FABAD J. Pharm. Sci., 50, 3, 513-530, 2025
Doi: 10.55262/fabadeczacilik.1766297
RESEARCH ARTICLE

Development and Characterization of a Fixed-Dose Orodispersible Film of Telmisartan and Indapamide for Enhancing Dissolution

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Development and Characterization of a Fixed-Dose Orodispersible Film of Telmisartan and Indapamide for Enhancing Dissolution

SUMMARY

Fixed-dose combination (FDC) of antihypertensive drugs improves efficacy, safety and patient adherence over monotherapy. However, an FDC of telmisartan (TEL) and indapamide (IND), both poorly soluble BCS Class II drugs, has not been available yet. This study aimed to develop an orodispersible film (ODF) containing TEL and IND cyclodextrin (CD) inclusion complexes (ICs) to enhance solubility and improve patient adherence. In the first phase of the study, phase-solubility analysis was performed with β-CD, then the ICs were prepared via kneading and assessed for solubility enhancement and entrapment efficiency. In the second phase, ICs were incorporated into hydroxypropyl-methylcellulose (HPMC) based ODFs using solvent casting. The films were characterized for thickness, mass, and content uniformity, surface pH, water content, folding endurance, Young's modulus, FTIR, in vitro disintegration, and dissolution. AL-type phase-solubility plots confirmed 1:1 complexation and enhanced solubility by 1.7–4.1 fold, with entrapment efficiency >95%. ICs-loaded ODFs were thin (0.138 mm), uniform in mass (236.39 mg) and content (TEL 97.22%, IND 102.09%), nearly neutral pH, and low in water (2.68%). Mechanical testing showed adequate flexibility and stiffness (100 N/mm² modulus). Disintegration occurred in <35 s. Dissolution exceeded 90% for both drugs within 15 minutes in 6.8 phosphate buffer, whereas in 0.1N HCl, TEL showed complete release in 15 minutes and IND reached 97% after 20 minutes. In conclusion, TEL and IND ICs–loaded HPMC ODFs successfully overcame solubility limitations, offering an immediate-release formulation across the gastrointestinal pH range with favorable physicochemical properties and potential to improve patient adherence.

Keywords: *Solubility Enhancement, Fixed-Dose Combinations, Orodispersible Film, Cyclodextrin, Telmisartan, Indapamide.*

Çözünürlüğü Artırmaya Yönelik Telmisartan ve İndapamid İçeren Sabit Dozlu Bir Ağızda Dağılan Filmin Geliştirilmesi ve Karakterizasyonu

ÖZ

Antihipertansif ilaçların sabit-doz kombinasyonları (SDK), monoterapiye kıyasla tedavi etkinliğini, güvenliğini ve hasta uyumunu artırmaktadır. Ancak, her ikisi de düşük çözünürlüğe sahip BCS Sınıf II ilaçlar olan telmisartan (TEL) ve indapamid (IND)'i birlikte içeren bir SDK formülasyonu henüz mevcut değildir. Bu çalışma, TEL ve IND'nin siklodekstrin (SD) inklüzyon komplekslerini (İK) içeren bir ağızda dağılan film (ADF) formülasyonu geliştirerek çözünürlüğü artırmayı ve hasta uyumunu desteklemeyi amaçlamıştır. Çalışmanın ilk aşamasında, β-SD faz-çözünürlük analizi gerçekleştirilmiş, ardından İK'ler yoğurma yöntemiyle hazırlanmış ve çözünürlük artışı ile enkapsülasyon etkinliği açısından değerlendirilmiştir. İkinci aşamada, İK'leri hidroksipropil-metilselüloz (HPMC) bazlı ADF'lerle çözücü döküm yöntemiyle birleştirilmiştir. Hazırlanan filmler; kalınlık, kütle ve içerik tekdüzeliği, yüzey pH'sı, su içeriği, katlanma dayanıklılığı, Young modülü, FTIR, in vitro dağılma ve çözünme özellikleri bakımından karakterize edilmiştir. AL-tip faz-çözünürlük grafikleri, 1:1 kompleks oluşumunu doğrulamış ve çözünürlüğü 1,7–4,1 kat artırmış; enkapsülasyon etkinliği ise %95'in üzerinde bulunmuştur. İK yüklü ADF'ler ince yapılı (0,138 mm), kütle (236,39 mg) ve içerik bakımından tekdüze (TEL %97,22, IND %102,09), neredeyse nötr pH'lı ve düşük su içeriğine sahip (%2,68) bulunmuştur. Mekanik testler, yeterli esneklik ve rijitlik göstermiştir (100 N.mm^{-2} modül). Filmler 35 saniyeden kısa sürede dağılmış, 6,8 fosfat tamponunda her iki ilaç da 15 dakika içinde %90'dan fazla çözünme göstermiştir. 0,1N HCl ortamında TEL 15 dakikada tamamen salınırken, IND 20 dakikada %97'ye ulaşmıştır. Sonuç olarak, TEL ve IND İK yüklü HPMC ADF'ler, çözünürlük sınırlamalarını aşarak gastrointestinal pH aralığında hızlı salım sağlayan, uygun fizikokimyasal özelliklere sahip ve hasta uyumunu artırma potansiyeli bulunan bir dozaj formu olarak başarılı şekilde geliştirilmiştir.

Anahtar Kelimeler: *Çözünürlük Artırma, Sabit Doz Kombinasyonları, Ağızda Dağılan Film, Siklodekstrin, Telmisartan, İndapamid.*

Recieved: 16.08.2025
Revised: 6.09.2025
Accepted: 6.09.2025

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INTRODUCTION

Hypertension is a chronic condition characterized by elevated arterial blood pressure, and it is a leading cause of cardiovascular disease. Today, hypertension has become one of the most prevalent global chronic diseases. Therefore, it represents a significant worldwide public health problem and a leading risk factor for mortality (Zhou et al., 2021). Currently, hypertension can be effectively controlled with low-cost pharmacological treatments. As recommended in the recent guidelines, most hypertension patients require more than one antihypertensive medication to achieve blood pressure control. However, this leads to a high medication burden and complex therapy, resulting in reduced medication adherence and uncontrolled blood pressure symptoms. Various initiatives implemented at the global, regional, and national levels increasingly recommend fixed-dose combinations (FDCs), which combine two or more active pharmaceutical ıngredients (APIs) in a single dosage form, to enhance treatment efficacy, simplify regimens, and improve patient adherence (An et al., 2020). According to the European Medicines Agency (EMA) guideline for the clinical development of fixed-dose combinations (EMA/CHMP/158268/2017), compared to monotherapy, FDCs can provide a more rapid, potent therapeutic effect, reduce adverse effects, and improve compliance by simplifying drug administration (EMA, 2017). For these reasons, the development of FDC formulations is supported by a strong scientific and clinical rationale. One of the adopted strategies in clinical practice is the FDC of an angiotensin receptor blocker (ARB) with a thiazide or thiazide-like diuretic (Coca, Whelton, Camafort, López-López, & Yang, 2024). However, there are no existing dual FDC products containing an ARB, telmisartan (TEL), and a thiazide-like diuretic, indapamide (IND) (Figure 1). In a notable recent advancement, in 2025, the Food and Drug Administration (FDA) approved a fixed-dose triple-combination tablet comprising telmisartan, amlodipine, and indapamide (WIDAPLIK^{TM}) for the management of hypertension, including as an initial therapeutic option (FDA, 2025).

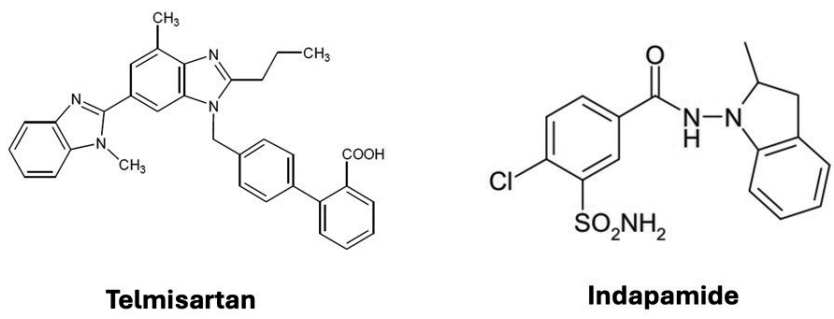

Figure 1. The chemical structures of telmisartan and indapamide.

