

Development and Optimization of Fast-Dissolving Oral Films Containing Metformin HCl and Curcumin- β -Cyclodextrin Inclusion Complex Using a Box–Behnken Design

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Development and Optimization of Fast-Dissolving Oral Films Containing Metformin HCl and Curcumin- β -Cyclodextrin Inclusion Complex Using a Box–Behnken Design

Box–Behnken Tasarımı Kullanılarak Metformin HCl ve Kurkumin- β -Siklodekstrin İnklüzyon Kompleksi İçeren Hızlı Çözünen Oral Filmlerin Geliştirilmesi ve Optimizasyonu

SUMMARY

The aim of this study was to develop and optimize rapidly dissolving oral films containing metformin HCl and curcumin- β -cyclodextrin (β -CD) inclusion complexes. Curcumin complexes were prepared in molar ratios of 1:1, 1:2, and 1:3, and characterization studies (FTIR, DSC, and solubility testing) confirmed successful complex formation. The 1:2 molar ratio demonstrated the greatest improvement in aqueous solubility. Oral films were prepared using HPMC E5 and chitosan as film-forming polymers and glycerin, polysorbate 80, and citric acid as supporting excipients. A Box–Behnken design was employed to evaluate the effects of polymer ratio, plasticizer (glycerin) level, and casting thickness on disintegration time, tensile strength, and surface pH. All formulations demonstrated acceptable homogeneity, physiologically compatible surface pH values, and consistent drug content. Response surface analysis revealed that both polymer ratio and film thickness significantly affected disintegration time and mechanical strength, while surface pH was not significantly affected by formulation variables. The optimized film consisted of a 2.5 HPMC E5:chitosan ratio, 15% plasticizer, and a cast thickness of 180 μ m, with a desirability value of 1,000. Overall, the developed films demonstrate strong potential as a rapid-release oral delivery platform supported by improved curcumin solubility and robust formulation optimization.

Keywords: Box–Behnken design, curcumin- β -cyclodextrin complex, fast-dissolving oral films, metformin HCl, response surface methodology (RSM).

ÖZ

Bu çalışmanın amacı, metformin HCl ve kurkumin- β -siklodekstrin (β -CD) inklüzyon kompleksleri içeren hızlı çözünen oral filmlerin geliştirilmesi ve optimize edilmesidir. Kurkumin kompleksleri 1:1, 1:2 ve 1:3 molar oranlarında hazırlanmış; karakterizasyon çalışmaları (FTIR, DSC ve çözünürlük testleri) başarılı kompleks oluşumunu doğrulamıştır. 1:2 molar oranı, sulu ortamda çözünürlükte en yüksek artışı göstermiştir. Oral filmler, film oluşturuç polimerler olarak HPMC E5 ve kitosan kullanılarak; yardımcı ekşiyanlar olarak gliserin, polisorb 80 ve sitrik asit ile hazırlanmıştır. Polimer oranı, plastikleştirici (gliserin) düzeyi ve döküm kalınlığının; dağılma süresi, çekme dayanımı ve yüzey pH'ı üzerindeki etkilerini değerlendirmek için Box–Behnken tasarımı uygulanmıştır. Tüm formülasyonlar kabul edilebilir homojenlik, fizyolojik olarak uyumlu yüzey pH değerleri ve tutarlı ilaç içeriği göstermiştir. Yanıt yüzeyi analizi, polimer oranı ve film kalınlığının dağılma süresi ile mekanik dayanımı anlamlı şekilde etkilediğini, buna karşın yüzey pH'ının formülasyon değişkenlerinden anlamlı düzeyde etkilenmediğini ortaya koymuştur. Optimize film; 2,5 HPMC E5:kitosan oranı, %15 plastikleştirici ve 180 μ m döküm kalınlığı ile elde edilmiş; desirability değeri 1.000 bulunmuştur. Sonuç olarak, geliştirilen filmler; artırılmış kurkumin çözünürlüğü ve güçlü formülasyon optimizasyonu sayesinde, hızlı salım sağlayan oral ilaç taşıma platformu olarak yüksek potansiyel göstermektedir.

Anahtar Kelimeler: Box–Behnken tasarımı, kurkumin-siklodekstrin kompleksi, hızlı çözünen oral filmler, metformin HCl, yanıt yüzeyi metodolojisi (RSM).

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INTRODUCTION

Periodontal diseases are among the most common chronic inflammatory disorders affecting the supporting structures of the teeth. These conditions can lead to the progressive destruction of the periodontal ligament and alveolar bone. Although conventional treatment methods such as scaling and root planing are widely used, mechanical therapy alone is often insufficient to fully control infection and inflammation. Therefore, the development of local drug delivery systems capable of maintaining therapeutic concentrations of active agents in the gingival region has become an important strategy in modern periodontal therapy. Local administration minimizes systemic side effects while improving patient compliance and therapeutic efficacy by ensuring prolonged contact of the drug with the diseased tissue (Villoria, Fischer, Tinoco, Meyle, & Loos, 2024; Zhang, Jiang, Lei, Yang, & Hu, 2022).

Metformin HCl, a biguanide derivative primarily known for its antihyperglycemic effect, has recently gained attention due to its pleiotropic biological activities, including anti-inflammatory, antioxidant, and osteogenic properties. Studies have shown that metformin can modulate inflammatory signaling pathways such as AMPK/NF- κ B, stimulate osteoblast differentiation, and reduce alveolar bone loss in experimental periodontitis models. Owing to its ability to promote tissue regeneration, metformin is considered a promising adjunctive agent in the treatment of periodontal diseases (LaMoia & Shulman, 2021; Sun et al., 2023; Yahoum et al., 2023).

Curcumin, the main bioactive constituent of *Curcuma longa*, is a well-documented natural compound with anti-inflammatory, antioxidant, and antimicrobial properties. Its pharmacological effects are primarily associated with the inhibition of pro-inflammatory cytokines, suppression of reactive oxygen species, and modulation of transcription factors such as NF- κ B and Nrf2. However, the low aqueous solubility and limited bioavailability of curcumin restrict

its therapeutic potential. Therefore, incorporating curcumin into suitable delivery systems can improve its solubility, local retention, and overall biological activity (Badirzadeh et al., 2022; Indriyani & Nur'aeny, 2025).

