ORIGINAL ARTICLE

Rapid-Release ODF Loaded With Ketoprofen– Tromethamine Multicomponent Crystals: Formulation And Evaluation

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ABSTRACT

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with low solubility and limited bioavailability. This study aimed to formulate and evaluate an orally dissolving film (ODFs) containing ketoprofen–tromethamine multicomponent crystals to improve dissolution performance. The multicomponent crystals were prepared using the solvent evaporation method and incorporated into ODFs produced by solvent casting. Various concentrations of HPMC K4M and different plasticizers (PEG 400, propylene glycol, and glycerin) were investigated. The formulations were evaluated for organoleptic properties, thickness, surface pH, folding endurance, moisture content, swelling index, disintegration time, and dissolution profile. Ketoprofen content in dissolution samples was determined using a validated UV–Visible spectrophotometric method, and the data were analyzed using Mann–Whitney U test. Among the ten formulations screened, (F07), containing 2% HPMC K4M and 30% PEG 400, exhibited excellent flexibility (>300 folds), a disintegration time of 37.21 ± 1.93 s, and released 70.17 ± 0.41% ketoprofen within 5 minutes, representing a 2.93-fold ($p < 0.05$) higher dissolution rate than pure ketoprofen ODFs. These findings demonstrate that combining ketoprofen–tromethamine multicomponent crystals with ODFs technology is a promising strategy to enhance dissolution while providing a patient-friendly dosage form for individuals with swallowing difficulties.

Keywords: Disintegration time; dissolution profile; ketoprofen-tromethamine multicomponent crystal; oral dissolving film; solvent casting.

Introduction

Ketoprofen (2-(3-benzoylphenyl) propionic acid) is a nonsteroidal anti-inflammatory drug (NSAID) used for joint inflammation and rheumatoid arthritis [1]. Compared with other NSAIDs, it has a lower incidence of gastrointestinal side effects [2]. However, as a Biopharmaceutical Classification System (BCS) class II drug, ketoprofen has low aqueous solubility and high permeability [3], resulting in dissolution-limited absorption and variable oral bioavailability. Enhancing solubility and dissolution is therefore essential to improve its therapeutic performance [4]. Various strategies have been investigated, including solid dispersions [5], inclusion complexes [6], nanosuspensions [7], and multicomponent crystal formation with tromethamine [8], glutamine [9], malic acid, or tartaric acid [10]. The ketoprofen–tromethamine multicomponent crystal (1:1 molar ratio) has been shown to increase solubility 2.95-fold and achieve 89.56% dissolution within 60 minutes [8]. The amine group of tromethamine (pKa 8.07) interacts with the carboxylic acid group of ketoprofen (pKa 4.45), resulting in a ΔpKa of 3.62. Because ΔpKa exceeds 3, proton transfer readily occurs, producing a salt-type multicomponent crystal that enhances wettability and dissolution through ionization-driven solubilization [8,11].

formulated into tablets or capsules that still require water for administration which

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limits their benefit for certain patient groups. Successful clinical application therefore also, depends on pairing the solubility-enhanced drug with an appropriate dosage form that facilitates administration. ODFs rapidly disintegrate in saliva without the need for water, making them particularly suitable for patients with dysphagia, which affects approximately 26% of the population [12]. Incorporating ketoprofen–tromethamine multicomponent crystals into ODFs preserves their solubility advantage while providing a convenient, fast-dissolving dosage form [13].

