



ENHANCING SOLUBILITY AND DEVELOPING AN ITRACONAZOLE-BETA-CYCLODEXTRIN COMPLEX FOR ANTIFUNGAL THERAPY IN ORALLY DISINTEGRATING TABLETS

AĞIZDA DAĞILAN TABLETLERDE ANTİFUNGAL TEDAVİ İÇİN ÇÖZÜNÜRLÜĞÜN
ARTIRILMASI VE İTRAKONAZOL-BETA-SİKLODEKSTRİN KOMPLEKSİNİN
GELİŞTİRİLMESİ

Tansel COMOĞLU^{1*}

¹Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 06560, Ankara, Türkiye

ABSTRACT

Objective: This study aimed to create an orally disintegrating tablet (ODT) formulation using an itraconazole (ITZ)-beta-cyclodextrin (β -CD) complex to enhance itraconazole's solubility, a drug with limited solubility. β -CD was chosen for its compatibility with ITZ.

Material and Method: The study prepared equimolar mixtures of ITZ and β -CD through kneading, assessing their solubility and dissolution rates. The inclusion complexes significantly increased ITZ's solubility. This complex was used to develop directly compressed ODTs with a lower ITZ content (25 mg), incorporating D-Mannitol as a bulking agent, sweetener, and to enhance mouthfeel, facilitating rapid disintegration and drug release.

Result and Discussion: ODT formulations containing the ITZ- β -CD complex showed a significantly higher dissolution rate of ITZ compared to formulations with pure ITZ. This enhancement in dissolution is expected to significantly improve ITZ's bioavailability, suggesting a potential for reducing ITZ dosage and minimizing adverse effects.

Keywords: β -cyclodextrin, complexation, itraconazole, kneading method, orally disintegrating tablet

ÖZ

Amaç: Bu çalışma, sınırlı çözünürlüğe sahip itrakonazolün (ITZ) hızlı ve tam çözünürlüğünü sağlamak üzere ITZ-beta-siklodekstrin (β -CD) kompleksi kullanarak oral olarak dağılan bir tablet (ODT) formülasyonu geliştirmeyi hedeflemiştir. ITZ ile uyumluluğu nedeniyle β -CD tercih edilmiştir.

Gereç ve Yöntem: İtrakonazol ve β -CD'nin ekimolar karışımları yoğurma yöntemiyle hazırlanmış, çözünürlük ve çözünme oranları değerlendirilmiştir. İnküzyon kompleksleri sayesinde ITZ'nin çözünürlüğünde önemli bir artış sağlanmıştır. Bu kompleksler kullanılarak, daha düşük ITZ içeriği (25 mg) ile doğrudan basılan ODT'ler geliştirilmiştir. D-Mannitol, hacim arttırıcı, tatlandırıcı olarak kullanılmış ve ağızda hızlı dağılma sağlamıştır.

Sonuç ve Tartışma: ITZ- β -CD kompleksini içeren ODT formülasyonları, saf ITZ içerenlere göre daha yüksek çözünmüş ilaç miktarı sergilemiştir. Bu, itrakonazolün çözünürlüğünde ve biyoyararlanımında önemli bir artış sağlamış, ITZ dozunun azaltılması ve yan etkilerin minimize edilmesi potansiyelini ortaya koymuştur.

* Corresponding Author / Sorumlu Yazar: Tansel Çomoğlu
e-mail / e-posta: comoglu@pharmacy.ankara.edu.tr, Phone / Tel.: +903122033164

Anahtar Kelimeler: *Ağızda hızlı çözünen tablet, β -siklodekstrin, itraconazol, kompleksleştirme, örme yöntemi*

INTRODUCTION

Oral itraconazole (ITZ) is a potent triazole antifungal agent widely used for the treatment of a broad range of fungal infections. Despite its broad antifungal spectrum and clinical efficacy, ITZ's clinical utility is significantly hampered by its poor aqueous solubility and low oral bioavailability. These limitations not only affect the drug's absorption and therapeutic effectiveness but also contribute to variability in patient responses and necessitate the development of alternative formulations to enhance its delivery and performance [1].

