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ORIGINAL ARTICLE / ÖZGÜN MAKALE

EVALUATION OF THE IMPACT OF DIFFERENT SUPERDISINTEGRANTS ON THE *IN VITRO* CHARACTERIZATION PARAMETERS OF ORALLY DISINTEGRATING TABLETS CONTAINING KETOPROFEN

FARKLI SÜPER DAĞITICILARIN KETOPROFEN İÇEREN AĞIZDA DAĞILAN TABLETLERİN İN VİTRO KARAKTERİZASYON PARAMETRELERİ ÜZERİNDEKİ ETKİSİNİN DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: *Orally Disintegrating Tablets (ODTs) have revolutionized pharmaceutical drug delivery, offering a patient-friendly alternative for those struggling with conventional tablet swallowing. This study delves into the impact of superdisintegrants (crospovidone, sodium starch glycolate, and croscarmellose sodium) on the in vitro characterization of Ketoprofen-containing ODTs. ODTs are designed to rapidly disintegrate in the oral cavity without water, enhancing patient compliance, ensuring faster therapeutic onset, and providing convenience.*

Material and Method: *The micromeritic properties of pre-compression Ketoprofen ODT blends were assessed for bulk density, tapped density, Hausner ratio, and compressibility index. ODTs were formulated using a direct compression method to maintain component uniformity. Comprehensive characterization included weight variation, tablet hardness, friability, wetting time, and in vitro disintegration time assessments. The drug content was determined through UV spectrophotometry of dissolved ODTs, and dissolution studies were conducted in pH 6.8 phosphate buffer using USP apparatus XXIV.*

Result and Discussion: *Results showed uniform tablet mass and favorable powder mixture flowability, ensuring ODT physical properties. Tablets exhibited excellent mechanical resistance with consistent hardness and low friability loss. All formulations demonstrated high and uniform drug content. Different superdisintegrants influenced wetting, disintegration, and dissolution times. Crospovidone exhibited the fastest wetting time but longer disintegration times, attributed to increased tablet hardness. Dissolution studies revealed that crospovidone-containing ODTs had faster drug release compared to croscarmellose sodium and sodium starch glycolate, aligning with literature findings. The study emphasized the importance of considering both wetting and disintegration times for a comprehensive evaluation of ODT performance. Croscarmellose sodium and sodium starch glycolate hindered drug release, forming gel-like masses impeding dissolution, while crospovidone enhanced drug release in formulated ODTs. In conclusion, the study provides valuable insights for pharmaceutical development and patient-centric drug delivery solutions, showcasing the influence of superdisintegrants on ODT performance and emphasizing the importance of considering various parameters for comprehensive evaluation.*

Keywords: *Croscarmellose sodium, crospovidone, ketoprofen, orally disintegrating tablet (ODTs),*

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sodium starch glycolate

ÖZ

Amaç: *Ağızda Dağılan Tabletler (ADT'ler), geleneksel tabletleri yutmakta zorluk çeken hastalar için önemli bir alternatif sağlayarak farmasötik ilaç dağıtımında önemli bir ilerleme kat etmiştir. Bu çalışma, Ketoprofen içeren ADT'lerin in vitro karakterizasyonu üzerinde krospovidon, sodyum nişasta glikolat ve kroskarmeloz sodyum gibi süper dağıtıcıların etkisine odaklanmaktadır. ODT'ler, hızlı parçalanma, gelişmiş hasta uyumu ve terapötik başlangıç hızı sağlamak üzere ağız içinde su kullanmadan tasarlanmıştır.*

Gereç ve Yöntem: *Basım öncesi ketoprofen içeren ADT toz karışımları mikromeritik özellikleri, hacim yoğunluğu, sıkıştırılmış yoğunluk, Hausner oranı ve sıkıştırılabilirlik indeksi değerlendirilmiştir. ADT'ler, doğrudan basım yöntemi kullanılarak hazırlanmıştır. Karakterizasyon çalışmaları kapsamında, ağırlık sapması tayini, tablet sertliği, kırılma dayanıklılığı, ıslanma süresi ve in vitro çözünme hızı testleri yapılmıştır. Etken madde miktarı, UV spektrofotometrik yöntem ile belirlenmiştir. Çözünme hızı çalışmaları, USP XXIV'e göre pH 6.8 fosfat tamponunda belirli zaman aralıklarında etken madde miktarının ölçülmesi ile değerlendirilmiştir.*