ODFs typically contain an active ingredient, a film-forming polymer, plasticizers, and auxiliary excipients. Among the available film-forming polymers, hydroxypropyl methylcellulose (HPMC) is widely used because of its excellent film-forming ability, transparency, flexibility, and compatibility with hydrophilic link drug delivery systems. HPMC K4M provides suitable mechanical strength while maintaining rapid hydration and disintegration [14,15]. Compared with alternative polymers such as HPMC E15 and pullulan, HPMC K4M produces films with adequate mechanical properties at relatively low polymer concentrations (2–4%), making it suitable for fast-dissolving ODF formulations [16]. Therefore, incorporating ketoprofen–tromethamine multicomponent crystals into HPMC K4M-based ODFs was expected to enhance dissolution through the combined effects of improved drug solubility and rapid hydration of the polymeric matrix. Plasticizers such as PEG 400, propylene glycol, and glycerin improve film flexibility and reduce brittleness, thereby ensuring acceptable mechanical properties and dissolution performance. PEG 400 was selected as the primary plasticizer for HPMC-based ODFs because of its excellent compatibility with HPMC, its hydrophilic nature that facilitates water uptake and rapid film disintegration, its ability to produce shorter disintegration times than glycerin, and its favorable safety profile for oral administration [17].

Despite published reports on ODF development for individual APIs and on multicomponent crystal formation for ketoprofen, the combination of these two approaches has not been systematically explored, highlighting the need for further investigation. Accordingly, this study aimed to formulate and evaluate HPMC K4M-based ODFs containing ketoprofen–tromethamine multicomponent crystals using different plasticizers to identify the optimum formulation with desirable physicochemical properties and enhanced dissolution performance, thereby providing a patient-friendly dosage form suitable for patients with swallowing difficulties.

METHODS

Materials

The study utilized ketoprofen (SIMS Manufacturing, USA), Tromethamine (Merck, Germany), hydroxypropyl methylcellulose/ HPMC K4M (Lawsim Zecha, Indonesia), propylene glycol (DOW, Singapore), polyethylene glycol/ PEG 400 (Merck, Germany), sorbitol (STBC, Indonesia), glycerin (P&G chemicals, Singapore), ethanol pro analysis (Merck, Germany), methanol (Merck, Germany), Sucrose (Avantor, USA), phosphate buffer 6.8 and distilled water.

Preparation of Ketoprofen and Tromethamine Multicomponent Crystal Using Solvent Evaporation

Multicomponent crystal ketoprofen and tromethamine with a 1:1 molar ratio using the solvent evaporation method previously describe by Fitriani [8]. Ketoprofen (2.543 g) was dissolved in ethanol pro analysis, while tromethamine (1.211 g) was dissolved in a small amount of distilled water. The ketoprofen and tromethamine solutions were then combined and stirred at 300 rpm and maintained at 40–50 °C for 24 hours to yield a solid phase. The resulting ketoprofen–tromethamine multicomponent crystals were stored at room temperature in a desiccator containing silica gel.

Characterization of Multicomponent Crystal

Physicochemical characterization was performed using Differential scanning calorimetry (DSC; DSC-60, Shimadzu, Japan) at a heating rate of 10 °C/min from 30 to 300 °C under nitrogen purge; and Powder X-ray diffraction (PAN analytical MPD PW3040/60 tipe XPERT-PRO, Netherlands) in the 2θ range 5–50°

Formulation of ODF

A total of ten ODF formulations (F01–F10) were

designed using a systematic approach varying two independent factors: HPMC K4M concentration (4% [F01–F06] or 2% [F07–F10]) and plasticizer type and concentration (PEG 400, propylene glycol, or glycerin at 20% or 40% polymer for F01–F06; PEG 400 at 30% or 40%, propylene glycol at 40% for F07–F10), as detailed in **Table 1**. The plasticizer concentrations were expressed as a percentage of the polymer mass. Formulation design was guided by preliminary screening of disintegration time, with the goal of identifying the formulation providing disintegration ≤ 60 s as per ODF specifications. The optimized formulation was selected based on the shortest disintegration time combined with acceptable mechanical and physicochemical properties.

The multicomponent crystal ODF were prepared by solvent casting method. HPMC K4M and the selected plasticizer were dissolved in distilled water (mixture A), while ketoprofen–tromethamine multicomponent crystal, sucrose, and sorbitol were dissolved separately in distilled water (mixture B). Both mixtures were combined and homogenized using an ultraturrax at 5000 rpm for 5 minutes, then left to stand to remove air bubbles. The solution was cast into molds and dried at room temperature for 72 h. The resulting films were removed from the molds and cut into 2 × 2 cm pieces, containing 25 mg of ketoprofen and stored in sealed desiccators until evaluation.