TEL is a widely prescribed antihypertensive agent classified as a non-peptide angiotensin II receptor blocker. According to the biopharmaceutics classification system (BCS), it belongs to class II, displaying high membrane permeability but low aqueous solubility (Battershill & Scott, 2006). Therefore, various formulation strategies have been attempted to enhance its solubility and systemic exposure, including solid dispersions (Turek, Gach-Janczak, Różycka-Sokołowska, Owsianik, & Bałczewski, 2025), nano-microparticles (Ha et al., 2024), self-emulsifying drug-delivery systems (Park et al., 2021), cocrystals (Dhibar et al., 2023), and cyclodextrin (CD) inclusion complexes (ICs) (Sharapova, Ol'khovich, & Blokhina, 2025). Likewise, although a thiazide-like diuretic, IND is well tolerated, clinically effective, and supported by a long history of therapeutic use. However its poor aqueous solubility remains a major impediment to optimal efficacy and

bioavailability. Because of its limited water solubility, IND is classified as BCS class II. Amorphous forms of IND have been developed as a potential approach to enhance its aqueous solubility; however, the inherent complexity of the amorphization process and the risk of residual solvents substantially limit their practical application (Cong et al., 2021; Wojnarowska et al., 2013). Taken together, there is a need to develop innovative strategies to enhance the dissolution of TEL and IND, thereby improving their oral bioavailability. Enhancing the solubility of BCS Class II drugs is a key strategy to overcome these limitations and improve oral bioavailability. Therefore, from past to present, a range of conventional methods such as super-critical fluid technology, cryogenic techniques, particle-size reduction, salt formation, and solid dispersion have been employed to enhance the solubility of these drugs, while newer approaches like vesicular systems, nanotechnological strategies, and cyclodextrin inclusion complexes have also been adopted in recent years (Kumari et al., 2023). Among these approaches, CD ICs have emerged as a prominent method in the pharmaceutical industry due to their versatility and safety in improving not only the solubility but also the stability and bioavailability of poorly water-soluble drugs. For example, in a recent study, Sharapova et al. showed that ICs of TEL with hydroxypropyl-β-cyclodextrin (HP-β-CD) and sulfobutylether-β-cyclodextrin (SBE-β-CD) improved its aqueous solubility by 23-fold and 7-fold, respectively, confirming the potential of cyclodextrins in enhancing poorly soluble drugs (Sharapova et al., 2025). However, studies on indapamide cyclodextrin systems remain scarce. To date, only a limited number of studies have described such complexes (Radi & Eissa, 2011).

Conventional oral dosage forms such as tablets and capsules have been widely used in the clinical management of diverse diseases because of their non-invasive nature, suitability for self-administration, long shelf life, and straightforward manufacturing processes. This condition also applies to FDC products used in hypertension management, the majority of which are administered in tablet form (Lesutan, Andersen, & Lamprou, 2025). However, today, orodispersible films (ODFs) thin polymeric strips that disperse on the tongue within seconds have gained interest as an alternative to traditional tablets due to their attractive advantages. Due to their ability to rapidly disintegrate in saliva without the need for chewing, ODFs improve medication intake in both populations with dysphagia, such as geriatric patients, and the general population. Their rapid disintegration also facilitates drug dissolution and absorption, less first-pass metabolism, resulting in faster onset of action and potentially higher bioavailability (Morath, Sauer, Zaradzki, & Wagner, 2022). These attributes are especially valuable for BCS II drugs whose clinical performance is dissolution-limited (Islam et al., 2023).

Based on these considerations, the present study aimed to develop and characterise an ODF as a dual FDC containing telmisartan β-CD and indapamide β-CD ICs. Complexation with β-CD and incorporating into a single ODF formulation of both BCS Class II antihypertensives is intended to overcome the dissolution limitations that constrain their oral bioavailability while simultaneously enhancing treatment adherence for elderly hypertensive patients who experience difficulty swallowing conventional tablets.

MATERIALS AND METHODS

Materials

Indapamide was a kind gift from ILKO Pharmaceuticals, Turkey. Telmisartan was kindly provided by Nobel Pharmaceutical Industry, Turkey. β-CD was purchased from Wacker Chemie AG as pharmaceutical-grade products (Cavamax® W7 Pharma). HPMC (hydroxypropylmethyl cellulose) was supplied by Shin-Etsu Chemical. Glycerin was obtained from Sigma-Aldrich. All other chemicals were of analytical grade. Purified water was utilized during the study.

Methods

Construction of a Calibration Curve of Telmisartan and Indapamide

Spectrophotometric analysis of TEL and IND in

the formulations and *in vitro* dissolution samples was performed using a Shimadzu UV-Vis spectrophotometer (UV-1800). To determine the maximum absorption wavelengths (λmax), stock solutions of each API were prepared at a concentration of 100 µg/mL in two different solvents: 6.8 phosphate buffer and 0.1 N HCL. From these stock solutions, appropriate dilutions were made in volumetric flasks to obtain final concentrations of 10 µg/mL for TEL and 6 µg/mL for IND. These solutions were scanned in the UV range of 200–400 nm, and TEL exhibited a maximum absorbance at 295 nm, while IND showed maximum absorbance at 240 nm. At these λmax values, calibration curves were constructed by preparing a series of dilutions ranging from 1 to 12 µg/mL for IND and from 4 to 16 µg/mL for TEL in both pH 6.8 phosphate buffer and 0.1 N HCl. The absorbance values of each dilution were spectrophotometrically measured at their respective λmax. Based on the obtained absorbance and concentration data, two separate calibration curves were plotted for each API, and linear least-squares regression analysis was performed for all calibration curves.

Phase Solubility Studies

Phase solubility studies were carried out in accordance with the method of Higuchi and Connors to evaluate the effect of β-CD on the solubility of TEL and IND and assess ICs' molecular stoichiometry (Higuchi & Connors, 1965). In a pH 6.8 phosphate buffer, β-CD solutions were prepared at concentrations of 3, 6, 9, 12, 15, and 18 mM, and an excess amount of either TEL or IND was added to each solution. All β-CD concentrations were carried out in triplicate. The resulting suspensions were agitated in a thermostatted shaking water bath at 300 rpm and 37 ± 2°C for 24 h to reach equilibrium. After 24 h, samples were centrifuged at 10,000 rpm for 15 minutes, and the supernatants were filtered through 0.45 µm Polytetrafluoroethylene (PTFE) syringe filters. Drug concentrations in appropriately diluted filtrates were measured spectrophotometrically against corresponding β-CD blank solutions. Phase-solubility diagrams were constructed by plotting the measured TEL and IND concentrations (mM) versus β-CD concentration (mM). The intrinsic solubility (S_0) of TEL and IND in the absence of β-CD (0 mM) was obtained from the y-intercept of the linear portion of the plot. According to Higuchi and Connors' method, apparent stability constants (K_s) can be calculated from the slope and intercept (S_0) of phase solubility curves using Equation (1):

$$Ks = \frac{Slope}{S_0 \times (1 - slope)} \qquad (1)$$

Preparation of Inclusion Complexes and Physical Mixture

Inclusion complexes of the TEL and IND with β-CD were prepared using a modified kneading method, based on the 1:1 molar ratios previously determined from phase solubility studies (Khan et al., 2020). Briefly, the accurately weighed β-CD and API, in a 1:1 molar ratio, were triturated in a mortar. A water : ethanol (1:1 v/v) mixture was then slowly added dropwise to this mixture, with continuous stirring, until a homogeneous paste consistency was obtained. The resulting paste was subsequently dried at room temperature until a solid mass formed. Once dried, the mass was pulverized into a fine powder and then passed through an 80 µm sieve to ensure a uniform particle size distribution. The obtained ICs were then stored at room temperature in a desiccator and protected from light until further use. The physical mixtures were obtained by simple homogenization of host (β-CD) and guest (TEL or IND) powders, using a spatula for 5 minutes, in a 1:1 molar ratio. The samples were stored at room temperature in a desiccator and protected from light.

Characterization of Inclusion Complexes

Solubility Analysis

Solubility studies of ICs were conducted in both medium: purified water and pH 6.8 phosphate buffer, at room temperature, to evaluate the enhancement in solubility of TEL and IND through inclusion complexation. Excess amounts of TEL β-CD and IND β-CD inclusion complexes were added to 10 mL of

each medium, and the suspensions were applied to the same procedure used in the phase-solubility studies. After equilibration and filtration, the concentration of solubilized TEL and IND was determined spectrophotometrically (n = 3).