The complementary mechanisms of metformin and curcumin suggest that their combined use may offer synergistic benefits in regulating inflammation, enhancing antioxidant defense, and supporting periodontal tissue regeneration. This synergy could help to better control oxidative stress and host-mediated tissue destruction two key factors in the pathogenesis of periodontitis. To achieve this, it is essential to develop a localized drug delivery platform that provides sufficient residence time, rapid onset of action, and ease of use for patients (Matacchione et al., 2022; Setiawan et al., 2021; Zarei, Sefidi-Heris, & Saadat, 2021).

Fast-dissolving oral films (FDOFs) have emerged as innovative dosage forms that offer several advantages, including rapid disintegration without the need for water, accurate dosing, simple administration, and improved patient compliance. When formulated with mucoadhesive polymers, these films can adhere to the oral or gingival mucosa, allowing prolonged and localized release of the active ingredients at the target site. Among mucoadhesive polymers, hydroxypropyl methylcellulose (HPMC E5) provides excellent film-forming ability and mechanical strength, while chitosan a natural cationic polysaccharide offers strong bioadhesion, biocompatibility, and inherent antimicrobial activity. The combination of these polymers can yield a film matrix capable of adhering to the gingival surface, rapidly swelling in saliva, and delivering the incorporated drugs directly to the site of inflammation (Isla et al., 2025). The EMA guidelines on patient-centric pharmaceutical development and the WHO recommendations on easy-to-administer dosage forms emphasize the importance of alternative oral drug delivery systems for adults and

elderly patients experiencing swallowing difficulties. For individuals who struggle with tablets or capsules, fast-dissolving oral films offer significant advantages, including ease of administration, the ability to be taken without water, and improved treatment adherence. In this context, the fast-dissolving oral film developed in this study, containing metformin and curcumin, aligns with international regulatory expectations for innovative, patient-friendly, and convenient dosage forms (Sayed, Kulkarni, Pardeshi, Kapile, & Nehe, 2022; Suresh, Aravindaraj, Krishnaswami, & Kandasamy, 2023; Kamali, Farzadnia, Movaffagh, & Abaspour, 2022).

Despite the extensive literature on β -CD inclusion complexes and fast-dissolving oral films, studies combining metformin HCl and curcumin within a single oral film platform remain very limited. The novelty of the present study lies in the development of a dual-drug fast-dissolving oral film incorporating a curcumin- β -CD inclusion complex together with metformin HCl for localized periodontal application. This approach simultaneously addresses the poor aqueous solubility of curcumin, enables co-delivery of two pharmacologically complementary agents, and provides a patient-friendly dosage form optimized through a Quality-by-Design strategy.

The primary aim of this study was to design, optimize, and evaluate a mucoadhesive fast-dissolving oral film containing metformin and curcumin for the local treatment of periodontal diseases. The rationale behind this approach was to combine the complementary pharmacological actions of metformin and curcumin within a patient-friendly, non-invasive dosage form that can rapidly disintegrate in the oral cavity and adhere to the gingival tissue, enabling localized and sustained drug release. To achieve this objective, a Design of Experiments (DoE) approach was employed to systematically optimize the formulation parameters. The optimized film was then comprehen-

sively characterized in terms of its surface pH, thickness uniformity, tensile strength, in vitro dissolution time, weight uniformity, drug content uniformity, in vitro dissolution studies and stability tests. Consequently, this study aims to develop a novel dual-drug oral film platform that utilizes the synergistic potential of metformin and curcumin to enhance local anti-inflammatory activity and preserve periodontal tissue integrity. The results are expected to contribute to the advancement of localized combination therapies and provide a solid foundation for future clinical applications of mucoadhesive oral film systems in periodontal treatment.

MATERIALS AND METHODS

Materials

Metformin was kindly provided by Abdi İbrahim Pharmaceuticals (Turkey). Curcumin, HPMC E5, chitosan (medium molecular weight), Parteck ODT[®], glycerol, sucrose, and acetic acid were purchased from Sigma-Aldrich as pharmaceutical-grade materials. Double-distilled water was used throughout the study.

Methods

Preparation of curcumin- β -CD inclusion complex

To enhance the aqueous solubility of curcumin, an inclusion complex with β -CD (β -CD) was prepared using the grinding method. Three different molar ratios of curcumin to β -CD (1:1, 1:2, and 1:3) were investigated to determine the optimal complexation ratio, based on the improvement in the solubility of curcumin in distilled water. Accurately weighed amounts of β -CD and curcumin were first mixed in a mortar. A mixture of ethanol and distilled water (1:1, v/v) was then added dropwise to the powder blend while continuously triturating, until a uniform, smooth paste was obtained. The resulting mass was passed through a No. 2 sieve, and subsequently dried in a hot air oven at 30 °C for approximately 6 hours. The dried material

was then sieved through a No. 1 mesh, yielding a fine, free-flowing powder, which was stored in an airtight container to protect it from moisture. The inclusion complexes prepared at the three molar ratios were evaluated for the enhancement of curcumin's aqueous solubility, and the ratio showing the highest solubility improvement was selected for incorporation into the oral film formulations (Benucci et al., 2022; Cabrera-Quñones, López-Méndez, & Guadarrama, 2023; Gatiatulin, Klimovitskii, Tagirov, Ziganshin, & Gorbatchuk, 2025).

Characterization of the inclusion complexes

The prepared curcumin- β -CD inclusion complexes were characterized to confirm complex formation and to evaluate the possible interactions between curcumin and β -CD. For this purpose, Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and solubility studies were performed (Abbas et al., 2022; Jiang et al., 2021; Li et al., 2021).

FTIR analysis

FTIR spectra of pure curcumin, β -CD, and the prepared inclusion complex were recorded using an FTIR spectrophotometer over the range of 4000–400 cm^{-1} . The characteristic stretching vibrations of curcumin—particularly those corresponding to C=O, aromatic C=C, and –OH groups—were carefully examined. The observed shifts, broadening, or partial disappearance of these peaks in the spectrum of the inclusion complex compared with the pure components were interpreted as evidence of hydrogen bonding and successful encapsulation of curcumin within the β -CD cavity (Khan, Yadav, & Saneja, 2025; Zhou, Guo, J., Gladden, I., Contreras, A., & Kong, 2022).

DSC analysis

The thermal behavior of the samples was analyzed by differential scanning calorimetry. Approximately 5

mg of each sample (pure curcumin, β -CD, and the inclusion complex) was placed in sealed aluminum pans and scanned from 25 °C to 300 °C at a heating rate of 10 °C/min under a nitrogen atmosphere. The disappearance or marked reduction of the sharp melting endothermic peak of curcumin in the thermogram of the complex indicated molecular encapsulation and amorphization as a result of host–guest interaction with β -CD (Kaya et al., 2023; Michel, Heggset, Syverud, Dufresne, & Bras, 2022).