Table 2. Formulation of ODF pure ketoprofen

Constituents	Formula
Ketoprofen (mg)	406.65
HPMC K4M (mg)	200
Polyethylene glycol 400 (mg)	60
Sucrose (mg)	500
Sorbitol (mg)	150
Aquades (g)	Ad 10

UV-Vis Analytical Method and Validation

Ketoprofen content was determined by UV-Vis spectrophotometry (UV-1900, Shimadzu, Japan) at an absorption maximum of ketoprofen in methanol p 75%. A calibration curve was constructed from five standard concentrations (4–12 µg/mL; n = 3 replicates per concentration). Method validation was performed according to ICH Q2(R1) guidelines and included linearity, precision, accuracy, Limit of Detection (LoD) and Limit of Quantification (LoQ) [18]. Therefore, the analytical method was considered suitable for the quantitative determination of ketoprofen content and dissolution testing of ketoprofen–tromethamine multicomponent crystal ODFs.

Drug Content Uniformity

Drug content uniformity was assessed by randomly selecting five ODF pieces (2 × 2 cm²) from each batch. Each film was cut into small fragments, and a quantity equivalent to 25 mg of ketoprofen was accurately weighed into a 25 mL volumetric flask, filled to volume with 75% methanol, shaken, and sonicated for 20 minutes. An aliquot of 1 mL was transferred into a 10 mL volumetric flask and diluted to volume with 75% methanol, then shaken and sonicated for an additional 5

Table 1. Formulations of ODF ketoprofen-tromethamine multicomponent crystal

Constituents	F01	F02	F03	F04	F05	F06	F07	F08	F09	F10
Ketoprofen-tromethamine MC (mg)	600.22									
HPMC K4M (mg)	400	400	400	400	400	400	200	200	200	200
Polyethylene glycol 400 (mg)	20	-	-	40	-	-	60	-	40	-
Propylene glycol (mg)	-	20	-	-	40	-	-	60	-	40
Glycerine (mg)	-	-	20	-	-	40	-	-	-	-
Sucrose (mg)	500	500	500	500	500	500	500	500	500	500
Sorbitol (mg)	150	150	150	150	150	150	150	150	150	150
Aquadest (g)	Ad 10	Ad 10	Ad 10	Ad 10	Ad 10	Ad 10	Ad 10	Ad 10	Ad 10	Ad 10

minutes. Subsequently, 5 mL of this solution was transferred into a 25 mL volumetric flask and diluted to volume with 75% methanol. A further 5 mL aliquot was then transferred into a 10 mL volumetric flask and diluted to volume with 75% methanol to yield a final concentration of 10 µg/mL. Ketoprofen content was quantified using UV-Vis spectrophotometry at the maximum absorption wavelength of ketoprofen. All measurements were performed in triplicate (n = 3), and results were expressed as mean ± standard deviation (SD). Content uniformity was considered acceptable if the measured ketoprofen content fell within 98.5–101.0%.

Evaluation of ODF

1. Organoleptic characteristics

The organoleptic properties of the ODF preparation were assessed in terms of color, odor, taste, homogeneity and texture [19].

2. Measurement of film thickness

Film thickness was measured using a micrometer on six ODF from each formula. An optimal and uniform thickness within the range of 5–200 µm is considered appropriate to ensure adequate absorption [20].

3. Folding Endurance

The folding endurance test was performed by repeatedly folding the film at the same site at an angle of 180° until it broke. Folding endurance was expressed as the number of folds the film could withstand without breaking. According to the literature, good quality films exhibit excellent flexibility with a folding endurance of approximately 300 folds per film [17,21–23].