Determination of Entrapment Efficiency

To determine the amount of TEL and IND entrapped in the ICs, 30 mg of each IC was accurately weighed and dissolved in their respective optimal solvents, 0.1 M NaOH for TEL and ethanol for IND, using 10 mL volumetric flasks. Obtained solutions were agitated on a horizontal shaker for 4 hours to ensure complete dissolution. Afterward, each solution was filtered through a 0.45 µm PTFE syringe filter. Appropriate dilutions were made and the drug content analysed spectrophotometrically. All measurements were performed in triplicate for each IC sample. The entrapment efficiency (EE%) was calculated based on the measured TEL and IND concentrations using the following Equation (2) (Al-Heibshy, Başaran, Öztürk, & Demirel, 2020).

$$EE\,\% = \frac{The\ measured\ amount\ of\ drugin\ ICs}{Initial\ Drug\ Content} \times 100 \quad (2)$$

Preparation of Orodispersible Film

ODF formulations were developed using the solvent casting method, based on previously reported methods, with hydroxypropyl methylcellulose (HPMC) as the film-forming polymer and glycerin as the plasticizer (Yin et al., 2024). To determine polymer and plasticizer ratios, blank ODF formulations were initially prepared by testing various concentrations of HPMC and glycerin. The resulting blank ODFs were evaluated in terms of thickness, uniformity of mass, folding endurance, and disintegration time. Based on the results, the optimal concentrations were determined as 11.42 mg/cm² for HPMC and 5.71 mg/cm² for glycerin. After determining the polymer and plasticizer ratios, blank and TEL and IND β-CD ICs loaded ODFs were prepared as follows. An appropriate amount of HPMC was added to purified water in a beaker and allowed to swell overnight under gentle stirring. The required amount of glycerin was then added dropwise to the swollen polymer solution with gentle stirring. In ICs loaded ODF, after the addition of glycerin, TEL β-CD ICs equivalent to a 40 mg/film dose of TEL and IND β-CD ICs equivalent to a 1.5 mg/film dose of IND were incorporated into the casting solution and stirred magnetically until complete dissolution. To remove air bubbles, the final casting solution was degassed by ultrasonication for 15 minutes. Then, the solution was cast onto petri plates and dried in an oven at 40°C for 48 hours to form thin films. Peeled films were cut into 2 × 3 cm pieces (6 cm² per film). The individual film pieces were wrapped in aluminum foil and stored in a desiccator until further use.

Characterization of Orodispersible Film

Thickness

Blank and ICs loaded ODF were cut into 3 × 2 cm (6 cm²) specimens for thickness determinations. Subsequently, ten film pieces were randomly selected, and each specimen was measured with a micrometer at five points: the four corners and the centre (Visser et al., 2017). The mean value and corresponding standard deviation were calculated for all measurements.

Uniformity of Mass

Uniformity of mass was assessed in accordance with the European Pharmacopoeia (9th edition, method 2.9.5), uniformity of mass for single-dose preparations. Twenty ICs-loaded ODFs were randomly selected and individually weighed using an analytical balance. The mean mass of the films was then calculated to evaluate uniformity.

Surface pH

To determine the surface pH, six blank and ICs-loaded ODFs were randomly selected. Since the pH of the dry films could not be measured directly, each film was first moistened with 2 mL of distilled water in a petri dish. The electrode of the pH meter was then placed in contact with the surface of the hydrated film at room temperature, and the pH value was recorded (Oudah & Al-Khedairy, 2025).

Water Content

Water content is a critical parameter in determining the hygroscopic nature of the film. In this study, the water content of three individual ODFs was measured using a moisture analyzer (OHAUS MB120) at 50 °C, and the measurement was continued until a constant film weight was obtained. Water content percent was calculated as per the following equation (3):

$$Water\ content\ \% = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100 \quad (3)$$

Content Uniformity

Content uniformity analysis was performed to assess whether each film contained a consistent amount of API. Ten randomly selected TEL and IND ICs loaded ODFs were tested for uniformity of content for single-dose preparations in accordance with the European Pharmacopoeia 9th edition (method 2.9.6). For this purpose, each selected film was dissolved in phosphate buffer (pH 6.8), and appropriate dilutions were made. The drug content was then analyzed using UV spectrophotometry at 295 nm for TEL and 240 nm for IND.

Folding Endurance

For the folding-endurance test, three films from blank and IC-loaded ODFs were repeatedly folded 180° at the same point until breakage occurred. The number of folds required to break the film was recorded as the folding-endurance value (Khan et al., 2020).

Mechanical Properties – Young's Modulus

The mechanical properties of the blank and IC-loaded ODFs were evaluated using a Dynamic Mechanical Analyzer (DMA 8000, PerkinElmer). Based on the obtained stress–strain curves, Young's modulus values were calculated.

Fourier Transform Infrared Spectroscopy (FTIR) Analysis

Fourier-transform infrared (FTIR) spectroscopy was employed to perform physicochemical characterization of both the cyclodextrin inclusion complexes and the orodispersible film formulations. Samples of pure telmisartan, indapamide, β-CD, the corresponding inclusion complexes, and physical mixtures of β-CD with each pure drug were analyzed. Additionally, for the ODF formulation, samples of HPMC, glycerin, blank and, ICs-loaded ODF formulations were also examined. All infrared spectra were recorded over the 4000–400 cm^{-1} range using a Bruker Vertex 70 IR spectrophotometer equipped with an attenuated transmittance reflectance.

Disintegration Time

The disintegration time of the blank and ICs-loaded ODFs was evaluated using two different methods: the petri dish and drop method (n:6). In the petri-dish method, 2 mL of purified water was added to a petri-dish, and the ODF was carefully placed onto the surface without agitation. The time required for the film to start disintegrating was recorded as the disintegration time. In the drop method, a single drop of purified water was applied onto the center of the ODF using a pipette. The time taken for the drop to form a visible hole in the film was measured (Pezik, Gulsun, Sahin, & Vural, 2021).

***In Vitro* Dissolution**

In vitro dissolution studies of TEL–β-CD and IND–β-CD ICs loaded ODF were conducted based on the USP 42–NF 37 monographs of telmisartan and indapamide using a Pharma Test PTWS 120D dissolution tester (Germany). Two different dissolution media were selected to comply with the pharmacopeial requirements for both APIs: 0.1 N HCL and phosphate buffer at pH 6.8. Each test was performed in 900 mL of dissolution medium using the USP Apparatus II (paddle method) at 37 °C and 75 rpm for 45 minutes and repeated in triplicate. At predetermined time intervals, 5 mL aliquots were withdrawn from the medium and immediately replaced with an equal volume of fresh dissolution medium to maintain sink conditions. The collected samples were analyzed using UV spectrophotometry at 295 nm for TEL and 240 nm for IND.

RESULTS AND DISCUSSION

Construction of a Calibration Curve of Telmisartan and Indapamide

According to the literature, the maximum wavelengths for TEL and IND were determined to be 295 nm and 240 nm, respectively (Chavhan, Lawande, Salunke, Ghante, & Jagtap, 2013; Tarkase Kailash, Jadhav Manisha, Tajane Sachin, & Dongare Umesh, 2012). At these wavelengths, there is no interaction or overlap between TEL and IND. At these wavelengths, calibration curves were constructed over the concentration range of 1 to 12 µg/mL for IND and 4 to 16 µg/mL for TEL in 6.8 phosphate buffer and 0.1 N HCL (Figure 2). The calibration curves for TEL and IND, generated in phosphate buffer (pH 6.8) and in 0.1 N HCl, exhibited excellent linearity with high correlation coefficients. Under buffered conditions, TEL showed a slope of 0.0483 with an intercept of 0.0131 (R^2 = 0.9996), while IND displayed a slope of 0.0575 with an intercept of 0.0176 (R^2 = 0.9996) (Figure 2a). In 0.1 N HCl, TEL's slope remained essentially unchanged at 0.0484 (intercept = 0.0157, R^2 = 0.9996), and IND's slope increased slightly to 0.0595 (intercept = 0.0023, R^2 = 0.9991) (Figure 2b). These findings confirm that both APIs comply with Beer's law over the tested concentration ranges, and the high linearity of the calibration curves underscores the suitability of the assay.

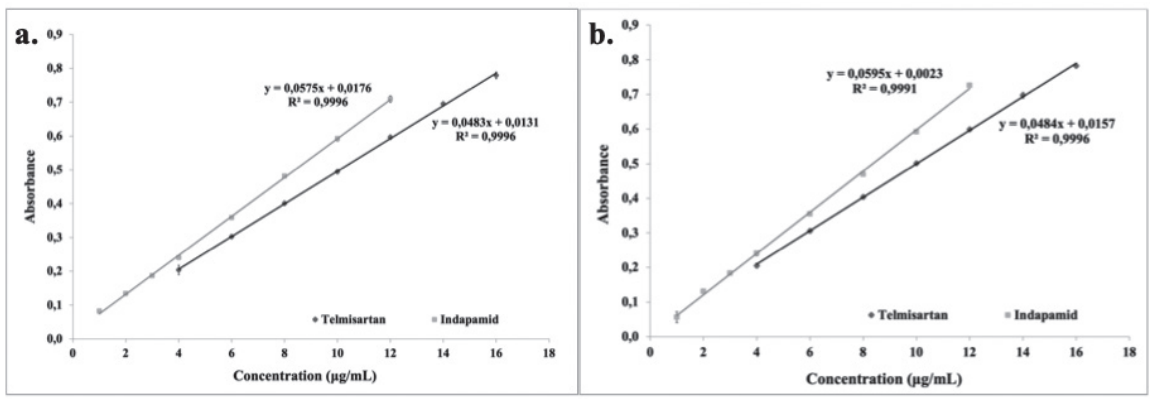

Figure 2. The calibration curve of TEL and IND in (a) phosphate buffer pH 6.8 and (b) 0.1 N HCl.

