG-400 concentration; Y_1–Y_5: Formulation responses

The positive coefficient of HPMC E15 in the disintegration time equation indicates that increasing HPMC E15 tended to increase disintegration time. The negative coefficient of PEG-
400 indicates that increasing PEG-400 reduced disintegration time. This supports the experimental trend that PEG-400 facilitated faster film breakup.
For folding endurance, both HPMC E15 and PEG-400 showed negative coefficients, with PEG-400 showing the stronger effect. This indicates that higher PEG-400 concentration reduced mechanical endurance in the studied range. For drug release, PEG-400 showed a positive effect, while HPMC E15 showed a slight negative effect. Drug content was minimally affected by both formulation variables, indicating relatively uniform drug distribution across the design space.

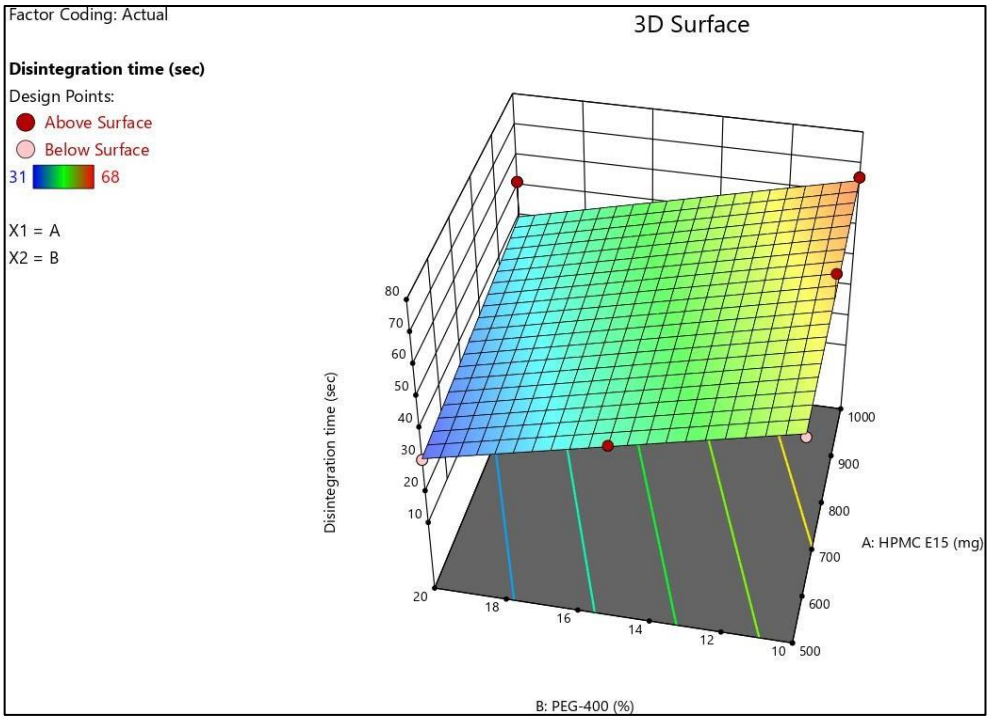


Figure 5: Response surface plot for effect of HPMC E15 and PEG-400 on disintegration time