4. pH measurement

The pH of the ODF was evaluated by measuring the surface pH using a calibrated digital pH meter, with each measurement performed in triplicate. The expected pH range was adjusted to match human salivary pH (6.8–7.2). When values were outside this range, adjustments were made using 0.1 N NaOH or 0.1 N HCl [24].

5. Moisture content

Moisture content was determined for three films from each formulation using a moisture balance at 105°C [25].

6. Swelling index

The swelling index was evaluated in phosphate buffer (pH 6.8) using Petri dishes. The film was weighed and the weigh recorded as Wo. The film immersed in 15 mL of buffer and reweighed at 5 s intervals until a constant weight (Wt) is achieved [26]. Calculate the swelling index using the following equation:

$$\text{SI } \frac{Wt-W0}{W0} \text{ x } 100\%$$

7. Disintegration time

The disintegration time was evaluated using the slide frame method. In this method, the film was placed horizontally in a Petri dish, and phosphate buffer solution pH 6.8 was dropped onto its surface. The time required for the film to rupture and completely disintegrate was recorded. An acceptable disintegration time for ODFs is ≤ 1 min [24].

8. Dissolution rate profile

The dissolution profiles of ketoprofen–tromethamine multicomponent crystals and pure ketoprofen formulated in the selected ODF were determined and compared. Dissolution testing was carried out using a USP type II apparatus at a paddle speed of 50 rpm. Each film was placed in a dissolution vessel containing 900 mL of phosphate buffer solution pH 6.8 maintained at 37 ± 0.5 °C. Samples were withdrawn at 30 s, 1, 3, and 5 min, with each 5 mL aliquot replaced by an equal volume of fresh medium. The ketoprofen content in the samples was quantified using a UV-Vis spectrophotometer [27].

Statistical Analysis

All data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using SPSS (Statistical Product and Service Solutions, IBM Corp., USA) and Microsoft Excel. Dissolution data of the optimized ketoprofen–tromethamine multicomponent crystal ODF were compared against those of the pure ketoprofen ODF using the Mann–Whitney U test, as the assumption of normality could not be confirmed for all datasets. A p-value of less than 0.05 was considered statistically significant.

RESULT AND DISCUSSION

Differential scanning calorimetry (DSC) is a thermal analysis method used to characterize solid-state

materials by recording changes in heat flow as a function of temperature or time. This technique allows the detection of thermal events in multicomponent crystals, including endothermic peaks associated with melting, phase transitions, and crystallization. The DSC analysis showed a melting point of ketoprofen–tromethamine multicomponent crystal (129.17°C), ketoprofen (96.48°C), and two distinct peaks for tromethamine at 141.35 °C and 172.62 °C, as shown in **Figure 1**. The appearance of a single, shifted melting peak supports the formation of a new crystalline phase, consistent with proton-transfer salt formation [8].

The physicochemical characterization using PXRD, as presented in **Figure 2**, was carried out by analyzing the 2θ positions within the range of 6°–50°, resulting in diffractograms for ketoprofen, tromethamine, and the ketoprofen–tromethamine multicomponent crystal. The crystalline phase was indicated by distinct sharp peaks in the diffractograms, reflecting the structural integrity of the compounds. Samples of ketoprofen, tromethamine, and the ketoprofen–tromethamine multicomponent crystal each exhibited distinct diffraction patterns. Ketoprofen showed characteristic peaks at 2θ = 6.41, 14.43, 15.62, 17.37, 18.46, 20.14, 24.20, and 30.23, while tromethamine exhibited peaks at 2θ = 14.28, 15.62, 20.22, 22.62, 24.20, 30.23, and 43.55. In the multicomponent crystal, changes in intensity, reductions in certain peaks, and the appearance of new peaks at 2θ = 15.62, 17.65, 17.98, 18.20, 20.59, 24.20, and 30.23 indicated the formation of a new crystalline phase. Based on pKa values, the type of interaction between the two components can be predicted: cocrystals are expected to form when ΔpKa < 3, while salts are formed when ΔpKa > 3. The pKa of ketoprofen is 4.45, and that of tromethamine is 8.07, giving a ΔpKa of 3.65 (>3). This suggests that the interaction between ketoprofen and tromethamine results in salt-type multicomponent crystals, consistent with previous findings [8]. Supported by DSC and PXRD characterization, the formation of multicomponent crystals was confirmed, demonstrating their potential application in the development of ODF formulations.