Sonuç ve Tartışma: *ADT'lerin fiziksel özellikleri, özellikle içerdikleri ketoprofen bakımından incelenerek toz karışımlarının homojenliğini ve istenen akıcılığı sağlama hedeflenmiştir. Tabletlerin mekanik direnci uygun, sertlik değerleri istenen aralıkta ve kırılganlıklarının yeterli düzeyde olduğu tespit edilmiştir. Ayrıca, tüm formülasyonlarda yüksek ve homojen etken madde içeriği gözlemlenmiştir. Farklı süper dağıtıcılarla hazırlanan ADT'lerin ıslanma, çözünme ve dağılma süreleri üzerindeki etkileri araştırılmış, krospovidonun diğerlerine göre daha hızlı ıslanma sağladığı belirlenmiştir. Ancak, krospovidon içeren tabletlerin in vitro çözünme sürelerindeki gecikmenin muhtemelen daha yüksek tablet sertliğinden kaynaklandığı gözlemlenmiştir. Çözünme hızı çalışmaları, krospovidon içeren ADT'lerin kroskarmeloz sodyum ve sodyum nişasta glikolat içerenlere göre daha hızlı etken madde salımı sağladığını göstermiş ve bu sonuç, literatürdeki bulgularla uyumlu bulunmuştur. Çalışma, ADT'lerin performansının kapsamlı bir değerlendirmesi için hem ıslanma hem de dağılma sürelerinin önemine vurgu yapmıştır. Kroskarmeloz sodyum ve sodyum nişasta glikolatın çözünmeyi geciktiren jel benzeri kütleler oluşturduğu, krospovidon içeren ADT'lerde ise etken madde salımının daha hızlı olduğu gözlemlenmiştir.*

Anahtar Kelimeler: *Ağızda hızlı dağılan tablet (ADTs), ketoprofen, kroskarmeloz sodyum, krospovidon, sodyum nişasta glikolat*

INTRODUCTION

Orally Disintegrating Tablets (ODTs) represent a significant advancement in pharmaceutical drug delivery, offering a patient-friendly alternative to traditional oral dosage forms. These tablets, designed to rapidly disintegrate in the oral cavity without the need for water, provide a convenient option for individuals facing challenges in swallowing conventional tablets or capsules. Formulated using techniques such as direct compression, freeze-drying, or sublimation, ODTs rely on carefully chosen excipients, including superdisintegrants to facilitate quick tablet breakdown. Their advantages include improved patient compliance, particularly in pediatric and geriatric populations, as well as a faster onset of therapeutic effects and enhanced convenience for on-the-go use. ODTs find applications across various therapeutic areas, from analgesics to antipsychotics, showcasing their versatility in accommodating different drug classes. Regulatory agencies, such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), provide guidelines to ensure the safety, efficacy, and quality of ODTs. Despite their benefits, challenges like taste-masking and stability maintenance persist, prompting ongoing research into innovative technologies like 3D printing and nanotechnology. In essence, ODTs have become a cornerstone in modern pharmaceutical development, reflecting a commitment to patient-centric drug delivery solutions [1].

The efficacy of ODTs depends critically on the selection and synergistic interaction of excipients. While crospovidone, sodium starch glycolate andcroscarmellose sodium are prominent superdisintegrants in orally disintegrating tablets (ODTs), their efficacy is fundamentally dependent on the synergistic interaction with other excipients. Superdisintegrants, are those substances, which facilitate the faster disintegration with smaller quantity in contrast to disintegrants. Widely

employed superdisintegrants, including croscarmellose sodium, crospovidone and sodium starch glycolate, demonstrate high efficiency at low concentration levels (2-5 w/w%) in tablet formulations, effectively enhancing the speed and completeness of tablet disintegration [2].

Croscarmellose sodium is derived from the sodium salt of cross-linked, partially O-carboxymethylated cellulose, whereas sodium starch glycolate originates from the sodium salt of a carboxymethyl ether of starch or a cross-linked carboxymethyl ether of starch. Both substances are anionic sodium salts, and their polymer backbones primarily consist of repeating glucose units [3].