Phase Solubility Studies

Phase-solubility studies revealed the stoichiometric ratios, apparent stability constants, and complexation efficiencies of TEL and IND when complexed with β-CD. Figure 3 shows the phase-solubility diagrams of TEL and IND, plotted as solubilized drug concentration versus β-CD concentration. A similar phase-solubility profile was observed for both APIs, with the solubility of TEL and IND increasing linearly as the β-CD concentration increased from 0.0 to 18 mM. This increased solubility confirmed the existence of intermolecular interactions between host and guest molecules. High correlation coefficients, R^2 = 0.9761 for TEL and R^2 = 0.9821 for IND, of both plots confirmed strong linearity and exhibited AL-type phase-solubility behavior according to the Higuchi–Connors classification. As shown in Figure 3, the slopes of the TEL β-CD (0.0006) and IND β-CD (0.0216) curves are both less than unity, indicating the formation of 1:1 stoichiometric ICs with β-CD (Jambhekar & Breen, 2016). Apparent stability constants (K_s) indicate the binding affinity between guest molecules and cyclodextrin. The calculated K_s values of 305.4 M^{-1} for TEL and 121.5 M^{-1} for IND fall within the typical 50–5000 M^{-1} range, indicating the formation of strong 1:1 ICs with β-CD, thereby resulting in enhanced aqueous solubility (Örgül, 2024).

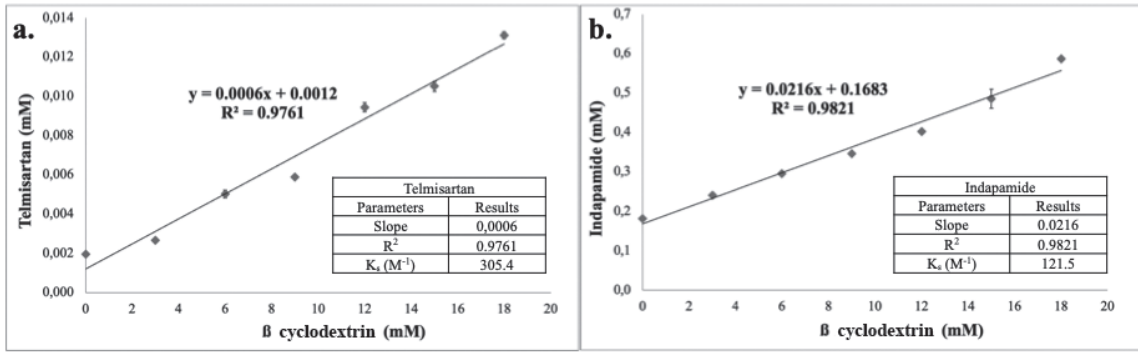

Figure 3. Phase-solubility diagrams of (a) telmisartan and (b) indapamide with β-cyclodextrin.

Characterization of Inclusion Complexes

Table 1 summarizes the solubility of TEL and IND both as free drugs and as β-CD ICs in two biorelevant media: purified water and pH 6.8 phosphate buffer. As expected for BCS Class II drugs, TEL and IND exhibited limited aqueous solubility; telmisartan dissolved to 0.79 ± 0.1 μg mL^{-1} in purified water and 1.01 ± 0.10 μg mL^{-1} in buffer, whereas indapamide reached 78.65 ± 2.30 μg mL^{-1} and 63.53 ± 2.10 μg mL^{-1}, respectively. Complexation with β-CD markedly improved these values. The TEL β-CD ICs achieved solubilities of 2.52 ± 0.7 μg mL^{-1} in water and 4.19 ± 0.1 μg mL^{-1} in buffer, corresponding to 3.2 and 4.1-fold increases over the free drug. Although the relative enhancement for IND was more moderate, it remained significant. IND β-CD ICs yielded 136.87 ± 5.2 μg mL^{-1} in purified water and 120.33 ± 4.9 μg mL^{-1} in buffer, representing 1.74 and 1.89 fold increases, respectively.

These solubility increases corroborate the well-established mechanism whereby cyclodextrins form soluble inclusion complexes by encapsulating poorly water-soluble drug molecules within their hydrophobic cavities. However, the magnitude of solubility enhancement differed between the two APIs due to their distinct physicochemical properties. TEL is a highly lipophilic molecule with log P about 7, therefore it exhibits strong affinity for the hydrophobic cavity of β-cyclodextrin (β-CD), resulting in a higher stability constant (K_s) and, consequently, a more pronounced increase in solubility (Ruiz Picazo et al., 2018). By contrast, IND has a polar sulfonamide group that imparts a degree of intrinsic aqueous solubility and limits the relative impact of solubility enhancement by complexation (Wojnarowska et al., 2013). Additionally, both APIs exhibited distinct solubility values in purified water and pH 6.8 phosphate buffer, both as free drug and β-CD ICs. These variations arise from their well-known pH-dependent solubility profiles and align with values previously reported in the literature (Ruiz Picazo et al., 2018; Wojnarowska et al., 2013). Entrapment efficiency values were 98.88 ±0.7 % for the TEL β-CD ICs and 95.67±0.3 % for IND β-CD ICs. These high EE values confirm that the guest molecules were successfully accommodated within the β-CD cavity and, demonstrate the effectiveness of the kneading method in achieving near-complete drug entrapment.

Table 1. Entrapment efficiency and solubility results of ınclusion complexes. Each value represents the mean standard deviation (n = 3).

APIs and Their β-CD ICs	Solubility (μg mL^{-1})		Entrapment Efficiency %
	Purified Water	pH 6.8 Phosphate Buffer	
Telmisartan	0.79±0.1	1.01±0.1	-
Telmisartan β-CD ICs	2.52±0,7	4.19±0.1	98.88 ±0.7 %
Indapamide	78.65±2.3	63.53±2.1	-
Indapamide β-CD ICs	136.87±5.2	120.33±4.9	95.67±0.3 %

Characterization of Orodispersible Film

ODFs are thin, fast-dissolving drug delivery systems designed to improve ease of administration and distinguished from other solid dosage forms by their rapid disintegration properties. In the present study, an HPMC-based ODF containing FDCs of TEL and IND was successfully prepared using the solvent-casting method. HPMC was selected because it offers superior mechanical strength, dissolution performance, and drug-loading capacity compared with many alternative film formers. Therefore, along with HPC, HPMC is one of the two most commonly used film-forming polymers in ODF formulations (Rani et al., 2021; Takeuchi, Umemura, Tahara, & Takeuchi, 2018). Using HPMC as a film-forming polymer and glycerin as a plasticizer, the resulting TEL–β-CD and IND–β-CD ICs loaded ODF was smooth, flexible, and visually homogeneous, confirming the suitability of the formulation and manufacturing approach for orodispersible applications. The prepared ODF formulations were characterized in terms of thickness, uniformity of mass and content, surface pH, water content, folding endurance, Young's modulus, FTIR analysis, disintegration time, and *in vitro* dissolution (Table 2).

Thickness

Film thickness is a key parameter affecting the disintegration time and mechanical properties of the ODF. Similar to previously reported ODF thickness values, all films in this study exhibited thicknesses within the mean range of 0.138–0.140 mm (Vlad et al., 2023). The thickness of the ICs loaded ODFs (0.138 ± 0.009 mm) and the blank ODFs (0.140 ± 0.008 mm) was found to be similar, indicating that the incorporation of ICs into the polymeric matrix did not significantly affect the film thickness. The solvent casting method produced films with uniform and reproducible thickness, suitable for orodispersible applications.

Uniformity of Mass

For the mass uniformity test, twenty ICs loaded ODFs were randomly selected and individually weighed using an analytical balance. The mean mass was found to be 236.39 ± 3.81 mg. All IC-loaded ODF formulations complied with pharmacopoeia criteria, indicating acceptable uniformity of mass.

Surface pH

The surface pH values of the developed blank and ICs-loaded ODF were found to be 7.04 ± 0.08 and 6.95 ± 0.05, respectively (Table 2). Since the pH of the buccal cavity ranges from 5.5 to 7.4, ODFs need to have a surface pH within this range to avoid mucosal irritation, as they rapidly dissolve upon placement in the oral cavity (Oudah & Al-Khedairy, 2025). The measured surface pH values indicate that the formulated films are compatible with the physiological pH of the oral environment and are therefore expected to ensure good patient compliance.