The complexation of ITZ with beta-cyclodextrin (β -CD) presents a promising approach to overcome these challenges. β -CD, a cyclic oligosaccharide, is known for its ability to enhance the solubility and stability of poorly soluble drugs by forming inclusion complexes. This interaction can significantly improve ITZ's solubility, leading to enhanced bioavailability, and potentially, improved therapeutic outcomes [2,3].

Orally disintegrating tablets (ODTs) offer a novel and patient-friendly dosage form, designed to disintegrate rapidly upon contact with saliva, allowing for the administration of the drug without the need for water. This feature makes ODTs particularly beneficial for patients who experience difficulty swallowing conventional tablets or capsules, such as pediatric, geriatric, and bedridden patients, or those with dysphagia. Furthermore, the rapid disintegration and dissolution of ODTs in the oral cavity can expedite drug absorption and onset of action, which is crucial for conditions requiring prompt antifungal intervention [4].

The development of ITZ and β -CD complex containing ODTs aims to combine the enhanced solubility provided by the complexation with the convenience and patient compliance offered by the ODT formulation. This innovative approach not only addresses the limitations associated with ITZ's physicochemical properties but also aligns with the growing demand for more accessible and easier-to-administer medications.

Such a formulation could significantly impact the management of fungal infections, offering a more effective and user-friendly therapeutic option for a wide range of patients, including those with special needs regarding drug administration. By improving the bioavailability and patient experience, ITZ and β -CD complex containing ODTs hold the potential to enhance adherence to antifungal therapy, thereby optimizing clinical outcomes and contributing to the more effective management of fungal diseases.

MATERIAL AND METHOD

Materials

Itraconazole (It was gifted by Nobel İlaç, Turkey), β -cyclodextrin (Roquette, France), D-Mannitol (Roquette, France), Low-substituted Hydroxypropylcellulose (Shin-Etsu, Japan), Ac-Di-Sol (Colorcon, UK), Mg stearate (Ataman Kimya, Türkiye), Aerosil (Degussa, Germany) Mint flavor (Ataman Kimya, Türkiye).

Methods

Measuring the Solubility of ITZ in Water

To examine the solubility of ITZ in water, an accurately weighed amount of ITZ is added to a predetermined volume of water, ensuring the drug's potential saturation. This mixture is then agitated continuously at a constant temperature, at 37°C to mimic body conditions, for 24 hours to reach equilibrium. After sufficient mixing, the solution is filtered or centrifuged to remove undissolved particles. The concentration of ITZ in the resultant clear solution is then quantified spectrophotometrically at a wavelength of 262 nm using a Shimadzu UV-1800 device [5].

Preparation of ITZ- β -CD Complex

Equimolar ITZ- β -CD solid systems were prepared by kneading equimolar physical mixtures with the minimum volume of an ethanol-water (50/50 v/v) solution. By using this method, complexes in three distinct molar ratios of ITZ to β -CD—1:1, 1:2, and 1:3 (w/w) were produced. The mixtures were kneaded for a duration of 20 minutes [6,7].

Determination of Solubilities of Pure ITZ and ITZ- β CD Inclusion Complexes

Excessive quantities of pure ITZ, its inclusion complexes with ITZ- β -CD, were added into distilled water. These mixtures were subjected to sonication for one hour at ambient temperature, followed by agitation for 24 hours at the same temperature. The concentration of ITZ present in these solutions was measured using spectrophotometry at a wavelength of 262 nm [7].