Solubility studies

To assess the improvement in aqueous solubility, excess amounts of pure curcumin and the inclusion complex were added separately to 10 mL of distilled water and shaken at 37 ± 0.5 °C for 24 hours. After equilibrium was reached, the samples were filtered through a 0.45 μm membrane filter, appropriately diluted, and analyzed spectrophotometrically at 425 nm. A remarkable increase in the solubility of curcumin from the inclusion complex compared with that of pure curcumin and its physical mixture confirmed the efficiency of the complexation process (Bhattacharyya et al., 2023; Cabrera-Quñones et al., 2023; Mashaqbeh, Obaidat, & Al-Shar'I, 2021).

Preparation of fast-dissolving oral film formulations

The required amount of chitosan was dissolved in 1% acetic acid solution by stirring at 200 rpm for approximately 1 hour. In a separate beaker, HPMC E5 was slowly dispersed in distilled water under continuous stirring until completely hydrated. To this HPMC E5 solution, glycerin (as a plasticizer), Parteckt (as a superdisintegrant), polysorbate 80 (wetting agent), and citric acid were sequentially added under stirring at 300 rpm. The resulting HPMC E5 solution was then slowly added to the chitosan solution under gentle mixing. The pH of the final mixture was measured and adjusted to 5.5–5.8 using sodium hydroxide (NaOH)

solution. Separately, 100 mg of metformin HCl was dissolved in a small volume of distilled water, while a curcumin- β -CD) complex equivalent to 2 mg of curcumin was dissolved in another portion of distilled water. These two drug solutions were then combined and incorporated into the previously prepared polymeric mixture under gentle stirring. For taste masking, 0.1 g of sucrose was added and mixed for approximately 1 minute. The final formulation was cast onto a glass surface (10 $\times$ 10 cm) at the desired thickness and dried in an oven at 40 $^{\circ}$ C for 8 hours. After drying, the films were cut into 2 $\times$ 2 cm pieces, wrapped in aluminum foil, and stored in a desiccator until further analysis. Table 1 shows the independent factors determined according to Box–Behnken experimental design. Table 2 shows the formulation ingredients found in each fast-disintegrating oral film (Çoban, Özcan, Engin, Tatar, & Soylu, 2024; Elshafeey & El-Dahmy 2021; Kshirsagar et al., 2021; Rohani Shirvan, Hemmatinejad, Bahrami, & Bashari, 2022).

Table 1. Formulations and independent factors

	Factor 1	Factor 2	Factor 3
Run	A:HPMC E5:Chitosan ratio	B:Plasticizer (Glycerin) ratio	C:Casting thickness
	ratio	w/w%	μ m
F1	2.5	10	120
F2	2.5	15	180
F3	4.0	20	180
F4	2.5	15	180
F5	4.0	10	180
F6	2.5	20	240
F7	1.0	15	240
F8	2.5	15	180
F9	4.0	15	120
F10	2.5	15	180
F11	2.5	15	180
F12	1.0	15	120
F13	4.0	15	240
F14	1.0	10	180
F15	2.5	10	240
F16	2.5	20	120
F17	1.0	20	180

Table 2. Composition of the fast-dissolving oral film formulations prepared according to the Box–Behnken design

Component of each film (g)								
Formulation	HPMC E5	Chitosan	Glycerin	Polysorbate 80	Citric acid	Sucrose	Metformin	Curcumin
F1	1.071	0.429	0.150	0.05	0.03	0.10	0.10	0.002
F2	1.071	0.429	0.225	0.05	0.03	0.10	0.10	0.002
F3	1.200	0.300	0.300	0.05	0.03	0.10	0.10	0.002
F4	1.071	0.429	0.225	0.05	0.03	0.10	0.10	0.002
F5	1.200	0.300	0.150	0.05	0.03	0.10	0.10	0.002
F6	1.071	0.429	0.300	0.05	0.03	0.10	0.10	0.002
F7	0.750	0.750	0.225	0.05	0.03	0.10	0.10	0.002
F8	1.071	0.429	0.225	0.05	0.03	0.10	0.10	0.002
F9	1.200	0.300	0.225	0.05	0.03	0.10	0.10	0.002
F10	1.071	0.429	0.225	0.05	0.03	0.10	0.10	0.002
F11	1.071	0.429	0.225	0.05	0.03	0.10	0.10	0.002
F12	0.750	0.750	0.225	0.05	0.03	0.10	0.10	0.002
F13	1.200	0.300	0.225	0.05	0.03	0.10	0.10	0.002
F14	0.750	0.750	0.150	0.05	0.03	0.10	0.10	0.002
F15	1.071	0.429	0.150	0.05	0.03	0.10	0.10	0.002
F16	1.071	0.429	0.300	0.05	0.03	0.10	0.10	0.002
F17	0.750	0.750	0.300	0.05	0.03	0.10	0.10	0.002

Characterization of films

Tensile strength determination

The mechanical strength of the prepared films was determined using a simple tensile testing method that can be easily applied under laboratory conditions. Rectangular strips of each film (10 mm × 50 mm) were cut, and their thickness was measured at three different points using a micrometer; the average value was used for calculations. The samples were conditioned at 25 ± 2 °C for 24 hours before testing. During the test, both ends of the film strips were fixed between grips lined with fine sandpaper to prevent slippage. The upper grip was kept stationary, while incremental weights were gradually applied to the lower grip. A waiting period of 2–3 seconds was allowed between each loading step, and the total weight at the point of film rupture was recorded. The tensile strength (σ) was calculated using the following equation:

$$\sigma = \frac{F_{\max}}{b \times t}$$

where b is the film width (mm) and t is the film thickness (mm). The results were expressed in MPa as the mean $\pm$ standard deviation (SD) of at least three replicates for each formulation (Salawi, 2022; Sengar, Yadav, & Niranjana, 2024; Shah et al., 2022).