On the contrary, crospovidone constitutes an insoluble, cross-linked homopolymer of *N*-vinyl-2-pyrrolidone and is characterized as nonionic. Chemically, the repetitive structure of crospovidone closely resembles that of N-methylpyrrolidone (NMP), a water-miscible, polar aprotic solvent renowned for its high interfacial activity and employed as a solubilizer in various applications. Crospovidone experiences substantial hydration and swelling, generating disruptive pressure within the tablet matrix. In contrast, croscarmellose sodium leverages its elastic properties; it readily undergoes deformation under compression, snapping back to its original shape and leading to tablet fragmentation [4].

Sodium starch glycolate is the sodium salt of carboxymethyl ether. Sodium starch glycoate is a white to off-white, bland, odorless, moderately free streaming powder. It absorbs water quickly, bringing about swelling which prompts fast breaking down of tablets and granules [5].

Bulking agents like microcrystalline cellulose provide the foundational framework for the tablet, while binders like polyvinylpyrrolidone ensure ingredient cohesion before the superdisintegrants exert their action. Lubricants like magnesium stearate facilitate smooth tableting and prevent unwanted sticking. Furthermore, flavorants and sweeteners play a crucial role in masking the often unpleasant taste of the active pharmaceutical ingredient (API) and its excipient partners. This delicately balanced composition of excipients, precisely harmonized, underpins the rapid disintegration that defines ODTs [1].

In this study, Ketoprofen was chosen as the model active ingredient, and the aim was to investigate the impact of superdisintegrants with different disintegration mechanisms namely; croscarmellose sodium, crospovidone and sodium starch glycolate on the *in vitro* characterization parameters of ODT formulations.

To comprehend the impacts of superdisintegrants in the prepared ODT formulations and compare superdisintegrants from different groups, several essential *in vitro* controls must be undertaken. Examining the micromeritic properties of a powder mass is essential for refining manufacturing processes, maintaining uniform dosage forms, predicting compression behavior, and improving the overall performance and stability of pharmaceutical formulations during storage. Special attention is given to evaluating disintegration time, which determines how quickly the tablet breaks down in the mouth. Ensuring uniformity in dosage units is achieved through tests like content uniformity. Friability testing assesses the tablet's resistance to abrasion during handling and transportation, ensuring its structural integrity. Additionally, hardness testing gauges the tablet's mechanical strength. *In vitro* dissolution studies are crucial for understanding the drug release profile from the ODT, offering valuable insights into its bioavailability. Evaluating wetting and *in vitro* dispersion time are also essential for ensuring the stability and shelf life of ODTs [6]. Collectively, a comprehensive range of *in vitro* tests validates the quality, functionality, and performance of ODTs, ensuring optimal outcomes for patients.

MATERIAL AND METHOD

Materials

Ketoprofen (Dolder, Germany), Aerosil (Colloidal silicon dioxide; Evonik Rohm GmbH, Germany), Polyvinylpyrrolidone K-30 (Crospovidone; Fluka, Germany), Microcrystalline cellulose (Avicel PH 101; FMC Biopolymer, Philadelphia), Aspartame (Deva Holding, Turkey), ++++Sodium starch glycolate (Explotab; JRS Pharma, Germany), Magnesium stearate (Riedel de Haen, Germany), Pregelatinized starch (Lyclatab, Roquette, France) and Menthol (OKimya, Turkey).

Methods

Micromeritic Properties of Ketoprofen ODTs

Before compression, the micromeritic properties of ketoprofen ODT blends were assessed for various formulations. The mixture blends for all formulations underwent pre-compression parameter evaluations, including tapped density, bulk density, compressibility index and Hausner ratio. These parameters were analyzed to compare the initial powder volume with the final (tapped) volume, providing insights into the flowability of the ODT powder blends. Bulk density was determined following the USP method I, while tapped density was determined using a tapped density tester (Aymes, Turkey) derved from the USP method II. The Hausner ratio and compressibility index were calculated using Equations (1) and (2) respectively [7]. These evaluations contribute to the comprehension of powder blend characteristics prior to compression, assisting in forecasting the flowability of ketoprofen ODT formulations.

$$\text{Hausner ratio} = \text{tapped density}/\text{bulk density} \quad \text{(Equation 1)}$$

$$\text{Compressibility index \%} = (\text{tapped density} - \text{bulk density}) \times 100 / \text{tapped density} \quad \text{(Equation 2)}$$

Tables 1 and 2 provide information on the composition of ketoprofen orally disintegrating tablets (ODTs) and the micromeritic properties of the ODT powder blends, respectively.