Evaluation of the Micromeritic Characteristics of Powders

The flow characteristics of powder blends are essential for the quality of ODTs. For each formulation, the powder mixture's properties, including the angle of repose, bulk density, and tapped density, were assessed. The angle of repose (θ) was determined using the fixed funnel technique and calculated with Equation 1. Where, θ is angle of repose, h is height of the cone, and r is radius of the cone base.

$$\tan \theta = h/r \quad (\text{Equation 1.})$$

The powder was thoroughly mixed, and around 2 grams of this finely blended powder was transferred into a funnel. The setup was adjusted so the funnel's lower tip lightly touched the apex of the powder mound. Positioned over a flat surface, the powder was allowed to flow freely through the funnel. The diameter of the resulting powder heap was measured for subsequent calculations based on the previously mentioned equation [8]. To measure bulk density, 2 grams of the well-mixed powder from each formulation was placed into a 10 ml graduated cylinder, and the volume of the powder was recorded [9]. The tapped density was determined by tapping the cylinder on a firm surface every 2 seconds, continuing the process until there was no further change in the powder's volume. The final volume was then recorded. The Carr's (Compressibility) index, indicative of the powder's compressibility, was calculated using the values obtained for bulk and tapped densities, applying Equation 2.

$$\text{Compressibility index} = (\text{Tapped Density} - \text{Bulk density}) / \text{Tapped Density} \times 100 \quad (\text{Equation 2})$$

Following the pre-compression evaluations, the powder mixture for each formulation was compacted utilizing a tablet machine (Korsch) equipped with a 12 mm punch.

Preparation of ODTs

To address the issue of ITZ's solubility, ODTs were formulated featuring a 1:2 molar ratio of inclusion complex and pure drug, created through direct compression techniques [7]. D-Mannitol, is a sugar alcohol used widely in pharmaceutical formulations, including ODTs, as a bulking agent, sweetener, and to enhance the mouthfeel of the final product. It is especially valuable in ODTs for its ability to promote rapid disintegration in the oral cavity, thereby facilitating faster drug release and absorption. Low-substituted Hydroxypropylcellulose (L-HPC) is employed in ODTs primarily as a disintegrant and binder, contributing to rapid tablet disintegration without compromising tablet cohesion. Magnesium stearate (Mg stearate) serves as a lubricant, ensuring the smooth ejection of tablets from the press and preventing sticking, though it's used sparingly to avoid impacting the tablet's dissolution profile. Aerosil, a colloidal form of silicon dioxide, acts as a glidant to improve powder flow during tablet compression and can also help in stabilizing blends by preventing segregation. Ac-Di-Sol, or croscarmellose sodium, is a superdisintegrant that facilitates rapid tablet break-up upon contact with saliva, ensuring quick release of the active pharmaceutical ingredient for absorption. Mint flavor is added to mask any unpleasant tastes of the active ingredients, enhancing patient compliance by improving the overall palatability of the ODTs [10]. Each of the selected excipients plays a crucial role in optimizing the formulation for effectiveness, manufacturability, and patient acceptability. The

components of the ODT formulations are detailed in Table 2.

Post-Compression Parameters of ODTs

The manufactured tablets underwent evaluations for post-compression attributes such as weight variation, hardness, and friability. To assess weight variation, twenty tablets from each batch were measured on an analytical scale (Sartorius BL 210 S). Tablet strength was gauged through tests of hardness and friability. The hardness for six tablets was determined using a Monsanto hardness tester, while the friability for ten tablets was assessed with a Roche friabilator, operating for 4 minutes at a speed of 25 rotations per minute [11].

Disintegration Time Measurement

The disintegration time was determined using a USP disintegration testing apparatus. This device includes a basket rack assembly with six vertically aligned open-ended tubes. Each tube's bottom is fitted with a number 10-mesh stainless steel wire screen. For the disintegration test, a single tablet from each formulation was placed into the apparatus's basket, with the temperature adjusted to $37 \pm 2^\circ\text{C}$. The duration until complete disintegration occurred was then meticulously documented [9].

Measurement of Wetting Time and Water Absorption Ratio

For this assessment, one tablet from each formulation was positioned on a piece of circular tissue paper, which had been folded twice, inside a Petri dish with a 10 cm diameter. A solution of 0.5% (w/v) phenol red in 10 ml of water was prepared and poured into the Petri dish. The time taken for the tablet to become completely wet was recorded with a stopwatch. To evaluate the water absorption ratio, the procedure was replicated without the addition of phenol red. The water absorption ratio (R) was then calculated using Equation 3. [7].

$$R = \frac{W_a - W_b}{W_b} \times 100 \quad (\text{Equation 3.})$$

W_a represents weight of tablet after wetting, while W_b represents weight of tablet before wetting.