Determination of *in vitro* disintegration time

The *in vitro* disintegration time of the oral films was determined in an enzyme-free simulated salivary medium. A USP disintegration test apparatus (e.g., Erweka ZT series, Germany) was used for the evaluation. The disintegration medium consisted of a simulated salivary fluid (pH 6.8) prepared by dissolving 8.0 g sodium chloride (NaCl), 0.19 g potassium dihydrogen phosphate (KH_2PO_4), and 2.38 g disodium hydrogen phosphate dihydrate ($\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$) in 1 L of distilled water. The temperature of the medium was maintained at 37 ± 0.5 °C throughout the experiment. Six film samples, approximately 1 cm in size, were placed on the compartmentalized disks of the disintegration apparatus. The disintegration time was recorded as the time required for complete disappear-

ance of the film mass without any visible residues on the disk. The experiment was performed in triplicate ($n = 3$), and the results were expressed as mean $\pm$ SD in seconds (Algellay et al., 2023; Alghaith et al., 2022; Özakar, Sevinç-Özakar, & Yılmaz, 2023).

Determination of surface pH

The surface pH values of the oral films were determined to evaluate their compatibility with the oral mucosa. Approximately 1 g of film was placed in a Petri dish, and 1 mL of distilled water was carefully added to its surface. The samples were allowed to equilibrate with the water on the film surface for about 30 seconds, after which the pH was measured directly on the film surface using a calibrated pH meter. Each measurement was performed in triplicate ($n = 3$), and the results were recorded as mean $\pm$ SD (Alhamhoom et al., 2024; Pamlényi, Kristó, Jójárt-Laczovich, & Regdon, 2021).

Thickness and weight uniformity

Film thickness was determined using a caliper. Measurements for each formulation were performed at least three times, and the results were reported as mean $\pm$ SD and RSD%. Mass uniformity was evaluated by individually weighing film units of a fixed area (2×2 cm; $n = 20$) using an analytical balance. The results were expressed as mass (mg) and areal density (mg/cm^2) in terms of mean $\pm$ SD and RSD% (Nurdi-anti, Sopyan, & Rusdiana, 2021; Yin et al., 2024).

Drug content and content uniformity

The drug content of the oral films was determined by extracting accurately weighed film units (2×2 cm) in an appropriate solvent mixture (water:methanol, 80:20 for metformin HCl and ethanol:water, 60:40 for the curcumin- β -CD complex) under sonication for 10–15 minutes. The obtained solutions were filtered through a $0.45 \mu\text{m}$ membrane filter and analyzed using a UV-Vis spectrophotometer. Absorbance was measured at 232 nm for metformin HCl and 425 nm for curcumin. Calibration curves were prepared in the concentration range of 2–20 $\mu\text{g}/\text{mL}$ and found to

be linear ($R^2 \geq 0.999$). The results were expressed as mean $\pm$ SD and RSD% of the drug content per unit film (mg/unit). Content uniformity was evaluated on ten individual film samples ($n = 10$) (Celebioglu, Wang, Kilic, Durgun, & Uyar, 2021; Rani et al., 2021).

Dissolution studies (in vitro release profile)

The *in vitro* dissolution profiles of the oral films were determined using a USP II (paddle) apparatus at 37 ± 0.5 °C. The dissolution medium volume was set to 250 mL, and simulated salivary fluid (pH 6.8) was used as the medium. The paddle speed was maintained at 50 rpm. Film samples were fixed beneath the paddle to prevent floating. Aliquots of 2–3 mL were withdrawn at 1, 2, 3, 5, 7, 10, and 15 minutes, and an equal volume of fresh medium was added to maintain sink conditions. The collected samples were filtered through a $0.45 \mu\text{m}$ membrane filter and analyzed using UV–Vis spectrophotometry (Sowjanya & Rao, 2023)

Stability studies

Stability studies were conducted on the optimized film formulation according to ICH Q1A(R2) guidelines. Film samples were packaged in aluminum foil sachets and stored under accelerated ($40 \text{ °C} \pm 2 \text{ °C} / 75\% \pm 5\% \text{ RH}$) condition. Evaluations were performed at 0, 1 and 3 months for accelerated studies. At each time point, films were tested for appearance, surface pH and disintegration time. All tests were performed in triplicate (Elshafeey & El-Dahmy 2021; ICH, 2003).

Statistical analysis

A Design of Experiments (DoE) approach was applied to evaluate the effects of formulation variables on the selected responses and to optimize the formulation. Statistical analyses were performed using Design-Expert software (Version 13, Stat-Ease Inc., Minneapolis, USA). The effects of independent variables (HPMC E5:chitosan ratio, plasticizer concentration, and casting thickness) on the dependent responses (disintegration time, tensile strength, and surface pH) were analyzed using a Box–Behnken design. The adequacy of the model was assessed by analysis of variance (ANOVA), and a significance level of $p < 0.05$ was considered statistically significant. Three-dimensional response surface plots and interaction diagrams were generated to visualize the relationships between formulation factors and the measured responses. Multi-response optimization was performed using the desirability function approach, and the optimum formulation composition was determined accordingly (Shah et al., 2022).

RESULTS AND DISCUSSION

Characterization results of the curcumin- β -CD complexes

Figure 1 presents the FT-IR spectra of pure curcumin, β -CD, the physical mixture of curcumin and β -CD, and the inclusion complex formed between the two components, while Figure 2 shows the DSC thermograms obtained from the same materials and mixtures.