Furthermore, the DSC thermogram of the ketoprofen-tromethamine ODF (**Figure 1**) showed loss of the sharp melting endotherm characteristic of crystalline multicomponent crystal, suggesting reduced crystallinity after incorporation into the HPMC matrix. This change is likely attributed to molecular dispersion of the multicomponent crystal within the HPMC matrix and interactions between the drug and polymer during film formation. Reduced crystallinity is generally associated with improved wettability and dissolution behavior compared with highly crystalline materials [28,29]. These findings may explain the enhanced dissolution observed for the multicomponent crystal ODF, although further solid-state characterization would be required to confirm the extent of crystallinity changes.

Preliminary evaluation results across all ten formulations are summarized in **Table 3**. All formulations passed organoleptic inspection (odorless,

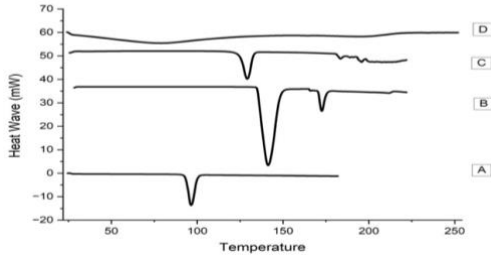


Figure 1: DSC Thermogram of (A) Ketoprofen, (B) Tromethamine, (C) Multicomponent Crystal, and (D) ODF Multicomponent Crystal

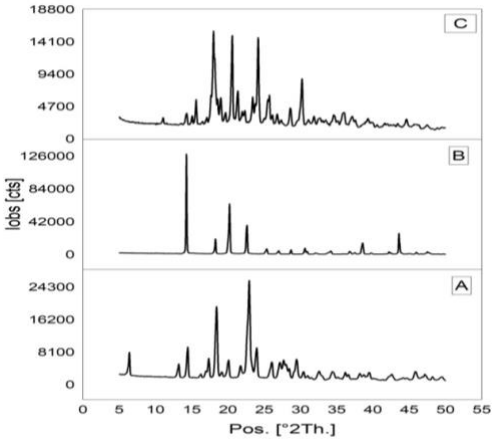


Figure 2: XRD Patterns of (A) Ketoprofen, (B) Tromethamine, and (C) Multicomponent crystal of ketoprofen and tromethamine

Table 3. Analytical Methods Validation Results

Analytical Method Validation		Results	Requirements
Linearity		r = 0.9992	r approaching 1
Precision (% RSD)	Morning	0.893 – 1.988	% RSD < 2
	Afternoon	0.634 – 1.485	
	Evening	0.509 – 1.643	
LOD (µg/ml)		0.445	-
LOQ (µg/ml)		1.484	-
Accuracy (%)	4	98.09	-
	8	102.63	
	12	98.96	

transparent or slightly turbid, non-sticky to slightly sticky), demonstrating adequate film formation with the excipients tested. Folding endurance exceeded 300 folds across all formulations, indicating acceptable mechanical flexibility and elasticity regardless of polymer or plasticizer type [17,21–23].