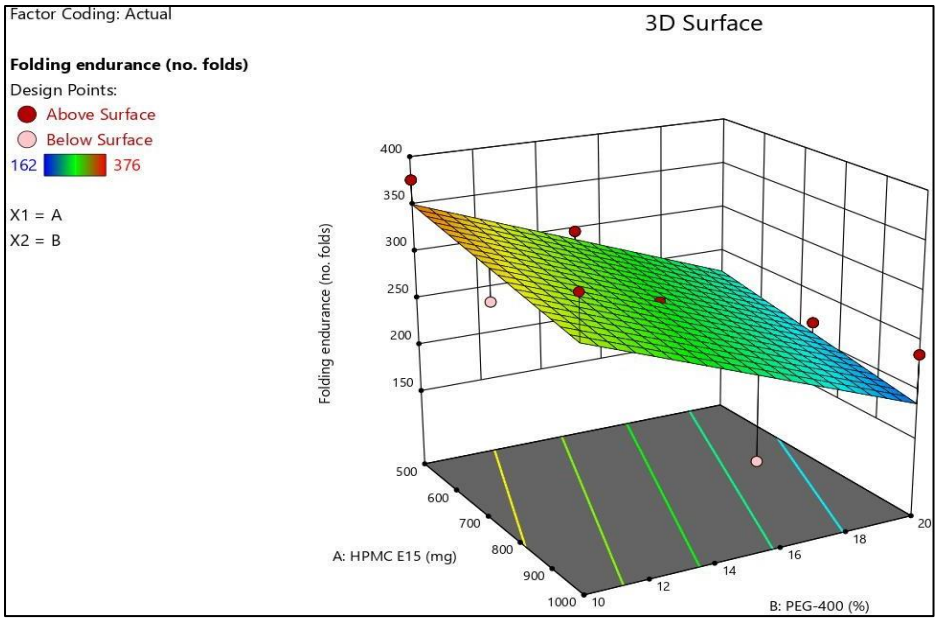


Figure 6: Response surface plot for effect of HPMC E15 and PEG-400 on folding endurance

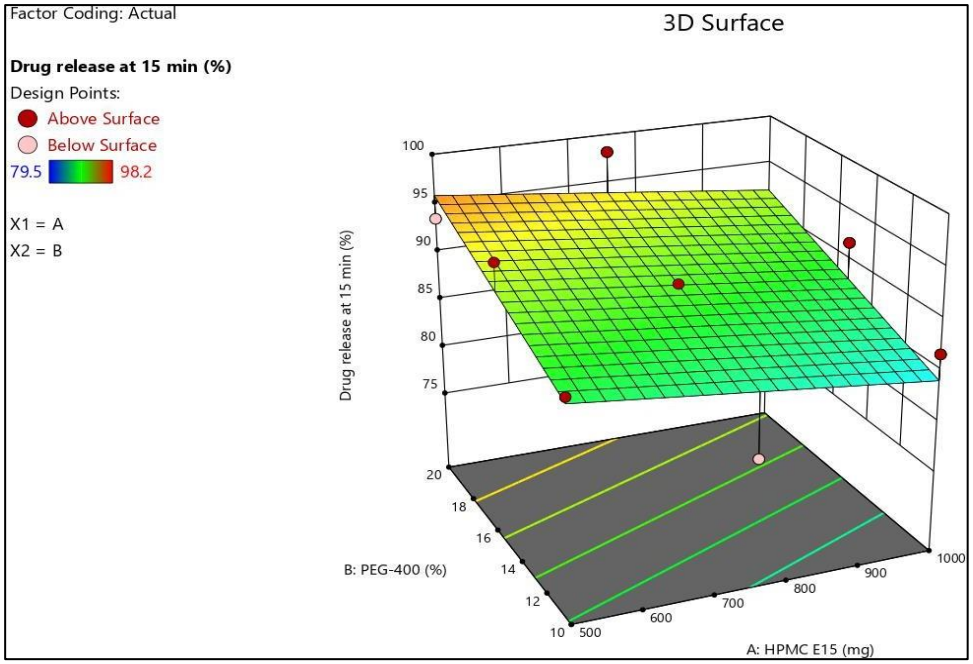


Figure 7: Response surface plot for effect of HPMC E15 and PEG-400 on drug release at 15 minutes