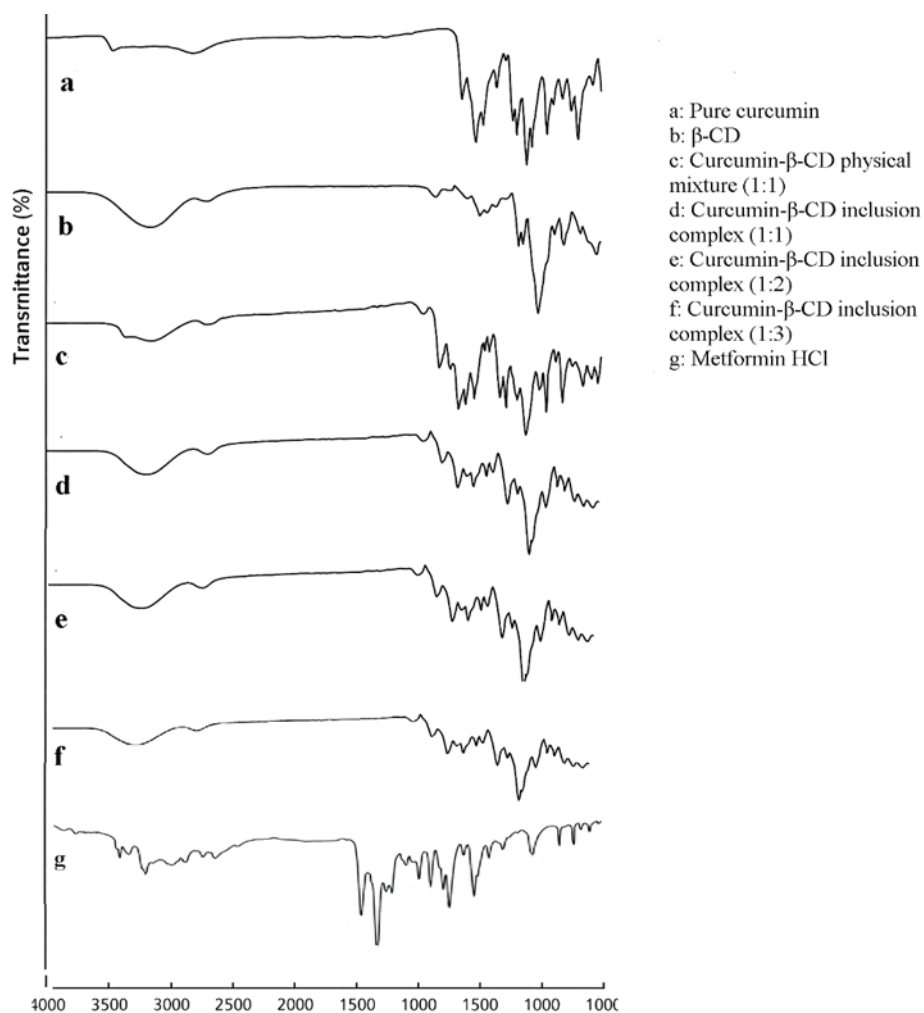


Figure 1. FT-IR spectra of pure curcumin, β-CD, curcumin-β-CD physical mixture, curcumin-β-CD inclusion complexes and metformin HCl

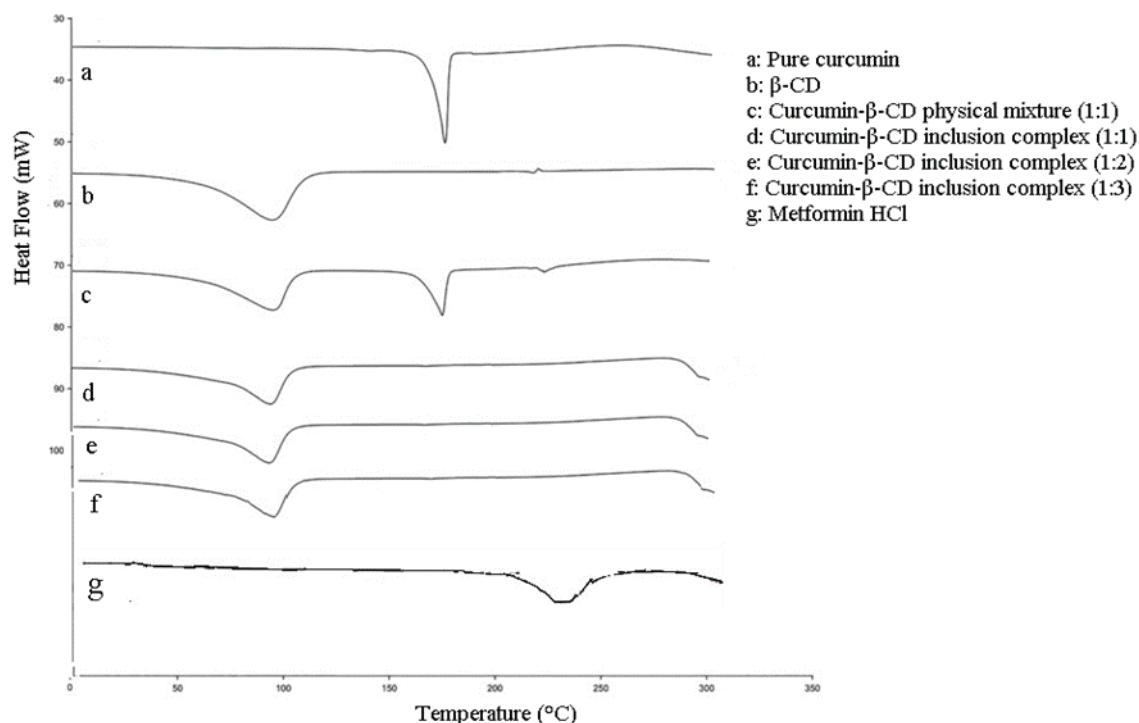


Figure 2. DSC thermograms of pure curcumin, β -CD, the physical mixture, and the curcumin- β -CD inclusion complexes

Metformin and curcumin were intentionally combined in the same formulation due to their complementary therapeutic profiles. Metformin HCl, with its high aqueous solubility, ensures a rapid onset of action, while curcumin provides potent antioxidant and anti-inflammatory activity that enhances metformin's effects. Complexing curcumin with β -CD improved its solubility, allowing both drugs to exhibit comparable dissolution rates within the film. This combination creates a meaningful synergistic effect, delivering fast dissolution together with broader therapeutic benefits in a single patient-friendly dosage form. Overall, the developed film successfully integrates the strengths of both actives into one optimized system (Shah et al., 2022; Wasana et al., 2022).

The results of this study demonstrate that the curcumin- β -CD inclusion complexes were successfully prepared. FT-IR spectra showed distinct shifts in the characteristic C=O and aromatic C=C stretching

bands of curcumin, indicating its incorporation into the hydrophobic cavity of β -CD. These spectral differences were not observed in the physical mixture, supporting the formation of a true inclusion complex. DSC thermograms further confirmed this finding. The sharp melting peak of crystalline curcumin disappeared completely in the complexes, suggesting that curcumin transitioned to an amorphous state as it interacted with β -CD. The FTIR and DSC analyses of metformin HCl also demonstrated that no interactions occurred between the drug and the formulation components. In the FTIR spectrum, the characteristic bands of metformin particularly the N-H stretching and C=N vibration regions remained unchanged, with no noticeable shifts or new peak formations. This indicates that metformin did not form chemical bonds or complexes with the polymers or other excipients. Likewise, the melting peak of metformin in the DSC thermogram was preserved, showing no significant

shift or disappearance within the formulation. Taken together, these findings confirm that metformin HCl remains physically stable within the film matrix, exhibiting only simple mixing interactions with the polymers while maintaining its chemical integrity (Nikolić et al., 2023; Zarei et al., 2021).