Measurement of Dispersion Time

A tablet was chosen at random from each formulation to determine the time it took for complete dispersion. This was done by adding 10 ml of water to a glass beaker and then introducing the tablet into the water. The time until the tablet was fully dispersed was timed with a stopwatch. This procedure was performed three times for each formulation to ensure accuracy and the results were documented accordingly [12].

Drug Content Analysis

To prepare the sample solution, 10 tablets from each batch were randomly chosen and pulverized into a fine powder using a pestle and mortar. An amount of the powder equivalent to 25 mg of ITZ was then dissolved in 100 ml of 0.1N HCl and subjected to sonication for 30 minutes. Following sonication, the solution was filtered, and the drug content was measured using a UV- visible spectrophotometer at a wavelength of 262 nm [12].

Dissolution Testing of ODTs

The dissolution behavior of ITZ ODTs and the ODT formulation containing ITZ- β -CD (1:2 molar ratio) complex were evaluated using a Type II dissolution apparatus. The procedure was performed over a duration of 45 minutes, utilizing 900 ml of distilled water maintained at $37 \pm 0.5^\circ\text{C}$ with a stirring speed of 50 rpm. To assess the in vitro release profile, 5 ml samples were withdrawn at predetermined time intervals (0, 5, 10, 15, 20, 25, 30, 35, 40, and 45 minutes) and immediately replaced with an equivalent volume of fresh medium. The collected samples were then subjected to analysis using a UV-visible spectrophotometer set to 262 nm [1].

Evaluation of Stability

To evaluate the stability of both active ingredient and F1 and F2 formulations, the studies were

conducted in accordance with International Council for Harmonisation (ICH) guidelines. Samples were meticulously wrapped in aluminum foil and placed in a humidity-controlled chamber. The conditions within the chamber were maintained at $40\pm 2^\circ\text{C}$ and $75\pm 5\%$ relative humidity for a duration of one month [9].

RESULT AND DISCUSSION

Solubility of ITZ in Water

Table 1 presents the solubility values for pure ITZ and the prepared the ITZ- β -CD inclusion complexes in pH 6.8 buffer solution. Based on the obtained results, the highest solubility of ITZ (5.22 ± 0.19 mg/ml) was achieved with the ITZ- β -CD complex prepared at a molar ratio of 1:2. Gökbulut and Özdemir, reported in their studies that on the preparation of cyclodextrin complexes with ITZ, prepared complexes of ITZ with HP- β CD and RAMEB at 1:1 and 1:2 ratios, first through physical mixtures, then employing kneading and co-precipitation methods. When solubility determinations were conducted in a pH 1.2 environment, they found that the solubility of ITZ, originally at 4.5 $\mu\text{g/ml}$, was highest in complexes prepared at a 1:2 molar ratio of IT:CD using the kneading method. Additionally, they reported that the formation of the ITZ- β -CD complex exhibits a BS-type solubility profile. In BS-type phase diagrams, the formation of complexes with limited solubility between a solute and solvent is depicted, indicating that the complex reaches its maximum solubility at a specific concentration. Beyond this point, any additional solute precipitates out, indicating a saturated solution. Consequently, it can be stated that the CD complexes of ITZ effectively increased the solubility of pure ITZ in pH 6.8 buffer. This enhancement in solubility can be attributed to the CD's ability to interact with both hydrophilic and hydrophobic structures, thereby improving the solubility of ITZ, which has poor solubility. However, it was determined that the highest solubility is achieved with a 1:2 molar ratio of ITZ: β -CD, beyond which the solubility of the complex decreases [3].