Disintegration time varied substantially between formulations (range: 37.21–78.00 s), and was most strongly influenced by HPMC K4M concentration and plasticizer type. Formulations prepared with 4% HPMC K4M (F01–F06) exhibited significantly longer disintegration times (60.0–178.0 s) compared to those with 2% HPMC K4M (F07–F10; 37.21–41.50 s). This inverse relationship between polymer concentration and disintegration rate is consistent with the known gel-forming behavior of HPMC, wherein higher polymer concentrations increase the viscosity and cohesive strength of the hydrated film matrix, thereby retarding water penetration and disintegration [14,15]. Among the formulations with 2% HPMC K4M, PEG 400 as plasticizer (F07, F09) produced shorter disintegration times than propylene glycol (F08, F10), attributable to the higher hydrophilicity and greater water-absorption capacity of PEG 400, which accelerates film swelling and rupture [17]. Glycerin-containing formulations (F03, F06) displayed slight turbidity, possibly due to glycerin-induced phase separation, and relatively longer disintegration times (≥ 64.6 s), which precluded their selection for further evaluation.

Based on these screening results, F07 (2% HPMC K4M, 30% PEG 400) and F09 (2% HPMC K4M, 40% PEG 400) were selected for advanced characterization due to their shortest disintegration times of 37.21 ± 1.93 s and 40.33 ± 5.57 s, respectively, combined with transparent appearance, non-sticky texture, and superior folding endurance.

Mechanical and physicochemical characterizations confirmed that all ODF possessed satisfactory performance. The pre-gel pH values for F07 (7.12 ± 0.00) and F09 (7.05 ± 0.004) fell within the physiological salivary range of 6.8–7.2, confirming mucosal compatibility and minimizing risk of irritation upon administration [24]. Film thickness was 0.096 ± 0.024 mm for F07 and 0.074 ± 0.007 mm for F09, both within the acceptable range of 0.005–0.200 mm [20].

Moisture content was significantly higher in F07 (11.97 ± 1.092%) than in F09 (9.65 ± 0.339%), which is consistent with the higher PEG 400 concentration in F07 and the hygroscopic nature of PEG 400. Elevated moisture content may improve film flexibility during handling but also predisposes the film to microbial growth and physical instability during long-term storage; this represents a recognized limitation of PEG 400-based ODFs that warrants evaluation in a formal stability study [17].

Swelling behavior was markedly different between the two formulations and provides mechanistic insight into their disintegration kinetics. F07 absorbed water rapidly and disintegrated within 15 seconds (swelling index at 5 s: 71.72 ± 4.27%; at 10 s: 96.93 ± 7.55%), while F09 retained structural integrity for up to 15 seconds (swelling index at 5 s: 31.58 ± 3.07%; at 10 s: 86.89 ± 18.45%; at 15 s: 94.97 ± 13.20%). The more rapid swelling of F07 is attributable to its higher PEG 400 content, which increases the hydrophilicity of the film matrix, lowers its cohesive strength upon hydration, and facilitates rapid water ingress [17]. This swelling mechanism, characterized by polymer chain relaxation followed by erosion, is consistent with the dissolution behavior typical of HPMC-based films at low polymer concentrations [14,17,30,31]. The significantly faster swelling rate of F07 directly explains its shorter

disintegration time relative to F09 (37.21 vs. 40.33 s) and supports its selection as the optimized formulation.

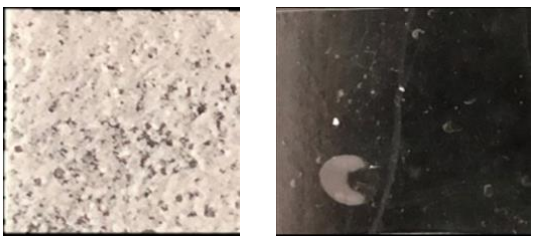
Based on **Table 3**, the validation results demonstrated that all obtained values closely approximated the true values, as the three concentration levels fell within the acceptance criteria. Accordingly, it can be concluded that the analytical method employed satisfies the requirements of method validation [18], rendering it suitable for the quantitative determination of ketoprofen content and the dissolution testing of ketoprofen–tromethamine multicomponent crystal ODFs.

Table 6. Drug Content Uniformity

Replicate	Absorbance	Ketoprofen Content (%)	Content Determination ± SD
1	0.633	99.93	99.65 ± 0.208
2	0.630	99.43	
3	0.631	99.60	

The ketoprofen content in the fabricated ODF formulations is presented in **Table 6**. The mean ketoprofen concentration in the ketoprofen–tromethamine multicomponent crystal ODFs was determined to be 99.65 ± 0.208%, which falls within the acceptance criteria for active pharmaceutical ingredient content of 98.5–101.0% [32].