Solubility results of the curcumin- β -CD complexes

The aqueous solubility of the inclusion complexes prepared at three different molar ratios at 25 °C are presented in Table 3.

Table 3. The aqueous solubility of the inclusion complexes and pure curcumin (n=3)

Samples	Aqueous solubility (mg/mL)
Pure curcumin	<LOQ
1:1 curcumin- β -CD inclusion complex	0.45 $\pm$ 0.05
1:2 curcumin- β -CD inclusion complex	1.17 $\pm$ 0.02
1:3 curcumin- β -CD inclusion complex	0.82 $\pm$ 0.03

LOQ: Limit of Quantification

According to solubility measurements, a significant increase in curcumin's water solubility was observed as the β -CD molar ratio increased. The 1:2 curcumin- β -CD complex showed the greatest solubility increase. While a moderate improvement in curcumin solubility was observed in the inclusion complex prepared with a 1:1 ratio, increasing the ratio to 1:3 did not result in a further increase in solubility. Therefore, the 1:2 curcumin- β -CD complex was preferred for the fast-disintegrating film formulation.

Solubility testing revealed that the highest improvement occurred at the 1:2 molar ratio. This ratio appears to provide an optimal fit between the molecular size of curcumin and the β -CD cavity. At the 1:1 ratio, the enhancement was limited, while the 1:3 ratio did not yield additional benefits. This pattern is consistent with previous reports and highlights the importance of maintaining appropriate stoichiometric balance during complex formation (Sun et al., 2024). The observed enhancement in cur-

cumin solubility is consistent with previous studies investigating curcumin- β -CD inclusion complexes. Cabrera-Quiñones et al. (2023) reported a substantial increase in aqueous solubility following complex formation with β -CD, while Mashaqbeh et al. (2021) demonstrated that cyclodextrin based inclusion systems significantly improved the dissolution behavior of curcumin. The findings obtained in the present study support these observations and confirm the suitability of β -CD complexation as an effective strategy for overcoming the poor water solubility of curcumin. The evaluation of the fast-dissolving oral films revealed clear influences of formulation variables on film performance. The HPMC E5:chitosan ratio significantly affected both tensile strength and disintegration time. HPMC E5 contributed to film robustness, whereas chitosan, being naturally more brittle, required careful balancing. The 2.5 ratio provided the most favorable compromise between strength and rapid disintegration. Increasing the plasticizer content reduced disintegration time and improved flexibility, likely due to glycerin's ability to loosen intermolecular interactions within the polymer matrix (Sarabia-Vallejo, Caja, Olives, Martín, & Menéndez, 2023). Film thickness was also a key determinant of performance. Thinner films dissolved more rapidly, while thicker films required more time for complete disintegration (Abou-Taleb et al., 2022; Steiner, Tidau, & Finke, 2022). Similar effects of polymer composition and plasticizer concentration have been reported in previous studies on fast-dissolving oral films. Shah et al. (2022) observed that increasing polymer content improved film strength but prolonged disintegration time, whereas higher plasticizer levels enhanced film flexibility and reduced brittleness. Comparable trends were observed in the present study, indicating that the balance between film-forming polymers and plasticizers is a critical determinant of oral film performance.

The three-dimensional response surface plots illustrated these relationships clearly. Significant interactions were observed, particularly between polymer ratio and plasticizer concentration. Contour plots

confirmed that small changes in factor levels could lead to noticeable differences in film behavior. The Box–Behnken models exhibited high R^2 values and statistically significant ANOVA results, supporting the reliability of the experimental design. The optimization study identified a formulation with a desirability value of 1.000, indicating excellent agreement between predicted and actual responses. A noteworthy outcome is the compatible dissolution behavior of metformin and curcumin within the same film. Curcumin, which normally exhibits low aqueous solubility, achieved rapid dissolution due to the inclusion complex. This allowed both active compounds to show similar release profiles from the film matrix. Such behavior suggests that the developed system may be useful for combination therapies requiring fast onset. The enhanced solubility of curcumin also addresses one of its major limitations and may improve its therapeutic performance in practical applications (Amalia, Nining, & Dandi, 2023; Zhao et al., 2023). The successful

application of the Box–Behnken design in this study is in agreement with previous reports demonstrating the usefulness of response surface methodology for optimizing oral film formulations. Similar optimization approaches have been employed by Kamali et al. (2022) and Shah et al. (2022), who reported that experimental design methodologies facilitate the identification of formulation variables affecting both mechanical properties and drug release performance.

Physicochemical characterization results of fast dissolving oral films

A Box–Behnken design was employed to prepare 17 oral film formulations. The independent factors were the HPMC E5:chitosan ratio, plasticizer ratio, and casting thickness, while the responses were disintegration time, tensile strength, and surface pH. Each factor was evaluated at three levels. The physicochemical evaluation results of the formulations are presented in Table 4.

Table 4. Physicochemical properties of the prepared oral film formulations

Formulations	Tensile Strength (mPa)±SD	Disintegration Time (s) ±SD	Surface pH±SD	Thickness (μm) ±SD	Weight (mg) ±SD	Metformin±SD-Curcumin±SD (%)
F1	4.5±0.5	40±1	6.4±0.1	120±2	13.1±0.1	2.1±0.1-0.20±0.05
F2	4.5±0.2	39.3±1	6.3±0.1	180±3	19.4±0.2	1.8±0.1-0.20±0.02
F3	5.0±0.1	43.9±1	6.4±0.2	180±5	19.6±0.2	1.4±0.1-0.10±0.02
F4	4.6±0.3	40.3±2	6.9±0.2	180±5	19.6±0.1	1.5±0.2-0.15±0.01
F5	6.0±0.1	52.3±1	6.6±0.1	180±2	19.7±0.1	1.6±0.2-0.25±0.01
F6	4.7±0.1	43.3±1	6.2±0.1	240±1	25.4±0.1	1.8±0.1-0.23±0.02
F7	4.2±0.3	39±0.5	6.4±0.1	240±1	26.2±0.3	1.8±0.1-0.30±0.01
F8	4.7±0.3	41±1	6.3±0.1	180±2	20.0±0.2	1.6±0.3-0.22±0.01
F9	4.8±0.1	42±1	6.5±0.2	120±3	13.5±0.2	1.5±0.2-0.27±0.02
F10	4.7±0.2	40±2	6.3±0.2	180±3	19.6±0.2	1.8±0.2-0.28±0.02
F11	4.6±0.2	40±2	6.3±0.1	180±2	19.8±0.3	1.5±0.2-0.28±0.01
F12	3.0±0.1	27±1	6.1±0.1	120±2	13.9±0.1	1.5±0.3-0.21±0.01
F13	6.0±0.3	55±1	6.5±0.1	240±3	25.8±0.1	1.9±0.3-0.25±0.01
F14	3.7±0.5	38±1	6.2±0.2	180±2	19.9±0.3	2.0±0.2-0.30±0.02
F15	5.3±0.2	52±2	6.3±0.2	240±5	25.9±0.3	2.2±0.2-0.28±0.01
F16	3.5±0.2	30±1	6.3±0.1	120±2	13.7±0.2	1.9±0.1-0.24±0.01
F17	3.3±0.4	26±1	6.1±0.1	180±2	19.5±0.2	2.0±0.1-0.24±0.02