Pre-compression Parameters

The evaluated formulation blends, comprising both drug, drug- β -CD complex and excipients, were subject to various tests to determine their flow properties and suitability for direct compression. These tests included measurements of the angle of repose, bulk density, tapped density, and compressibility index. The bulk density was observed to range from 0.35 to 0.52 g/ml, while the tapped density varied between 0.28 and 0.47 g/ml. The angle of repose values fell within the range of 23.10 to 29.31. Additionally, the powder blends across all formulations demonstrated a compressibility index ranging from 11.35 to 12.47, as detailed in Table 3. These findings indicate that the powder blends exhibit ideal characteristics for manufacturing via the direct compression method [13].

Post-compression Parameters

ODTs containing both pure ITZ and ITZ- β -CD complex (1.2 molar ratio) were meticulously prepared and the composition of ODTs were given in Table 2. These formulations were crafted utilizing the direct compression technique, a method noted for its efficiency and precision. Subsequent to their preparation, these tablets underwent rigorous evaluation through a series of post-compression tests aimed at assessing various parameters critical to their performance and stability. These parameters included tablet thickness, hardness, friability, weight variation, drug content, wetting time, and disintegration time, with the results collated in Table 4 for comprehensive analysis [13].

Table 1. Solubility results of ITZ- β -CD inclusion complexes in water

Formulation code (ITZ: β -CD)	Molar ratio	Solubility in water (mg/ml)
C1	1:1	3.06 ± 0.19
C2	1:2	5.22 ± 0.23
C3	1:3	3.69 ± 0.41
Pure ITZ	-	0.47 ± 0.26

Table 2. Composition of ODTs

Formulation	Ingredients (mg)	
	F1	F2
ITZ	25	-
C2 (ITZ- β -CD inclusion complex equivalent to 25 mg ITZ)	-	105
D-Mannitol	250	170
L-HPC	6	6
Ac-Di-Sol	6	6
Mg stearate	6	6
Aerosil	6	6
Mint flavor	1	1

Table 3. Pre-compression parameters of the formulations

Parameters (n=3 \pm SD)	F1	F2
Bulk Density (g/ml)	0.52 \pm 0.13	0.35 \pm 0.24
Tapped Density (g/ml)	0.47 \pm 0.28	0.28 \pm 0.41
Hausner's Ratio	1.27 \pm 0.59	1.19 \pm 0.36
Angle of Repose	29.31 \pm 0.44	23.10 \pm 0.64
Compressibility Index (%)	12.47 \pm 0.62	11.35 \pm 0.39

Table 4. Post-compression parameters of the formulations

Parameters (n=3 \pm SD)	F1	F2
Hardness (kg/cm ²)	4.83 \pm 0.32	4.94 \pm 0.38
Thickness (mm)	3.20 \pm 0.11	3.21 \pm 0.21
Weight variation	300.01 \pm 0.14	299.49 \pm 0.15
Friability (w/w%)	0.37 \pm 0.52	0.39 \pm 0.43
Disintegration time (sec)	>3min	50
Wetting time (sec)	>3min	56
Drug content (%)	99.98 \pm 0.51	100.02 \pm 0.15

The tablets exhibited hardness values ranging from 4.83 to 4.94 kg/cm², comfortably within the acceptable range of 5-8 kg/cm². This indicated that the tablets possess commendable mechanical strength, essential for enduring the physical and mechanical stresses encountered during handling and transportation. Furthermore, the thickness of these tablets varied between 3.20 to 3.21 mm, aligning with the acceptance criterion of \pm 5%, showcasing uniformity in size and shape across all formulations [7].

In terms of friability, a parameter indicative of the tablet's resistance to crumbling under stress, values were recorded at less than 1% for all formulations, satisfying Pharmacopoeial standards. Specifically, the loss in weight percentage due to friability ranged from 0.37 to 0.39, well beneath the permissible limits set by official guidelines [7].