Table 1. Formulation details for Orally Disintegrating Tablets (ODTs) containing ketoprofen

Component	Amount (mg)	Function	F1	F2	F3
Ketoprofen	100	Active Pharmaceutical Ingredient (API)	✓	✓	✓
Microcrystalline cellulose	150	Bulking agent	✓	✓	✓
Pregelatinized starch	50	Disintegrant	✓	✓	✓
Polyvinylpyrrolidone	30	Binder	✓	✓	✓
Colloidal silicon dioxide	10	Glidant	✓	✓	✓
Magnesium stearate	5	Lubricant	✓	✓	✓
Aspartame	5	Sweetener	✓	✓	✓
Menthol	2	Flavorant	✓	✓	✓
***Superdisintegrant**					
*Croscarmellose sodium	5	Swelling and mechanical disruption	✓		
* Crospovidone	5	Wicking and swelling		✓	
* Sodium starch glycolate	5	Wicking and gel formation			✓

Table 2. Micromeritic properties of ketoprofen Orally Disintegrating Tablets (ODTs) (n=3±SD)

ODT Formulations	F1	F2	F3
Bulk density (g/ml)	0.51±0.33	0.45±0.22	0.33±0.37
Tapped density (g/ml)	0.58±0.42	0.528±0.37	0.31±0.29
Hausner ratio	1.16±0.52	1.16±0.63	1.04±0.41
Compressibility index (%)	14.06±0.41	14.24±0.51	19.67±0.31

Preparation of Ketoprofen ODTs

The preparation of the ODTs containing Ketoprofen involves a systematic direct compression method to ensure optimal therapeutic efficacy and patient compliance. Commencing with the accurate weighing of each component, including the active pharmaceutical ingredient (API) Ketoprofen, bulking agent microcrystalline cellulose, disintegrant (with each ODT formulation containing the same amount

but featuring a different type), binder polyvinylpyrrolidone, glidant colloidal silicon dioxide, lubricant magnesium stearate, sweetener aspartame, flavorant menthol, and the critical superdisintegrant croscarmellose sodium, the formulation is assembled. For the preparation of all formulations (F1, F2, and F3), precise weighing of all components, excluding the lubricant and glidant, was followed by thorough mixing in a cubic mixer (Erweka, Germany) for 15 minutes. Subsequently, the resulting blend underwent lubrication with magnesium stearate for an additional 5 minutes, after which the mixture was directly compressed into tablets. The quantities of all tablet components, except superdisintegrants, were consistently maintained. Using an eccentric single-punch tabletting machine (Korsch, Germany), flat-faced tablets weighing 357 mg and measuring 12 mm in diameter were manufactured. The tablet thickness and hardness were consistently controlled at 3.0 ± 0.1 mm and 3.5 ± 0.5 kg, respectively, across all formulations. Detailed information on the physical properties of the ODT formulations is presented in Table 3.

Table 3. Physical properties of ketoprofen Orally Disintegrating Tablets (ODTs) (n=3±SD)

	F1	**F2**	**F3**
Hardness (kg)	3.50±0.24	3.92±0.28	3.32±0.32
Friability (%)	0.68±0.15	0.59±0.29	0.48±0.21
Content uniformity (%)	99.85±0.36	100.04±0.29	99.97±0.33
Wetting time (sec)	44.33±2.48	34.67±3.10	62.00±2.31
***In vitro* disintegration time (sec)**	39.27±3.25	47.67±1.15	40.20±4.16

Characterization of ODTs

Weight Variation

To evaluate weight variation, twenty randomly chosen Orally Disintegrating Tablets (ODTs) from each formulation were individually weighed using a Sartorius BL 210S scale in Göttingen, Germany. The individual weights were subsequently compared with the average weight to ascertain the extent of weight variation. Additionally, the diameter and thickness of ten ODTs from each formulation were measured using a micrometer [8].

Tablet Hardness

To evaluate tablet hardness, which signifies the force required to break a tablet through radial compression, we utilized a tablet hardness tester, specifically the Monsanto tablet hardness tester. This measurement was performed to assess the tablets' crushing tolerance [8].