Water Content

Water content is a critical parameter in ODFs, as it affects film flexibility, mechanical strength, stability, and disintegration time. The percentage of water content was calculated 3.13 ± 0.25 % for blank ODFs and 2.68 ± 0.29 % for IC-loaded ODFs (Table 2). The residual water content of commercial films is typically below 10 %, with most falling under 5 % (Borges, Sil-

va, Coelho, & Simões, 2017). In this context, the obtained water content values are considered acceptable, and the low moisture levels observed suggest good stability of the prepared ODFs.

Uniformity of Content

Content-uniformity testing showed that telmisartan and indapamide were evenly dispersed in the films. Telmisartan yielded 38.89 ± 1.71 mg per unit (97.22 ± 4.28 %), while indapamide gave 1.53 ± 0.05 mg per unit (102.09 ± 3.33 %). All values fell within the limits specified by Ph. Eur. 9.0 (method 2.9.6), confirming that the formulation meets the pharmacopoeial requirement for content uniformity.

Folding Endurance

Folding endurance is an indicator of an ODF's resistance to repeated bending and is used to evaluate its suitability in terms of mechanical strength and flexibility. The folding endurance values for the blank and ICs-loaded ODFs were found to be 182.21 ± 5.09 and 164.33 ± 4.16, respectively (Table 2). Although the incorporation of ICs slightly reduced the folding endurance compared to blank films, all ODFs exhibited high folding endurance values. These results suggest that the prepared films possess adequate flexibility and mechanical robustness, which are essential for storage and handling (Takeuchi, Ikeda, Tahara, & Takeuchi, 2020).

Table 2. Physicochemical and performance characteristics of blank and IC-loaded ODF.

ODFs	Parameters							
	Thicknes	Uniformity of mass	Surface pH	Water content	Folding endurance	Content uniformity	Disintegration time	
							Petri Method	Drop Method
Blank ODF	0.140 ± 0.008 mm	-	7.04 ± 0.08	3.13 ± 0.25%	182.21 ± 5.09	-	29.7±3.8	34.3±2.1
ICs loaded ODF	0.138 ± 0.009 mm	236.39 ± 3.81 mg	6.95 ± 0.05	2.68 ± 0.29%	164.33 ± 4.16	97.22 ± 4.28 %(TEL) 102.09 ± 3.33 %(IND)	25.3±3.1	32.4±2.5

Mechanical Properties – Young's Modulus

The stress–strain curves obtained from DMA analysis exhibited a clear linear relationship with high correlation coefficients ($R^2 > 0.997$), indicating elastic behavior of both blank and ICs-loaded ODFs (Figure 4). The calculated Young's modulus of the blank ODFs was found to be 70 N/mm², while the ICs-loaded ODFs showed a higher modulus of 100 N/mm². This increase in stiffness can be attributed to the incorporation of ICs into the polymer matrix, which may enhance intermolecular interactions and structural integrity. Similarly, in the literature, an increase in Young's modulus, also known as elastic modulus, has been reported with higher amounts of formulation components (Orgul, Eroglu, & Hekimoglu, 2017). Nevertheless, both values remained below the 550 N/mm² threshold reported for ODFs, confirming that the mechanical flexibility and performance of the films remain within acceptable limits for buccal application (Visser et al., 2015).

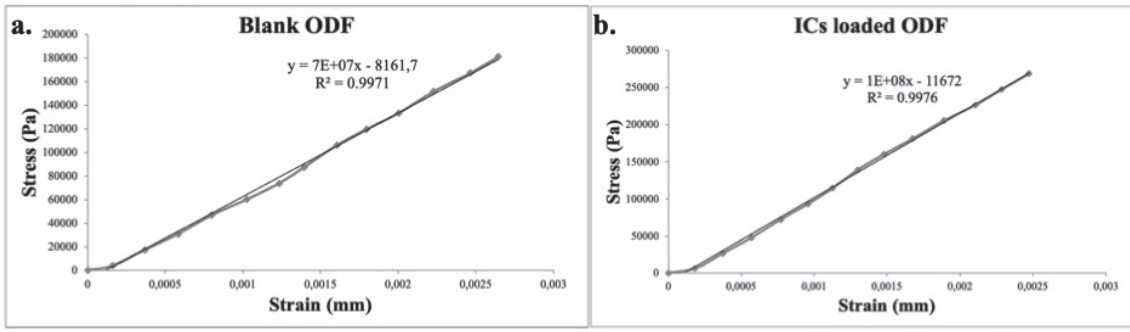

Figure 4. Stress–strain curves of (a) blank ODF and (b) ICs loaded ODF obtained from dynamic mechanical analysis.

FTIR Analysis

FTIR analysis was first used to evaluate the ICs between IND, TEL, and β-CD in the solid state, and the spectra of APIs, β-CD, physical mixture, and ICs were shown in Figure 5. Characteristic peaks of TEL were observed at 3500 cm−1 as a broad band attributed to O–H stretching of the carboxylic acid, 3061 cm^{-1} for aromatic C–H stretching, 2956 cm^{-1} for aliphatic C–H stretching, a sharp intense band at 1695 cm^{-1} corresponding to C=O stretching of the carboxylic acid, around 1600 cm^{-1} for aromatic C=C stretching, 1384 cm^{-1} arising from O–H bending/C–O stretching of the carboxylic acid and a diagnostic doublet at 757 and 741 cm^{-1} assigned to 1,2-disubstituted benzene ring vibrations in line with previously reported (Kaur et al., 2014) (Figure 5a). Further, the spectrum of IND exhibited characteristic peaks consistent with those reported in the literature (Gumieniczek et al., 2018). A strong band at 3296 and 3202 cm^{-1} corresponds to N–H stretching vibrations of the sulfonamide group. A weak absorption band around 2943 cm^{-1} was attributed to aliphatic C–H stretching. A sharp and intense peak at 1655 cm^{-1} was assigned to C=O stretching of the amide group. The peak at 1598 cm^{-1} is indicative of aromatic C–H stretching, while the bands at 1384 and 1168 cm^{-1} are characteristic of the S=O stretching vibrations of the sulfonamide group (Figure 5b). Similarly, the absorption bands in the FTIR spectrum of β-CD match those reported in the literature (Örgül, 2024). In the spectra of the physical mixture, characteristic peaks of both APIs (TEL or IND) and β-CD were visible with minimal shifts and slightly reduced intensity due to overlapping bands of β-CD. The presence of characteristic peaks with only slight changes suggests the absence of significant chemical interactions between the API and β-CD in the physical mixture, supporting their mutual compatibility. Conversely, the FTIR spectra of the ICs exhibited noticeable shifts, broadening, and intensity reductions in the characteristic peaks of both APIs. These spectral modifications confirm that telmisartan and indapamide have been successfully incorporated into the β-CD cavity through non-covalent interactions such as hydrophobic, van der Waals, and hydrogen bonding, thereby forming stable ICs. In addition, in this study, possible interactions between the components of the ODF formulations were evaluated using FTIR spectra of HPMC, glycerin, blank ODF, and ICs-loaded ODF as depicted in Figure 6. HPMC spectrum exhibits distinct peaks such as a broad O–H stretching band around 3450 cm^{-1}, which is typical for cellulose derivatives, the C–H stretching peak at about 2940 cm^{-1}, and the strong band in the 1050–1100 cm^{-1} region corresponds to C–O–C ether stretches (Mahdavinia, Ettehadi, Amini, & Sabzi, 2015). The spectrum of glycerin is dominated by a broad and strong O–H stretching band around 3300–3200 cm^{-1}, which is typical for polyols with extensive hydrogen bonding. The C–H stretching bands appear in the 2930–2870 cm^{-1} range, while the C–O stretching vibrations, indicative of alcohol groups, are clearly visible in the 1110–1020 cm^{-1} range (Wu, Feng, Hedoux, & Shalaev, 2022). These

spectral features are consistent for pure HPMC and glycerin, confirming their identity and chemical integrity. The blank ODF spectrum exhibits the characteristic profile of the HPMC–glycerin matrix, particularly in the fingerprint region. The prominent bands include a broad O–H stretching band at around 3300 cm^{-1}, aliphatic C–H stretches near 2930 cm^{-1}, a moisture-related H–O–H bending band at around 1640 cm^{-1}, and strong C–O–C ether peaks between 1100 and 1020 cm^{-1}. These results confirm that HPMC and glycerin are compatible, and the solvent casting method did not chemically alter the excipients. The ODF containing ICs largely preserves the characteristic HPMC and glycerin bands observed in the blank ODF. Superimposed on this baseline are ICs peaks that emerge as broadened shoulders or markedly attenuated peaks for example, a low-intensity shoulder at about 1690 cm^{-1} attributable to the C=O stretch of the TEL β-CD IC, a diminished peak near 1650 cm^{-1} arising from the amide C=O of the IND β-CD IC, and a marked attenuation of the diagnostic aromatic doublet at 760–740 cm^{-1} (Figure 6). These ICs' specific bands, together with the unchanged HPMC and glycerin peaks, indicate that the inclusion complexes are molecularly dispersed within the film matrix without the formation of new covalent bonds, confirming the good physicochemical compatibility of all formulation components.