The wetting time, a measure of the time required for a tablet to become sufficiently wet to disintegrate, found to be 56 sec for F2 formulation prepared using the complexation technique. The wetting time of ITZ ODTs (F1) exceeding 3 minutes can be attributed to a key factor, primarily rooted in the inherent properties of ITZ. ITZ, classified as a Biopharmaceutics Classification System (BCS) Class II drug, is known for its poor water solubility, which is a significant challenge when developing a rapidly disintegrating oral dosage form. The drug's hydrophobic nature directly impacts the wetting and subsequent disintegration of the tablets, as the low solubility hinders water's ability to penetrate the tablet matrix efficiently [14].

Disintegration time, which is the time taken for the tablet to disperse into smaller particles, was determined to be 50 seconds for F2 formulation. This value is significantly lower than the acceptable standard of 3 minutes, underscoring the rapid disintegration capability of the tablet, a hallmark of

effective orally disintegrating formulations. In the F1 formulation containing ITZ, the disintegration results were again found to be more than 3 minutes. As explained above, the delay in disintegration can be attributed to ITZ being a BCS Class II drug, characterized by its low solubility active ingredient [14].

Dissolution studies further illuminated the efficiency of these formulations, with a particular focus on the cumulative percentage of drug release over time, as depicted in Figure 1. This analysis revealed that formulations which contained ITZ- β -CD complex, respectively, demonstrated a remarkably fast drug release rate, achieving %89.03 drug release within 30 minutes. This performance starkly contrasted with ITZ ODT formulations featuring β -CD which is a complexation agent. The notably enhanced dissolution rate observed in orally ODT formulation containing the ITZ- β -CD complex, in comparison to ODTs with free ITZ, can be attributed to the molecular encapsulation mechanism facilitated by β -CD. This cyclodextrin is known for its ability to form inclusion complexes with hydrophobic molecules like ITZ, significantly improving their aqueous solubility. The process involves the hydrophobic core of beta-cyclodextrin encapsulating the ITZ molecule, effectively masking its hydrophobicity and thus enhancing its solubility in water. This inclusion complex formation is crucial for ITZ, a BCS Class II drug characterized by its low solubility and high permeability, as it directly influences the drug's bioavailability by improving its dissolution profile. Moreover, the enhanced dissolution rate of ITZ when complexed with β -CD in ODT formulations can be further explained by the improved wettability and dispersibility of the complex within the gastrointestinal fluid. The presence of β -CD reduces the interfacial tension between the hydrophobic drug and the aqueous medium, facilitating quicker water penetration and, consequently, rapid disintegration and dissolution of the ODT. Additionally, the structural properties of β -CD, which include a toroidal shape with a hydrophobic cavity and a hydrophilic outer surface, contribute to its effectiveness as a solubility enhancer. This unique structure allows it to interact favorably with both the drug molecule and the aqueous environment, promoting the dissolution of poorly soluble drugs [15].

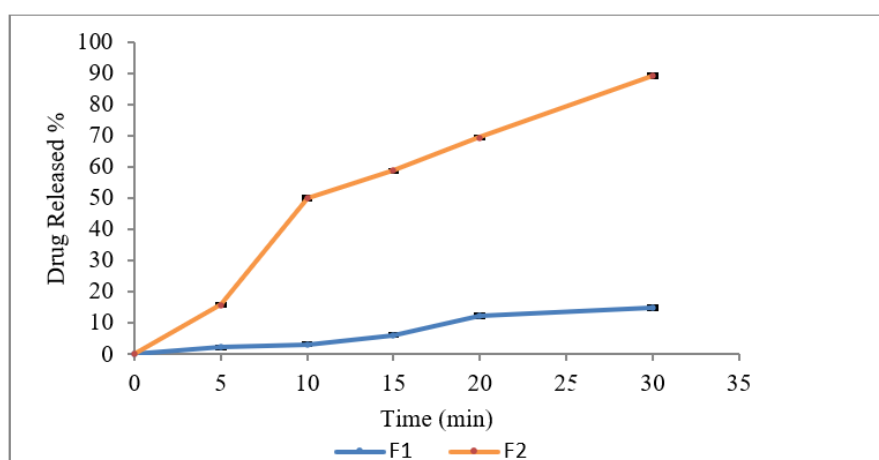


Figure 1. Drug release (%) of formulations versus time (min) ($n=3\pm SD$)

Additionally, the significant improvement in the dissolution rate of ODT formulations containing the ITZ- β -CD complex can be further enhanced by the incorporation of formulation excipients such as L-HPC, D-Mannitol, and Ac-Di-Sol. Each of these excipients plays a critical role in optimizing the formulation for rapid disintegration and dissolution, thereby complementing the solubility enhancement provided by the complex.