Measurement of Friability

To measure friability, ten tablets were weighed and introduced into the friabilator (Roche Friabilitor, Ludwigshafen, Germany). The tablets underwent rotation at 25 rpm, and subsequently, the friability percentage was computed [9].

Measurement of Wetting Time and *In Vitro* Disintegration Time

A folded piece of paper tissue (10.75 mm x 12 mm) was arranged in a culture dish with a diameter of 6.5 cm, filled with 6 ml of water. Subsequently, a tablet was positioned on the paper, and the duration for full wetting was documented. After achieving complete wetting, the tablet was then weighed. The *in vitro* disintegration time test assessed the tablets' capacity to break down into small fragments in fluid. The time taken for the tablet to completely disintegrate in the fluid was recorded. Three repetitions for each formulation were conducted [7].

Determination of Drug Amount

In the initial stage, ten Orally Disintegrating Tablets (ODTs) were weighed and finely powdered using a mortar from Ildam Kimya, Turkey. The average weight of a tablet was then calculated. An amount equivalent to the average weight of the tablet's content was accurately measured from the

powdered tablets. A small quantity of ethyl alcohol was added to dissolve the active material, and the solution was adjusted to a volume of 100 ml in a volumetric flask from Ildam Kimya, Turkey. The mixture underwent sonication for 10 minutes and was subsequently filtered. Next, 1 ml of this solution was transferred to another volumetric flask and diluted to 25 ml with pH 6.8 phosphate buffer. The absorbance value at 261 nm in this solution was determined using UV spectrophotometry, and the drug amount in the sample was calculated using the calibration equation [7].

Dissolution Studies

In vitro drug release was evaluated employing USP apparatus XXIV (paddle assembly) with a rotation speed of 50 rpm, while maintaining the temperature at 37 ± 5°C in 900 ml of pH 6.8 phosphate buffer as the dissolution medium. The percentage of drug release was calculated by withdrawing a 5 ml aliquot at different time intervals, filtering it through Whatman filter paper, and assaying it at 261 nm. To maintain the original volume, an equal volume of fresh dissolution medium was replenished. The dissolution studies were carried out in triplicate [7].

RESULT AND DISCUSSION

Physical Properties of the Tablet Blend

To ensure the uniformity of tablet mass, an analysis of the powder mixture's flow properties was conducted prior to compression. The powder mixture exhibited favorable flowability, as indicated by low Hausner's ratio (ranging from 1.04 ± 0.41 to 1.16 ± 0.63) and compressibility index values (ranging from 14.06 ± 0.41 to 19.67 ± 0.31). The free-flowing nature of the tablet powder mixture resulted in tablets with uniform weight and acceptable weight variation (3.61 %) due to consistent die fill. The tablets demonstrated good mechanical resistance, reflected in hardness values (ranging from 3.32±0.32 to 3.92±0.28 kg/cm²) and low friability loss (ranging from 0.48±0.21 to 0.68±0.15 %). Additionally, all ketoprofen ODT formulations exhibited high and uniform drug content, ranging from 99.85±0.36 to 100.04±0.29 (Table 3).

The Impact of Superdisintegrant Selection on the Wetting, Disintegration, and Dissolution Times of Ketoprofen ODTs

In the development of ODTs, optimizing the wetting time is crucial, as wetting serves as the initial stage of both disintegration and dissolution. In this study, the wetting time for ketoprofen ODTs ranged from 34.67±3.10 to 62.00±2.31 seconds, meeting the official requirements (not exceeding <3 minutes) for orodispersible tablets [10]. All the ODTs incorporating various disintegrants exhibited water absorption, leading to slight swelling and subsequent disintegration. This behavior aligns with the findings from literature research, indicating that sodium starch glycolate, crospovidone, and croscarmellose sodium disintegrate through analogous wicking and swelling processes. Due to their porous particle morphology, these disintegrants draw water into the tablet via capillary action, inducing secondary swelling, breakage of interparticle bonds, and ultimately facilitating tablet disintegration [11]. The wetting time of orally disintegrating tablets (ODTs) containing different superdisintegrants followed the order; crospovidone < sodium starch glycolate < croscarmellose sodium. Crospovidone demonstrated faster wetting of the tablets compared to croscarmellose sodium and sodium starch glycolate. ODTs with crospovidone (F2 formulation) outperformed those with other superdisintegrants, exhibiting a shorter wetting time 34.67±3.10 seconds (Table 3). The rapid swelling and dispersion of crospovidone in water, attributed to its superior hydration capacity, were evident. The high degree of swelling of crospovidone, was associated with a wicking mechanism that drew water into the tablet through capillary action.