SD: Standart Deviation

Dissolution study results

The dissolution profiles of the optimized fast-dissolving oral film formulation containing the curcumin-

inclusion complex and metformin HCl in artificial saliva are presented for both active compounds in Figure 3.

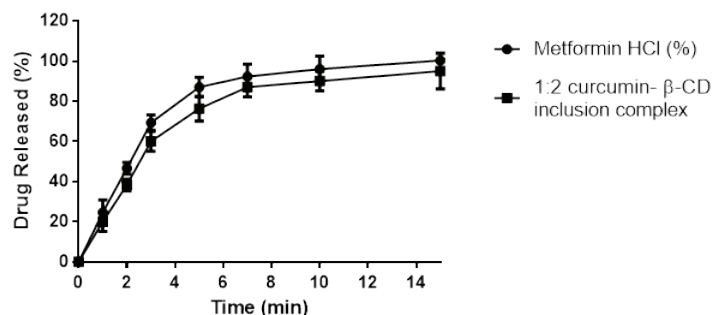


Figure 3. Dissolution profiles of curcumin- β -CD complex and metformin HCl from oral film

Response surface methodology (RSM) and Box–Behnken design results

Based on the physicochemical results of the fast-dissolving oral films (Table 3.), the effects of the independent formulation factors on the measured re-

sponses were evaluated. The statistical outcomes and model adequacy parameters obtained from ANOVA are presented in Table 5. Figure 4 presents the contour plots, while Figure 5 shows the 3D surface plots, which visualize how each response changes across the experimental design space.

Table 5. ANOVA results and model adequacy parameters for the fitted response surface models

Response 1: Disintegration time (s)						
Source	Sum of squares	Mean Square	F-value	p-value	Lack of peak p-value	Predicted R ²
Model	1007.99	112.00	348.44	<0.0001	0.9136	0.9136
A-HPMC E5:Chitosan ratio	496.13	496.13	1543.50	<0.0001		
B-Plasticizer ratio	190.12	190.12	591.50	<0.0001		
C-Casting thickness	312.50	312.50	972.22	<0.0001		
Response 2: Tensile strength						
Source	Sum of squares	Mean Square	F-value	p-value	Lack of peak p-value	Predicted R ²
Model	10.88	1.81	174.10	<0.0001	0.1786	0.9848
A-HPMC E5:Chitosan ratio	7.28	7.28	698.73	<0.0001		
B-Plasticizer ratio	1.10	1.10	105.87	<0.0001		
C-Casting thickness	2.35	2.35	226.07	<0.0001		
Response 3: Surface pH						
Source	Sum of squares	Mean Square	F-value	p-value	Lack of peak p-value	Predicted R ²
Model	0.3701	0.1234	557.22	<0.0001	0.7006	0.9905
A-HPMC E5:Chitosan ratio	0.3403	0.3403	1537.23	<0.0001		
B-Plasticizer ratio	0.0153	0.0153	69.17	<0.0001		
C-Casting thickness	0.0144	0.0144	65.27	<0.0001		