L-HPC acts as a disintegrant that facilitates water uptake and swelling of the tablet, leading to rapid disintegration. Its effectiveness is particularly notable in ODT formulations where the immediate release of the active pharmaceutical ingredient (API) is crucial. The mechanism by which L-HPC operates involves absorbing water rapidly upon contact with saliva, expanding, and creating porosity within the tablet matrix, which promotes quick disintegration.

D-Mannitol, a polyol with excellent taste-masking properties, serves as a bulking agent and also

enhances the palatability of ODTs. Its inclusion in the formulation contributes to the overall sensory acceptance of the dosage form. Furthermore, D-Mannitol has a high aqueous solubility, which aids in the dissolution process by creating a more favorable environment for the disintegration and dissolution of the drug-cyclodextrin complex.

Ac-Di-Sol, a superdisintegrant, significantly accelerates the disintegration of tablets by drawing water into the tablet matrix through capillary action and swelling. This rapid expansion exerts a disintegrative force within the tablet, leading to its breakdown. The use of Ac-Di-Sol in ODT formulations is particularly advantageous for achieving the quick release of the API, which is essential for ensuring rapid onset of action [4].

The synergistic effect of these excipients with the ITZ- β -CD complex significantly enhances the dissolution rate of ITZ from ODT formulations. By improving the wettability, porosity, and overall disintegration behavior of the tablet, these formulation aids ensure that the solubility enhancement achieved through the inclusion of β -CD is effectively translated into superior bioavailability and therapeutic efficacy.

The stability of pure ITZ and the F1 and F2 formulations was rigorously assessed under the challenging storage conditions of $40\pm 2^\circ\text{C}$ and $75\pm 5\%$ relative humidity, mimicking the harsh environments that might be faced in tropical regions or during uncontrolled transport, over a one-month period. Initial measurements showed ITZ concentrations of 84.35%, 90.29%, and 95.13% in the pure ITZ, F1, and F2 formulations, respectively, indicating the drug's potency at the beginning of the study. Despite the demanding storage conditions, the formulations demonstrated remarkable stability after one month. This study is essential for maintaining the therapeutic effectiveness and safety of the medication throughout its shelf life, ensuring the reliability of these formulations under various global climatic conditions [16].

AUTHOR CONTRIBUTIONS

Concept: T.C.; Design: T.C.; Control: T.C.; Sources: T.C.; Materials: T.C.; Data Collection and/or Processing: T.C.; Analysis and/or Interpretation: T.C.; Literature Review: T.C.; Manuscript Writing: T.C.; Critical Review: T.C.; Other: -

CONFLICT OF INTEREST

The author declares that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The author declares that the ethics committee approval is not required for this study.