In contrast, F3 formulation that contains sodium starch glycolate, known for its high water absorption rate and a swelling capacity of 6%, exhibited swelled tablets with wetting time 62.00 ±2.31seconds.

ODTs formulated with croscarmellose sodium (F1 formulation) displayed moderate swelling and wetting time 44.33±2.48 seconds (Table 3). Despite croscarmellose sodium's limited water solubility, it exhibited a higher degree of swelling, up to 4-8 times its initial volume.

The *in vitro* disintegration time of all ODTs was also assessed, and Table 3**.** presents the average disintegration time for all ODT samples, ranging from 39.27±3.25 to 47.67±1.15seconds. In the case of sodium starch glycolate and croscarmellose sodium, the *in vitro* disintegration times consistently proved shorter than the wetting times for all ODTs in this study. However, for ODTs containing crospovidone, a different trend emerged compared to the wetting test, with *in vitro* disintegration times longer than the wetting times. This difference is likely attributed to the greater hardness of the ODTs containing crospovidone.

In the realm of physiological circumstances, the breakdown of ODTs in the mouth involves two phases. The first phase encompasses saliva absorption, initiated upon placing the tablet on the tongue, followed by the second phase where the tablet breaks down into minute particles. This second phase is associated with the pressure between the tongue and the upper hard palate. Neglecting this pressure aspect, relying solely on wetting time calculations may prove insufficient for defining ODTs and could introduce biases in result evaluation.

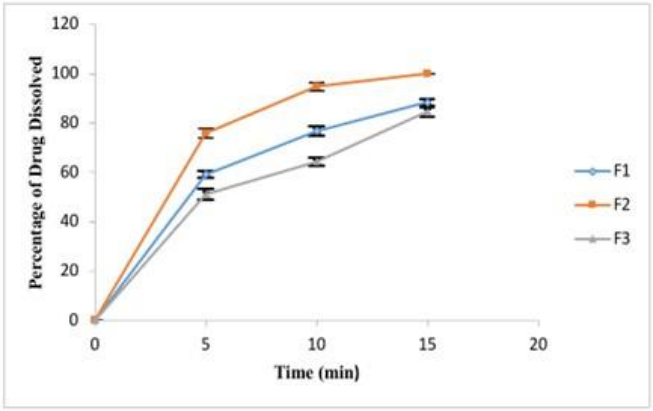

Figure 1. *In vitro* dissolution parameters in pH 6.8 phosphate buffer (n=3 ± SD)

Table 4. *In vitro* dissolution parameters in pH 6.8 phosphate buffer (n=3)

Formulation Code	D_5(%)[a]	D_{10} (%)[a]	D_{15} (%)[a]	$t_{\%50}$[b]	$t_{\%90}$[b]
F1	59.12±0.66	76.77±0.91	88.42±0.69	>30	>30
F2	75.86±0.98	94.73±0.84	≥100	>30	>30
F3	51.08±1.16	64.33±0.89	84.62±0.93	>30	>30

a D5, D10, D15: percent of drug dissolved in 5, 10 and 15 min.
b $t_{50\%,}t_{90\%}$: time to dissolve 50% and 90% of drug from tablet

The influence of superdisintegrants on the dissolution of ketoprofen from ODTs is depicted in Figure 1 and summarized in Table 4. *In vitro* dissolution studies were conducted to assess the impact of Croscarmellose Sodium (F1), Crospovidone (F2) and Sodium Starch Glycolate (F3) on the release profile of ketoprofen in the formulated ODTs. ODTs incorporated F1 and F3, the drug release improved to 64.33±0.89 to 76.77±0.91 % in 10 minutes respectively, though deemed insufficient for an ODT formulation. This behavior is attributed to the swelling ofCroscarmellose Sodium and Sodium starch glycolate, forming a gel-like mass that entraps some of the drug, hindering its release. Consistent with the literature, drug release from ketoprofen orally disintegrating tablets (ODTs) containing Crospovidone has been observed to be faster in dissolution rate studies [12].

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.

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