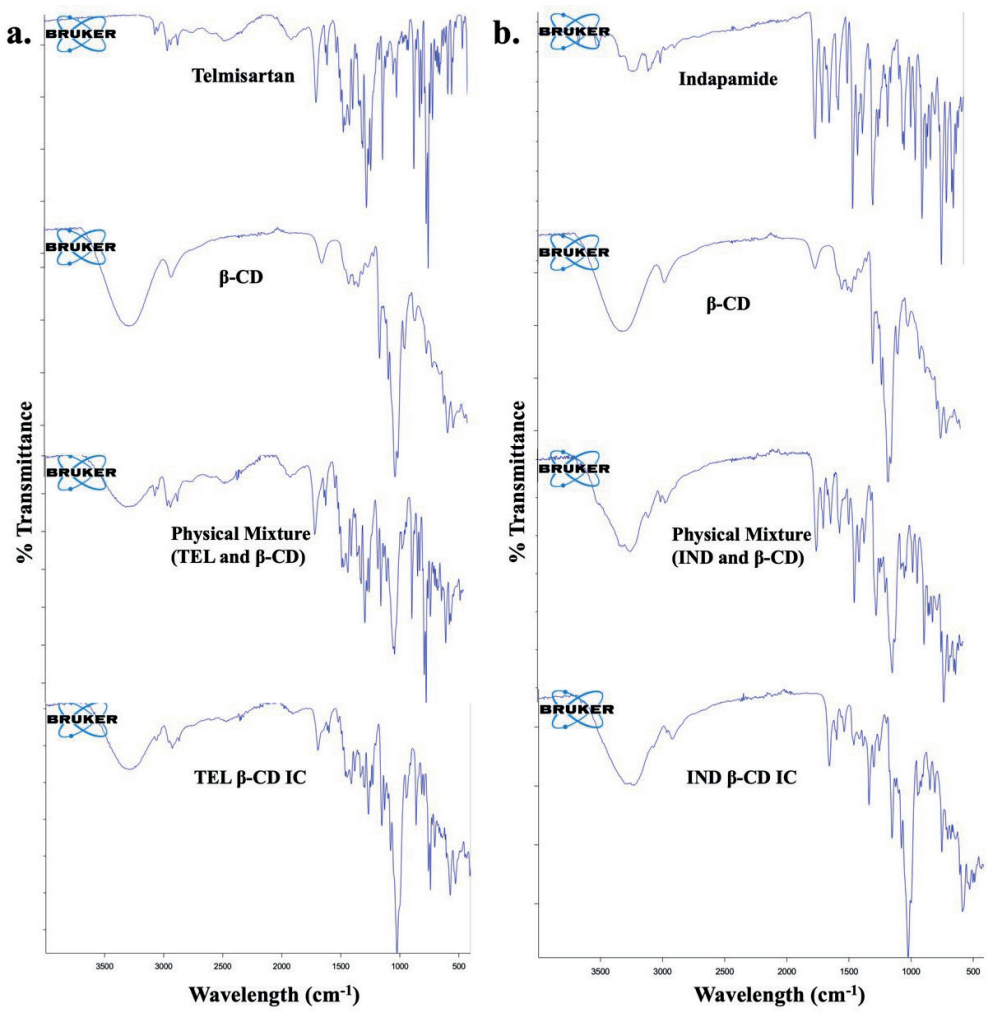

Figure 5. FTIR spectra of (a) TEL and (b) IND, β-CD, physical mixtures, and corresponding ICs.

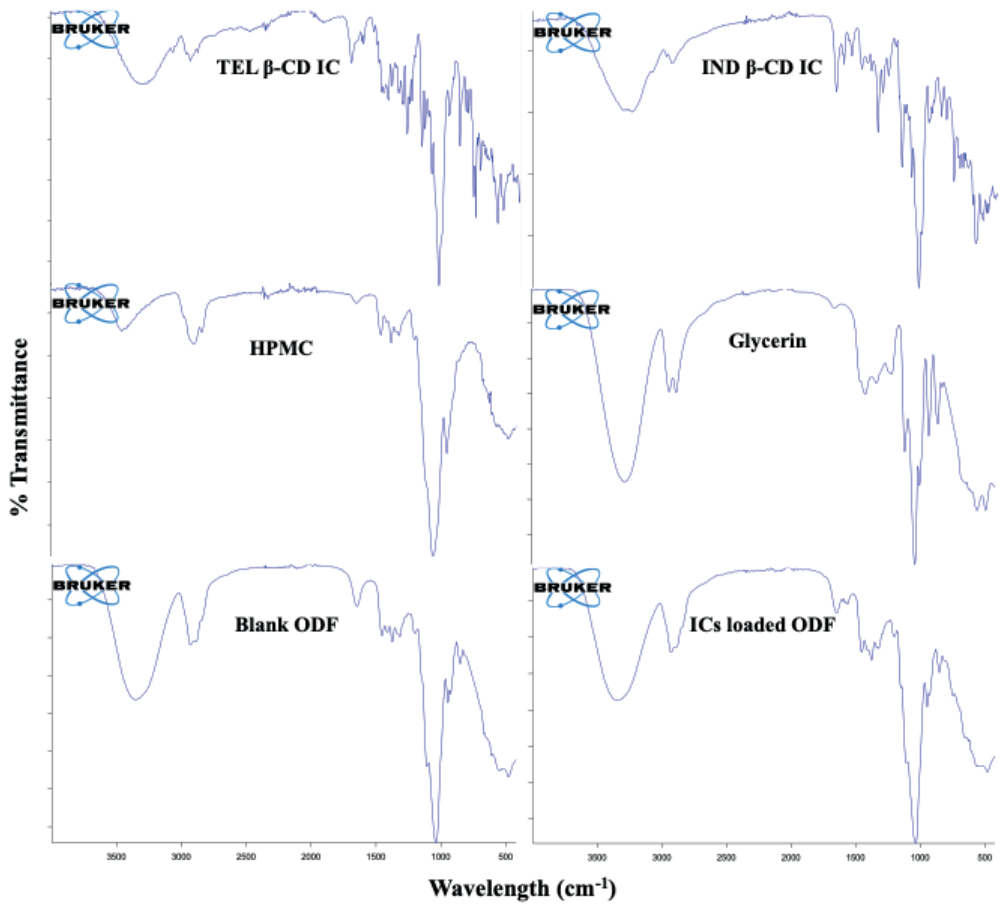

Figure 6. FTIR spectra of individual components (TEL β-CD IC, IND β-CD IC, HPMC, and glycerin), blank ODF, and ICs-loaded ODF formulation.

Disintegration Time

Disintegration time is a critical quality attribute for ODFs, specifically designed to dissolve rapidly in the oral cavity. As shown in Table 2, the disintegration times of the developed ODF formulations ranged between 25.3 ± 3.1 and 34.3 ± 2.1 seconds. Although the drop method resulted in slightly longer disintegration times compared to the petri dish method, all values remained below 35 seconds, with no statistically significant difference observed between blank and ICs-loaded ODFs for either method. According to the European and United States Pharmacopoeia (USP), the maximum allowable disintegration time for orodispersible dosage forms is 180 seconds. With the prepared ODF formulations, disintegration times were achieved well below this limit. Factors such as the film-forming polymer, film thickness, and production method are known to influence disintegration behavior. In this study, the use of HPMC, a hydrophilic polymer, facilitated faster water penetration into the film matrix, contributing to shorter disintegration times. These findings are in agreement with the literature, confirming that HPMC-based ODFs can achieve rapid disintegration suitable to enable oral administration (Zaki et al., 2023).

***In Vitro* Dissolution**

The release profiles of TEL and IND from TEL β-CD and IND β-CD ICs loaded ODF in 0.1 N HCl and phosphate buffer pH 6.8 are given in Figure 7. As shown in Figure 7a, TEL exhibited a rap-

id dissolution profile in 0.1 N HCl, achieving nearly 100% drug release within 15 minutes, whereas IND showed a slightly slower yet efficient release, reaching approximately 97% within 20 minutes. In pH 6.8 phosphate buffer (Figure 7b), both APIs demonstrated fast-release profiles, with more than 90% of the drug released within the first 15 minutes and complete release observed by 30 minutes. Although TEL is highly soluble in acidic or basic conditions, it has limited solubility under neutral pH (Ruiz Picazo et al., 2018). However, the formation of β-CD IC successfully overcame this pH-dependent solubility limitation, enabling immediate drug release (>90% in 15 minutes) even under neutral conditions. Similarly, IND which is a weak base with pH-dependent solubility (Wojnarowska et al., 2013), showed a similar rapid dissolution across both media due to complexation with β-CD. These findings confirm that the β-CD ICs significantly enhanced the solubility and dissolution rates of both poorly soluble drugs. In addition to the formation of ICs, the enhanced dissolution profiles were also attributed to the high hydrophilicity of the HPMC-based ODF matrix, increased surface area, and resulting rapid disintegration of the films.