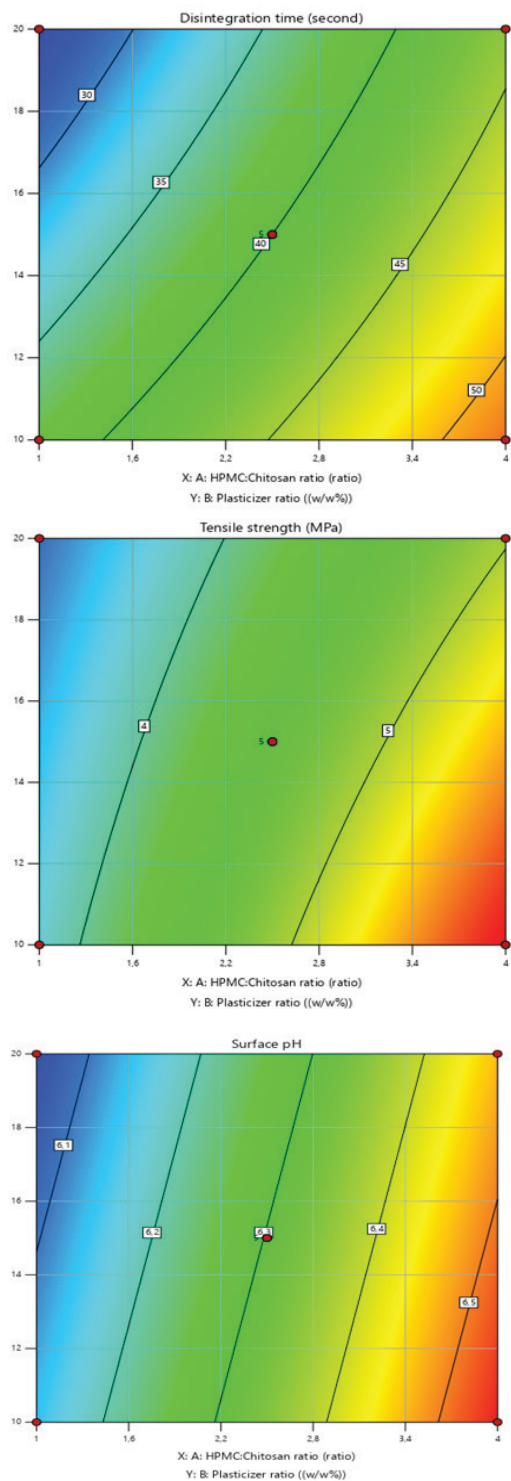


Figure 4. Contour graphs

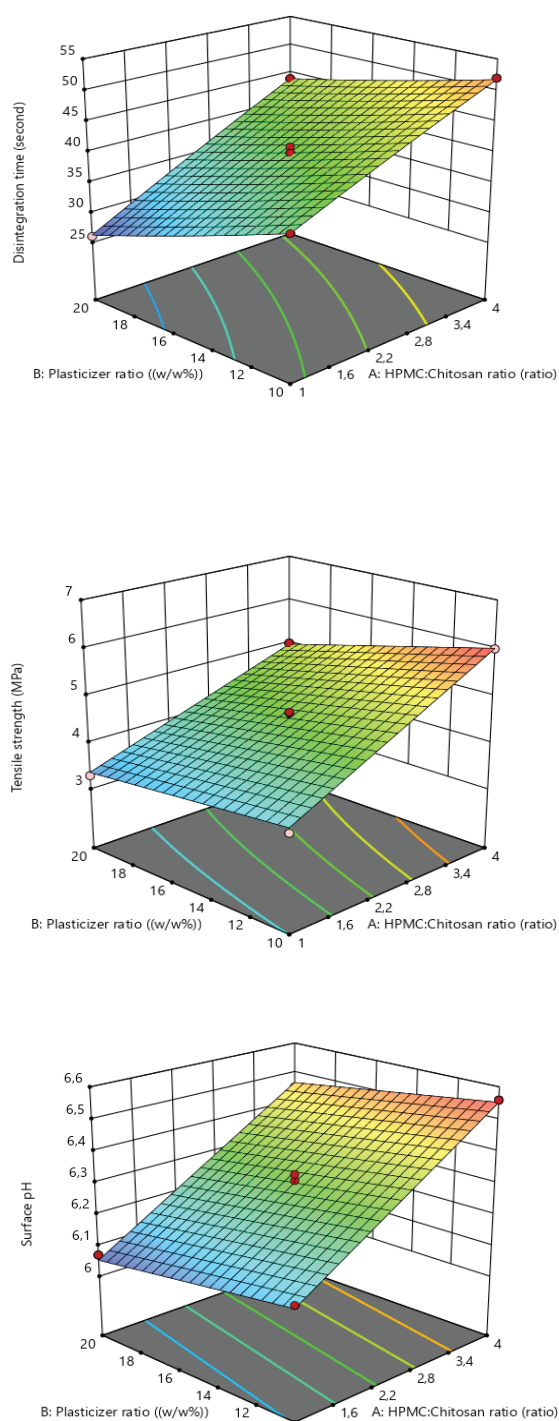


Figure 5. 3D surface graphs

Model equations

The experimental data were fitted to a second-order polynomial model, and the coded equations for the three responses (dependent variables) are given below:

Disintegration time (Y_1):

$$Y_1 = 40.0 + 7.88A - 4.87B + 6.25C + 1.00AB + 0.25AC + 0.25BC - 0.25A^2 + 0.25B^2 + 1.00C^2$$

Tensile strength (Y_2):

$$Y_2 = 4.54 + 0.95A - 0.37B + 0.54C - 0.15AB - 0.005AC + 0.12BC$$

Surface pH (Y_3):

$$Y_3 = 6.30 + 0.20A - 0.04B - 0.04C$$

In the equation; A represents the HPMC E5:Chitosan ratio, B represents the Plasticizer ratio, and C represents the casting thickness. When the design of experiment results were evaluated statistically, the optimal film formulation was identified as the one containing a 2.5 HPMC E5:chitosan ratio, 15% plasticizer (glycerin), and a casting thickness of 180 μm , with a desirability value of 1000.

Stability study results

Table 6 presents the results of the accelerated stability study for the optimized film formulation.

Table 6. Stability study results of the optimized fast-dissolving oral film

Parameter	Initial	1 month	3 months	Acceptance Criteria	Interpretation
Appearance	Smooth, uniform, no cracks	No change	No change	No discoloration, no cracking or sticking	Pass
Surface pH	5.7 ± 0.1	5.7 ± 0.1	5.8 ± 0.1	5.5–6.8	Pass
Disintegration time (s)	29 ± 2	30 ± 2	31 ± 3	≤ 45 s; ≤ 10 –20% deviation	Pass

The optimized film maintained its physical integrity and drug content over three months of accelerated stability testing. No significant changes were observed in thickness, surface pH and disintegration time. These findings confirm that the formulation is stable under ICH recommended conditions (Cupone, Sansone, Marra, Giori, & Jannini, 2022; Olechno, Basa, & Winnicka, 2021). Overall, the study confirms that the inclusion complexes and film formulations were successfully developed. The films exhibited rapid disintegration, consistent drug content, acceptable mechanical strength and improved solubility for curcumin. These results contribute to the growing field of fast-dissolving oral films and demonstrate the value of using response surface methodology for formulation optimization. The dual-drug film system developed here provides a solid foundation for future research on rapid-release dosage forms incorporating poorly soluble compounds.

CONCLUSION

This study demonstrated that fast-dissolving oral films containing metformin HCl and curcumin- β -CD

inclusion complexes can be successfully formulated using HPMC E5 and chitosan. All films met the essential quality requirements, showing acceptable thickness, mass uniformity, surface pH, mechanical strength, and drug content. Characterization results confirmed the formation of stable curcumin- β -CD complexes with markedly improved solubility, especially at the 1:2 molar ratio. The Box-Behnken design and RSM analysis highlighted that polymer ratio, plasticizer content, and casting thickness strongly influenced disintegration time and tensile strength, while surface pH remained unaffected. The 3D response surfaces helped identify the formulation ranges that provide fast disintegration without compromising mechanical integrity. Overall, the optimized films offer a promising and patient-friendly platform for rapid oral delivery, combining improved solubility with quick disintegration and suitable mechanical performance.

Future studies should focus on evaluating the in vivo performance, mucoadhesive behavior, and therapeutic efficacy of the optimized oral film formulation

in relevant periodontal models. Furthermore, clinical investigations may help to confirm its potential as a patient-friendly platform for localized periodontal drug delivery.

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AUTHOR CONTRIBUTION STATEMENT

As this was a single-authored manuscript, all stages of the study, including conception, implementation, data collection, evaluation, and manuscript preparation, were carried out by EDÖ.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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