The ODFs formulated with ketoprofen–tromethamine multicomponent crystals (MC) and pure ketoprofen using the same film base are shown in **Figure 3**. The ODF prepared with MC exhibited a clear and transparent appearance with a smooth texture, while those containing pure ketoprofen were white with a rough texture. This difference can be attributed to the low aqueous solubility of ketoprofen; when combined with water, the initially dissolved ketoprofen tends to precipitate, resulting in poor film uniformity.



(a) (b)

Figure 3: Comparison between ODF containing (a) pure ketoprofen and (b) ketoprofen-tromethamine multicomponent crystal

Based on the dissolution test results, the ODF containing ketoprofen–tromethamine multicomponent crystals exhibited a significantly higher dissolution profile compared to pure ketoprofen ODF [8]. At the 5th minute, the MC-ODF released 70.17 ± 0.41% of ketoprofen, while the pure ketoprofen ODF released only 24.00 ± 0.90%, representing a 2.93-fold increase, the difference between formulations was statistically significant ($p < 0.05$). This enhancement is likely attributed to the co-crystallization with tromethamine, which improves the solubility and dissolution rate of ketoprofen through salt formation [33] and partial reduction in crystalline during film formation, thereby facilitating drug release [34,35].

Beyond the intrinsic solubility enhancement of the ketoprofen–tromethamine multicomponent crystal itself, the ODF matrix contributed additionally to the fast release observed here. As a bulk powder, the multicomponent crystal previously required 60 minutes to reach 89.56% dissolution [8], whereas the same crystal loaded into the HPMC K4M-based ODF (F07) released 70.17 ± 0.41% of ketoprofen within only 5 minutes. This acceleration is consistent with the thin-film geometry, which maximizes the surface area exposed to the dissolution medium, combined with the rapid hydration and swelling of HPMC K4M that promotes fast disintegration and immediate liberation of the embedded crystals [14,15]. This indicates that the dissolution advantage of the multicomponent crystal is amplified, rather than merely preserved, when delivered through a fast-hydrating ODF matrix.

Whether this solubility advantage would be equally expressed in other dosage forms remains an open question. In a slower-hydrating matrix, such as a conventional compressed tablet, drug release would likely remain rate-limited by disintegration and diffusion through a thicker matrix, so the intrinsic

Table 4. Evaluation results of the selection polymer and plasticizer stage

Formula	Category					
	Organoleptic			Thickness ± SD (mm)	Folding endurance	DT ± SD (second)
	Visual	Odor	Texture			
F01	Transparent	Odorless	Non sticky	0.159 ± 0.021	>300	112 ± 4.97
F02	Not transparent	Odorless	Non sticky	0.129 ± 0.021	>300	60 ± 2.16
F03	Not transparent	Odorless	Slightly sticky	0.159 ± 0.013	>300	64.6 ± 10.8
F04	Transparent	Odorless	Non sticky	0.173 ± 0.014	>300	60.6 ± 3.30
F05	Transparent	Odorless	Non sticky	0.127 ± 0.023	>300	73.3 ± 4.78
F06	Not transparent	Odorless	Slightly sticky	0.134 ± 0.011	>300	178 ± 4.55
F07*	Transparent	Odorless	Non sticky	0.096 ± 0.024	>300	37.2 ± 1.93
F08	Transparent	Odorless	Slightly sticky	0.072 ± 0.008	>300	62.1 ± 7.22
F09*	Transparent	Odorless	Non sticky	0.074 ± 0.007	>300	40.3 ± 5.57
F10	Not transparent	Odorless	Slightly sticky	0.097 ± 0.016	>300	41.5 ± 8.90