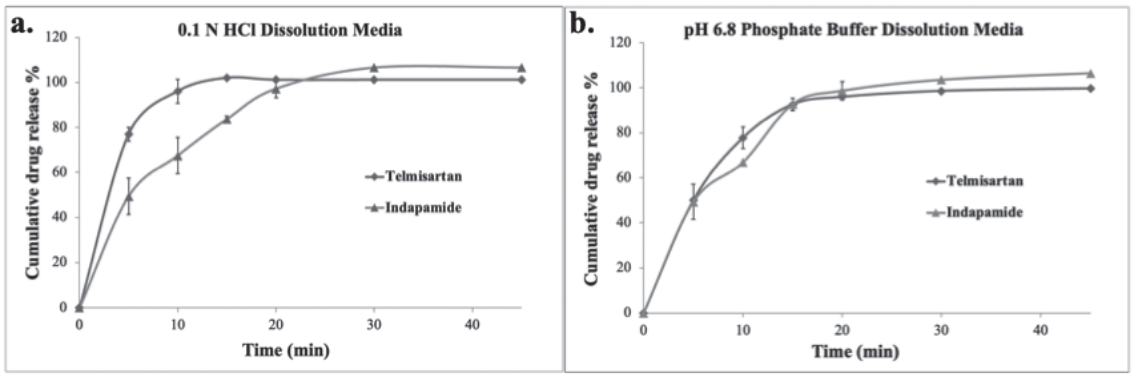

Figure 7. *In vitro* cumulative drug release profiles of Telmisartan and Indapamide from their β-CD ICs loaded ODFs in (a) 0.1 N HCl and (b) pH 6.8 phosphate buffer (n = 3, mean ± SD).

Conclusion

In this study, an FDC ODF formulation containing TEL and IND β-ICs was successfully manufactured by solvent casting using HPMC and glycerin. β-CD complexation increased the solubility of both APIs, with greater than 90% encapsulation efficiency, confirming effective host–guest interaction. Incorporating these ICs into an HPMC-based ODF produced proper, flexible, and thin films with uniform mass and content that disintegrated in less than 35 seconds and achieved almost complete release of both APIs within 20 minutes in both acidic (0.1 N HCl) and neutral (pH 6.8) media. Furthermore, compatibility of components was confirmed through physicochemical analysis, and all critical quality attributes of the ODFs met pharmacopeial limits, demonstrating the robustness of the process. Overall, the developed ODF in this study effectively overcame the solubility limitations of TEL and IND, providing an immediate-release FDC dosage form that improves patient adherence and is suitable for in vivo evaluation.

ACKNOWLEDGEMENT

This work was supported by The Scientific and Technological Research Council of Turkey (TUBITAK) [Application number: 2209-B, 1139B412202184].

AUTHOR CONTRIBUTION STATEMENT

The conceptualization, methodology, investigation, data curation, formal analysis, visualization, writing – original draft, writing – review & editing, project administration (DO), the investigation, literature review, writing – original draft, data curation, formal analysis, project administration (AY), the conceptualization, methodology, formal analysis, data cu-

ration, project administration (YG), the formal analysis, data curation, writing – review & editing (SA).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Al-Heibshy, F. N., Başaran, E., Öztürk, N., & Demirel, M. (2020). Preparation and in vitro characterization of rosuvastatin calcium incorporated methyl beta cyclodextrin and Captisol® inclusion complexes. *Drug Development and Industrial Pharmacy, 46*(9), 1495-1506. https://doi.org/10.1080/03639045.2020.1810264

An, J., Derington, C. G., Luong, T., Olson, K. L., King, J. B., Bress, A. P., & Jackevicius, C. A. (2020). Fixed-dose combination medications for treating hypertension: A review of effectiveness, safety, and challenges. *Current Hypertension Reports, 22*, 1-19. https://doi.org/10.1007/s11906-020-01109-2

Battershill, A. J., & Scott, L. J. (2006). Telmisartan: a review of its use in the management of hypertension. *Drugs, 66*, 51-83. https://doi.org/10.2165/00003495-200666010-00004

Borges, A. F., Silva, C., Coelho, J. F., & Simões, S. (2017). Outlining critical quality attributes (CQAs) as guidance for the development of orodispersible films. *Pharmaceutical Development and Technology, 22*(2), 237-245. https://doi.org/10.1080/10837450.2016.1199567

Chavhan, V., Lawande, R., Salunke, J., Ghante, M., & Jagtap, S. (2013). UV spectrophotometric method development and validation for telmisartan in bulk and tablet dosage form. *Asian J Pharm Clin Res, 6*(4), 19-21. Retrieved from https://journals.innovareacademics.in/index.php/ajpcr/article/download/167/315

Coca, A., Whelton, S., Camafort, M., López-López, J., & Yang, E. (2024). Single-pill combination for treatment of hypertension: Just a matter of practicality or is there a real clinical benefit? *European Journal of Internal Medicine*, *126,* 16-25. https://doi.org/10.1016/j.ejim.2024.04.011

Cong, Y., Du, C., Wang, M., Jiang, Z., Xing, K., Bian, Y., & Wang, M. (2021). Investigation on the Hansen solubility parameter, solvent effect and thermodynamic analysis of indapamide dissolution and molecular dynamics simulation. *Journal of Molecular Liquids, 334*, 116489. https://doi.org/10.1016/j.molliq.2021.116489

Dhibar, M., Chakraborty, S., Basak, S., Pattanayak, P., Chatterjee, T., Ghosh, B., & Abourehab, M. A. (2023). Critical analysis and optimization of stoichiometric ratio of drug-coformer on cocrystal design: molecular docking, in vitro and in vivo assessment. *Pharmaceuticals, 16*(2), 284. https://doi.org/10.3390/ph16020284

EMA. (2017). Guideline on clinical development of fixed combination medicinal products. *European Medicines Agency: EMA/CHMP/158268/2017*. Retrieved from https://www.ema.europa.eu/en/clinical-development-fixed-combination-medicinal-products-scientific-guideline

FDA. (2025). Food and Drug Administration Retrieved from https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Gumieniczek, A., Galeza, J., Berecka, A., Mroczek, T., Wojtanowski, K., Lipska, K., & Skarbek, J. (2018). Chemical stability and interactions in a new antihypertensive mixture containing indapamide and dihydralazine using FT-IR, HPLC and LC-MS methods. *RSC advances, 8*(63), 36076-36089. https://doi.org/10.1039/c8ra06707d

Ha, E.-S., Park, H., Jeong, J.-S., Lee, S.-K., Kang, H.-T., Baek, I.-h., & Kim, M.-S. (2024). Effect of Process Parameters on Nano-Microparticle Formation During Supercritical Antisolvent Process Using Mixed Solvent: Application for Enhanced Dissolution and Oral Bioavailability of Telmisartan Through Particle-Size Control Based on Experimental Design. *Pharmaceutics, 16*(12), 1508. https://doi.org/10.3390/pharmaceutics16121508

Higuchi, T., & Connors, A. (1965). Phase-solubility techniques. *Advanced Analytical Chemistry of Instrumentation*, *4*, 212-217.