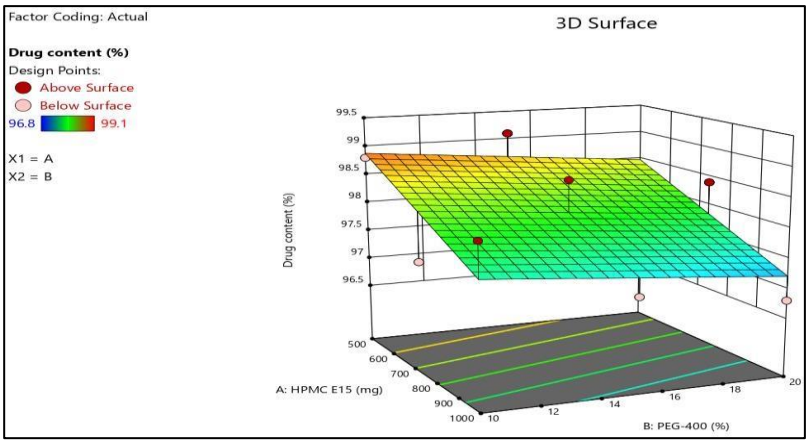


Figure 8: Response surface plot for effect of HPMC E15 and PEG-400 on drug content

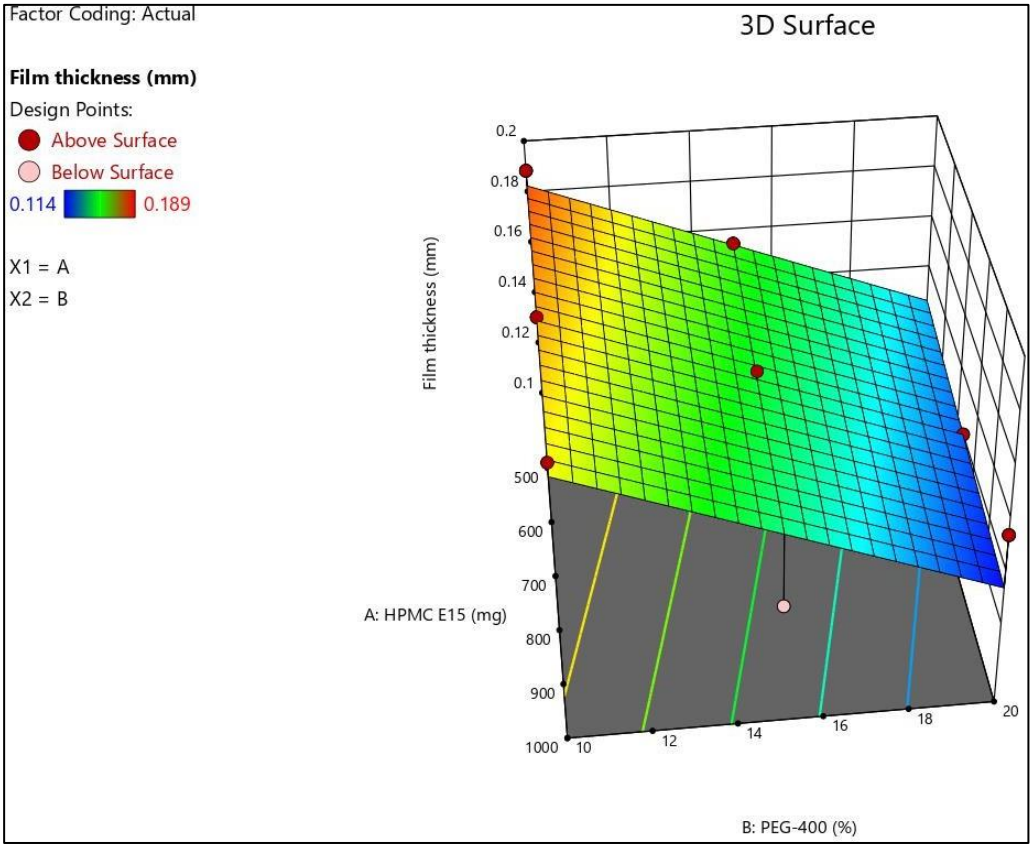


Figure 9: Response surface plot for effect of HPMC E15 and PEG-400 on film thickness

3.13 Selection of Optimized Formulation

The optimized formulation was selected by considering the QTPP and CQA targets: rapid disintegration, high drug release, acceptable folding endurance, uniform drug content, and suitable film thickness.