REFERENCES

1. Yoo, S.D., Lee, S., Kang, E., Jun, H., Jung, J., Park, J.W., Lee, K. (2000). Bioavailability of itraconazole in rats and rabbits after administration of tablets containing solid dispersion particles. *Drug Development and Industrial Pharmacy*, 26(1), 27-34. [[CrossRef](#)]
2. Rouf, M.A., Vural, İ., Bilensoy, E., Hincal, A.A., Erol, D. (2010). Rapamycin-cyclodextrin complexation: Improved solubility and dissolution rate. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 70(1-2), 167-175. [[CrossRef](#)]
3. Gökbulut, E., Özdemir, N., (2017). Enhancement of solubility of itraconazole by complexation with β cyclodextrin derivatives. *Fabad Journal of Pharmaceutical Sciences*, 42(1), 1-6.
4. Çomoglu, T., Özyilmaz, E.D. (2019). Orally disintegrating tablets and orally disintegrating mini tablets-novel dosage forms for pediatric use. *Pharmaceutical Development and Technology*, 24(7), 902-914. [[CrossRef](#)]
5. Yin, X., Daintree, L.S., Ding, S.L., Ledger, D.M., Wang, B., Zhao, W., Qi, J., Wu, W. (2015). Itraconazole solid dispersion prepared by a supercritical fluid technique: Preparation, *in vitro* characterization, and bioavailability in beagle dogs. *Drug Design Development and Therapy*, 2015, 2801-2810. [[CrossRef](#)]
6. Shaheen, N., Zaman, S.U. (2018). Development of fast dissolving tablets of flurbiprofen by sublimation method and its *in vitro* evaluation. *Brazilian Journal of Pharmaceutical Sciences*, 54(4), e17061. [[CrossRef](#)]

7. Özyılmaz, E.D., Çomoğlu, T. (2023). Evaluation of two different orally disintegrating tablet formulations containing flurbiprofen inclusion complex and its solid dispersion. *Tropical Journal of Pharmaceutical Research (Online)*, 22(4), 705-711. [\[CrossRef\]](#)
8. Nijhu, R.S., Khatun, A., Hossen, M.F. (2024). A comprehensive review of particle size analysis techniques. *International Journal of Pharmaceutical Research and Development*, 6(1), 01-05. [\[CrossRef\]](#)
9. Vemula, S.K., Neduri, K. (2015). Lovastatin fast dissolving tablets: Formulation and *in vitro* evaluation. *Applied Science Reports*, 11(2), 76-82. [\[CrossRef\]](#)
10. Mishra, D.N., Bindal, M., Singh, S.K., Kumar, S.G.V. (2006). Spray dried excipient base: A novel technique for the formulation of orally disintegrating tablets. *Chemical & Pharmaceutical Bulletin*, 54(1), 99-102. [\[CrossRef\]](#)
11. Khinchi, M.P., Gupta, M.K., Bhandari, A., Sharma, N., Agarwal, D. (2011). Design and development of orally disintegrating tablets of famotidine prepared by direct compression method using different superdisintegrants. *Journal of Applied Pharmaceutical Science*, 1(1), 50-58.
12. Brniak, W., Jachowicz, R., Pelka, P. (2015). The practical approach to the evaluation of methods used to determine the disintegration time of orally disintegrating tablets (ODTs). *Saudi Pharmaceutical Journal*, 23(4), 437-443. [\[CrossRef\]](#)
13. Devi, M.S., Saraswathi, L., Chitraksh, A.S., Ch, M., Sairaj, M., Tajudin, S., Aishwarya, C. (2023). A study on evaluate pre-compression and post compression parameters of the formulated tablets using folic acid. *European Chemical Bulletin*, 12(5), 6356-6363.
14. Miyake, K., Irie, T., Arima, H., Hirayama, F., Uekama, K., Hirano, M., Okamoto, Y. (1999). Characterization of itraconazole/2-hydroxypropyl- β -cyclodextrin inclusion complex in aqueous propylene glycol solution. *International Journal of Pharmaceutics*, 179(2), 237-245. [\[CrossRef\]](#)
15. Hassan, H.A., Al-Marzouqi, A.H., Jobe, B., Hamza, A.A., Ramadan, G.A. (2007). Enhancement of dissolution amount and *in vivo* bioavailability of itraconazole by complexation with β -cyclodextrin using supercritical carbon dioxide. *Journal of Pharmaceutical and Biomedical Analysis*, 45(2), 243-250. [\[CrossRef\]](#)
16. Badawi, A., El-Nabarawi, M.A., El-Setouhy, D.A., Alsammit, S.A. (2011). Formulation and stability testing of itraconazole crystalline nanoparticles. *AAPS PharmSciTech*, 12(3), 811-820. [\[CrossRef\]](#)

Early access