Islam, N., Khan, N. U., Razzaq, A., Menaa, F., Khan, Z. U., Hussain, A., & Ni, J. (2023). Loratadine oral bioavailability enhancement via solid dispersion loaded oro-dispersible films: Formulation, characterization and pharmacokinetics. *Colloids and Surfaces B: Biointerfaces, 230*, 113526. https://doi.org/10.1016/j.colsurfb.2023.113526

Jambhekar, S. S., & Breen, P. (2016). Cyclodextrins in pharmaceutical formulations I: Structure and physicochemical properties, formation of complexes, and types of complex. *Drug discovery today, 21*(2), 356-362. https://doi.org/10.1016/j.drudis.2015.11.017

Kaur, M., Bhatia, R. K., Pissurlenkar, R. R., Coutinho, E. C., Jain, U. K., Katare, O. P., & Madan, J. (2014). Telmisartan complex augments solubility, dissolution and drug delivery in prostate cancer cells. *Carbohydrate polymers, 101*, 614-622. https://doi.org/10.1016/j.carbpol.2013.09.077

Khan, Q.-u.-a., Siddique, M. I., Rasool, F., Naeem, M., Usman, M., & Zaman, M. (2020). Development and characterization of orodispersible film containing cefixime trihydrate. *Drug Development and Industrial Pharmacy, 46*(12), 2070-2080. https://doi.org/10.1080/03639045.2020.1843477

Kumari, L., Choudhari, Y., Patel, P., Gupta, G. D., Singh, D., Rosenholm, J. M., & Kurmi, B. D. (2023). Advancement in solubilization approaches: A step towards bioavailability enhancement of poorly soluble drugs. *Life, 13*(5), 1099. https://doi.org/10.3390/life13051099

Lesutan, V.-N., Andersen, S. K., & Lamprou, D. A. (2025). Poorly water-soluble APIs in fixed-dose combinations: development, challenges, and opportunities in manufacturing techniques. *Journal of Drug Delivery Science and Technology*, 107212. https://doi.org/10.1016/j.jddst.2025.107212

Mahdavinia, G. R., Ettehadi, S., Amini, M., & Sabzi, M. (2015). Synthesis and characterization of hydroxypropyl methylcellulose-g-poly (acrylamide)/LAPONITE® RD nanocomposites as novel magnetic-and pH-sensitive carriers for controlled drug release. *RSC advances, 5*(55), 44516-44523. https://doi.org/10.1039/c5ra03731j

Morath, B., Sauer, S., Zaradzki, M., & Wagner, A. H. (2022). Orodispersible films–recent developments and new applications in drug delivery and therapy. *Biochemical Pharmacology, 200*, 115036. https://doi.org/10.1016/j.bcp.2022.115036

Orgul, D., Eroglu, H., & Hekimoglu, S. (2017). Formulation and characterization of tissue scaffolds containing simvastatin loaded nanostructured lipid carriers for treatment of diabetic wounds. *Journal of Drug Delivery Science and Technology, 41*, 280-292. https://doi.org/10.1016/j.jddst.2017.08.001

Oudah, S. A., & Al-Khedairy, E. B. (2025). Development and characterization of bilastine nanosuspension for enhanced dissolution in orodispersible films. *OpenNano, 21*, 100230. https://doi.org/10.1016/j.onano.2024.100230

Örgül, D. (2024). Comparison the solubility and dissolution rate effects of beta-cyclodextrin and gamma-cyclodextrin complexations of rosuvastatin calcium. *Journal of Research in Pharmacy, 28*(3), 797-807. https://doi.org/10.29228/jrp.740

Park, S. Y., Jin, C. H., Goo, Y. T., Chae, B. R., Yoon, H. Y., Kim, C. H., & Choi, Y. W. (2021). Supersaturable self-microemulsifying drug delivery system enhances dissolution and bioavailability of telmisartan. *Pharmaceutical Development and Technology, 26*(1), 60-68. https://doi.org/10.1080/10837450.2020.1834580

Pezik, E., Gulsun, T., Sahin, S., & Vural, I. (2021). Development and characterization of pullulan-based orally disintegrating films containing amlodipine besylate. *Eur J Pharm Sci, 156*, 105597. https://doi.org/10.1016/j.ejps.2020.105597

Radi, A.-E., & Eissa, S. (2011). Electrochemical study of indapamide and its complexation with β-cyclodextrin. *Journal of Inclusion Phenomena and Macrocyclic Chemistry, 71*, 95-102. https://doi.org/10.1007/s10847-010-9906-1

Rani, K. C., Parfati, N., Aryani, N. L. D., Winantari, A. N., Fitriani, E. W., Pradana, A. T., & Angelica, F. (2021). Development, evaluation, and molecular docking of oral dissolving film of atenolol. *Pharmaceutics, 13*(10), 1727. https://doi.org/10.3390/pharmaceutics13101727

Ruiz Picazo, A., Martinez-Martinez, M. T., Colón-Useche, S., Iriarte, R., Sánchez-Dengra, B. r., González-Álvarez, M., & Bermejo, M. (2018). In vitro dissolution as a tool for formulation selection: telmisartan two-step IVIVC. *Molecular Pharmaceutics, 15*(6), 2307-2315. https://doi.org/10.1021/acs.molpharmaceut.8b00153

Sharapova, A., Ol'khovich, M., & Blokhina, S. (2025). Complexation of telmisartan with cyclodextrins as a tool of solubility enhancement: A comparative analysis of influence of the cyclodextrin type and method of solid dispersion preparation. *Colloids and Surfaces A: Physicochemical and Engineering Aspects, 705*, 135662. https://doi.org/10.1016/j.colsurfa.2024.135662

Takeuchi, Y., Ikeda, N., Tahara, K., & Takeuchi, H. (2020). Mechanical characteristics of orally disintegrating films: Comparison of folding endurance and tensile properties. *International Journal of Pharmaceutics, 589*, 119876. https://doi.org/10.1016/j.ijpharm.2020.119876

Takeuchi, Y., Umemura, K., Tahara, K., & Takeuchi, H. (2018). Formulation design of hydroxypropyl cellulose films for use as orally disintegrating dosage forms. *Journal of Drug Delivery Science and Technology, 46*, 93-100. https://doi.org/10.1016/j.jddst.2018.05.002

Tarkase Kailash, N., Jadhav Manisha, B., Tajane Sachin, R., & Dongare Umesh, S. (2012). Development and validation of UV-Spectrophotometric methods for estimation of Indapamide in bulk and tablet dosage form. *Der Pharma Chem, 4*, 1128-1132. Retrieved from https://www.academia.edu/download/30539612/dpc-2012-4-3-1128-1132.pdf

Turek, M., Gach-Janczak, K., Różycka-Sokołowska, E., Owsianik, K., & Bałczewski, P. (2025). Mechanochemical synthesis of telmisartan-based co-amorphous solid dispersions with enhanced solubility and unexpected cytotoxic synergy on normal cell lines. *Advanced Powder Technology, 36*(7), 104936. https://doi.org/10.1016/j.apt.2025.104936

Visser, J. C., Dohmen, W. M., Hinrichs, W. L., Breitkreutz, J., Frijlink, H. W., & Woerdenbag, H. J. (2015). Quality by design approach for optimizing the formulation and physical properties of extemporaneously prepared orodispersible films. *International Journal of Pharmaceutics, 485*(1-2), 70-76. https://doi.org/10.1016/j.ijpharm.2015.03.005

Visser, J. C., Weggemans, O. A., Boosman, R. J., Loos, K. U., Frijlink, H. W., & Woerdenbag, H. J. (2017). Increased drug load and polymer compatibility of bilayered orodispersible films. *European Journal of Pharmaceutical Sciences, 107*, 183-190. https://doi.org/10.1016/j.ejps.2017.07.010

Vlad, R.-A., Pintea, A., Coaicea, M., Antonoaea, P., Rédai, E. M., Todoran, N., & Ciurba, A. (2023). Preparation and evaluation of caffeine orodispersible films: the influence of hydrotropic substances and film-forming agent concentration on film properties. *Polymers, 15*(9), 2034. https://doi.org/10.3390/polym15092034

Wojnarowska, Z., Grzybowska, K., Hawelek, L., Dulski, M., Wrzalik, R., Gruszka, I., & Bujak, P. (2013). Molecular dynamics, physical stability and solubility advantage from amorphous indapamide drug. *Molecular Pharmaceutics, 10*(10), 3612-3627. https://doi.org/10.1021/mp400116q

Wu, K., Feng, S., Hedoux, A., & Shalaev, E. (2022). Water structure in glycerol: Spectroscopic and computer simulation investigation of hydrogen bonding and water clustering. *Journal of Molecular Liquids, 355*, 118916. https://doi.org/10.1016/j.molliq.2022.118916

Yin, H., Jin, W., Wang, J., Ke, J., Zhang, W., Liu, C., & Wang, W. (2024). Oral fast dissolving films for co-administration of breviscapine and matrine: Formulation optimization and in vitro characterization. *Journal of Drug Delivery Science and Technology, 95*, 105548. https://doi.org/10.1016/j.jddst.2024.105548

Zaki, R. M., Alfadhel, M., Seshadri, V. D., Albagami, F., Alrobaian, M., Tawati, S. M., & Almurshedi, A. S. (2023). Fabrication and characterization of orodispersible films loaded with solid dispersion to enhance Rosuvastatin calcium bioavailability. *Saudi Pharmaceutical Journal, 31*(1), 135-146. https://doi.org/10.1016/j.jsps.2022.11.012

Zhou, B., Carrillo-Larco, R. M., Danaei, G., Riley, L. M., Paciorek, C. J., Stevens, G. A., & Singleton, R. K. (2021). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *The lancet, 398*(10304), 957-980. Retrieved from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01330-1/fulltext?s=09