Among the prepared batches, F3 showed the shortest disintegration time of 31 seconds. However, F6 showed a comparable disintegration time of 32 seconds and the highest drug release of 98.2% at 15 minutes. F6 also showed acceptable drug content of 98.4%, folding endurance of 218 folds, and film thickness of 0.121 mm.

Table. 8 Model-predicted responses of the optimized Domperidone oral film formulation F6 with experimental Results

Response	Predicted value	Experimental value provided	Difference
Disintegration time	35.89 s	32 s	−3.89 s
Folding endurance	206.89 folds	218 folds	+11.11 folds
Drug release at 15 min	93.97%	98.20%	+4.23%
Drug content	97.84%	98.40%	+0.56%
Film thickness	0.121 mm	0.121 mm	0.000 mm

Although F1 showed the highest folding endurance, its disintegration time and drug release were not superior to F6. Similarly, F3 showed the fastest disintegration, but F6 provided higher drug release and better overall performance. Therefore, F6 was selected as the optimized formulation.

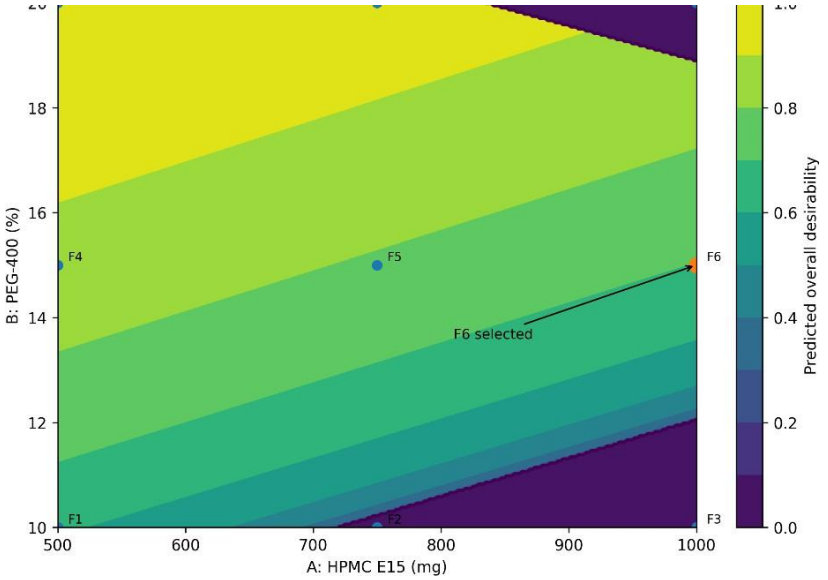


Figure 10: Overlay plot indicating optimized design space for Domperidone mouth-dissolving films

4. CONCLUSION

Domperidone–β-cyclodextrin solid dispersion, HPMC E15, PEG-400, Tween-80 and citric acid were utilized to effectively prepare domperidone mouth-dissolving films through the solvent casting method. The films that were prepared exhibited satisfactory performance in terms of in vitro drug release, disintegration time, folding endurance, drug content and film thickness, as well as acceptable morphological characteristics..

Film thickness ranged from 0.114 to 0.189 mm, folding endurance from 162 to 376 folds, disintegration time from 31 to 68 seconds, drug content from 96.8% to 99.1%, and drug release at 15 minutes from 79.5% to 98.2%. All formulations achieved more than 75% drug release within 15 minutes, confirming the suitability of the β-cyclodextrin solid dispersion approach for rapid release of Domperidone from mouth-dissolving films.

The QbD analysis demonstrated that PEG-400 significantly impacted drug release and disintegration time, while it also diminished folding endurance. HPMC E15 showed a tendency to increase disintegration time and slightly reduce drug release. Based on the combined evaluation of critical quality attributes, F6 was selected as the optimized formulation.

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