Note: * = Selected formula

Table 5. Evaluation result of the selected ODF formula

Category		Formula		Target
		F07*	F09	
pH		7.12 ± 0	7.05 ± 0.004	6.8 – 7.2
Organoleptic	Appearance	Transparent	Transparent	Transparent
	Odor	Odorless	Odorless	Odorless
	Texture	Non sticky, smooth texture	Non sticky, smooth texture	Non sticky, smooth texture
	Taste	Less sweet	Less sweet	Sweet
	Homogenity	Homogeneous	Homogeneous	Homogeneous
Thickness (mm)		0.096 ± 0.024	0.074 ± 0.007	0.005 – 0.200
Folding Endurance		>300	>300	>300
Moisture content (%)		11.97 ± 1.092	9.65 ± 0.339	-
Swelling index (%)	5 second	71.72 ± 4.27	31.58 ± 3.07	-
	10 second	96.93 ± 7.55	86.89 ± 18.45	
	15 second	Dissolved	94.97 ± 13.20	
	20 second	Dissolved	Dissolved	
Disintegration time (second)		37.21 ± 1.93	40.33 ± 5.57	< 60

Note: * = Selected formula

solubility gain of the multicomponent crystal may only be partially realized. A comparable pattern is observed clinically for other tromethamine NSAID salts: dexketoprofen trometamol is formulated as fast-dissolving sachets or effervescent tablets specifically to exploit its salt-driven solubility for a rapid onset of action [NEW REF – penulis mohon verifikasi dan tambahkan sitasi yang sesuai]. This supports the view that dosage-form selection is a co-determinant, alongside crystal engineering, of overall dissolution performance, and this interaction merits systematic investigation across dosage for ms in future work.

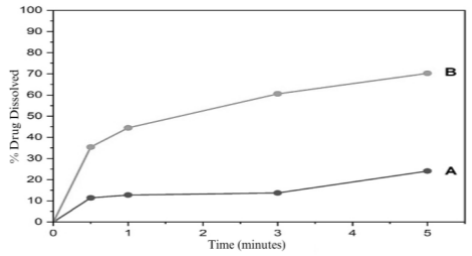


Figure 4: Graph comparing the dissolution profiles of (A) pure ketoprofen and (B) ketoprofen-tromethamine multicomponent crystal

This study has several limitations that should be acknowledged. Solid-state characterization of the multicomponent crystal was limited to DSC and PXRD; complementary techniques such as FTIR were not performed and could provide additional molecular-level confirmation of the proposed proton-transfer interaction. In addition, the dissolution profile was evaluated only up to 5 minutes, and longer-term release behavior was not assessed. Formal stability testing under accelerated conditions was beyond the scope of the present work, despite the elevated moisture content observed in the PEG 400-based optimized formulation (F07), which may pose a risk to long-term physical stability. Finally, the therapeutic relevance of the enhanced in vitro dissolution was not confirmed through in vivo pharmacokinetic evaluation. These aspects are recommended as priorities for future investigation.

CONCLUSION

This study successfully developed an orally dissolving film incorporating ketoprofen–tromethamine multicomponent crystals, with the optimized formulation F07 (2% HPMC K4M, 30% PEG 400) achieving a disintegration time of 37.21 ± 1.93 s and releasing 70.17 ± 0.41% ketoprofen within 5 minutes—a 2.93-fold improvement over the pure ketoprofen ODF ($p < 0.05$). The enhanced performance was attributed to the dual mechanism of proton-transfer salt formation and enhanced hydration of the polymer matrix, confirmed by DSC, and PXRD characterization. The combination of crystal engineering and ODF technology presents a pharmaceutically significant approach to addressing both the solubility limitations of BCS Class II NSAIDs and the clinical challenge of dysphagia, with potential to improve therapeutic outcomes in patients with swallowing difficulties. Future work should focus on accelerated stability evaluation under ICH Q1A conditions, in vivo pharmacokinetic studies in an appropriate animal model, and scale-up feasibility assessment for commercial manufacturing.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation.

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