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Research Paper

Ketoprofen-Tromethamine: Binary Phase Diagram of Multicomponent Crystal, Dissolution Rate, and Analgesic Activity Evaluation

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Abstract
Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) whose formulation options are limited due to its low dissolution rate in aqueous media. This research aimed to enhance the solubility of ketoprofen in distilled water and to compare the anti-inflammatory and analgesic effects of its resulting multicomponent crystal with tromethamine. The binary phase diagram of ketoprofen-tromethamine was created across molar ratios ranging from 1:9 to 9:1. The multicomponent crystal comprising ketoprofen and tromethamine in the selected ratio was synthesized using a solvent drop grinding method and subjected to further characterization for thermal properties, crystallinity, chemical groups, and morphology. The dissolution rate assessments were evaluated in CO_2-free distilled water. Pharmacological analyses examined the anti-inflammatory and analgesic effects of the multicomponent crystal. The binary phase analysis identified the 5:5 (1:1) molar ratio as optimal in forming a multicomponent crystal. Thermograms and diffractograms revealed crystalline alterations attributed to a new crystalline phase. The new multicomponent crystal exhibited approximately 2.7 times higher dissolution rate after 30 minutes, outperforming pure ketoprofen. Pharmacological assessments demonstrated superior analgesic effects of the multicomponent crystal. In summary, the ketoprofen-tromethamine cocrystal in 1:1 molar ratio offers enhanced dissolution rate and provides better analgesic activity than ketoprofen alone.

Keywords
Analgesic, Dissolution, Ketoprofen, Multicomponent Crystal, Tromethamine

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1. INTRODUCTION

The International Association for the Study of Pain (IASP) define pain as an horrid sensory and emotional experience resulting from tissue damage, either actual or potential, or described in terms of the damage (Raja et al., 2020). Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used drugs for pain relief (Swieboda et al., 2013). NSAID ketoprofen has antipyretic, analgesic, and anti-inflammatory activity and is indicated to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea, and pain management (Kuczyńska and Nieradko-Iwanicka, 2021). Studies have shown the anti-inflammatory efficacy of ketoprofen to be up to 20 times higher than ibuprofen, and up to 160 times higher than aspirin, and the analgesic effect to be 70 times that of aspirin (Sarzi-Puttini et al., 2013).

Ketoprofen (Figure 1) is a weak acid compound that is practically insoluble in water. Based on the solubility and permeability of ketoprofen, it belongs to Biopharmaceutical Classification System (BCS) class II drug with low solubility and good permeability (Zayed, 2014). Approaches to increase the ketoprofen solubility include modification of crystallization methods with a view to different coformers, solid dispersions with excipients, and nanopharmaceuticals (Beliatskaya et al., 2019; Belkacem et al., 2015; Browne et al., 2020; Das et al., 2021; Devi et al., 2022; Gobbo et al., 2020; Patel et al., 2023; Wais et al., 2017; Wicaksono et al., 2018; Yadav et al., 2013). In 2023, Sanas and Pachpute revealed that the formulation of ketoprofen as a nanosuspension significantly improved its bioavailability and drug release properties. In vitro experiments showed increased dissolution rates compared to conventional formulations, and in vivo studies with the nanosuspension revealed its superior pharmacokinetic parameters and therapeutic efficacy (Sanas and Pachpute, 2023).

Tromethamine (Figure 1) is a small amine molecule and

effective coformer in multicomponent crystals. For example, the crystalline modification of active pharmaceutical ingredient (API) combination indomethacin and mefenamic acid by incorporation of tromethamine conferred >1000 times higher solubility for the multicomponent crystal than for indomethacin (Bookwala et al., 2018), and the salt formation between mefenamic acid and tromethamine improved the dissolution efficiency of mefenamic acid 2.5-fold (Yuliandra et al., 2019).

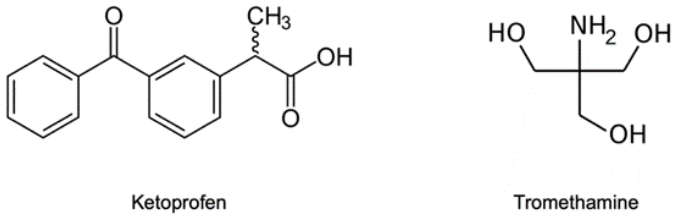

Figure 1. Molecular Structure of Ketoprofen and Tromethamine

When APIs are co-crystallized with pharmaceutically acceptable coformers, new crystalline forms with modified physicochemical properties are obtained (Lutfiyah et al., 2022). Crystal engineering strategies identify functional groups to form supramolecular synthons, intermolecular structural units held together by weak non-covalent interactions, mainly hydrogen bonds, resulting in homogeneous solid phases at room temperature. Tools to inform selection of coformers include the pKa-based models, the supramolecular synthon approach, the Cambridge Structural Database, the Hansen solubility parameter, hydrogen bond calculations, and binary and ternary phase diagrams (Dudek et al., 2020; Gyawali et al., 2021). In thermal analyses, solid phase transitions within a binary mixture can elucidate the connection of cocrystal formation and exothermic peaks (Yamashita et al., 2013).

The aim of this study was to formulate a ketoprofen cocrystal applying the binary phase diagram method and to compare the therapeutic effectiveness of the ketoprofen multicomponent crystal with that of pure ketoprofen.

2. EXPERIMENTAL SECTION

2.1 Materials

Ketoprofen was purchased from BOC Science (USA). Tromethamine, ethanol pro analysis, and λ-carrageenan were obtained from Merck (Germany). Carboxymethyl cellulose sodium was purchased from Bratachem (Indonesia).

2.2 Ketoprofen-Tromethamine Binary Phase Diagram Construction

A binary phase diagram between ketoprofen and tromethamine was established at molar ratios ranging from 1:9 to 9:1. Each ratio was prepared by weighing the respective components and dry grinding in an agate mortar for 15 minutes. The resulting ground solids were analyzed using differential scanning calorimetry (DSC). The two-phase diagram was constructed based on the endothermic peaks observed in each formula. Subsequent data analysis aimed to identify molar ratios with the potential to form multicomponent crystals.

2.3 Ketoprofen Multicomponent Crystalline Preparation

A ketoprofen-tromethamine multicomponent crystal was prepared in a 1:1 molar ratio. Ketoprofen and tromethamine were ground using an agate mortar and pestle with a few drops of ethanol for approximately 15 minutes, and the resulting dry mass was stored in a sealed container in a desiccator.

2.4 Multicomponent Crystal Characterization

The physicochemical properties were characterized for ketoprofen, tromethamine, and the multicomponent crystal of ketoprofen-tromethamine. Differential scanning calorimetry (DSC) (Shimadzu DSC 60 plus instrument, Japan) was employed to analyzed the thermal properties of each sample by heating from 30 °C to 200 °C at a rate of 10 °C per minute. X-ray diffraction (XRD) analysis was carried out using a PANalytical MPD PW3040/60 XPert Pro instrument (Netherlands) to determine the crystallinity. The analysis employed Cu Kα radiation at an operating voltage of 40 kV and a current of 40 mA, within the 2-theta range of 10-40°. Fourier-transform infrared (FT-IR) spectroscopy (Thermo Scientific, USA) was utilized to identify functional groups, analyzing a sample-KBr pellet in the wave number range of 4000-500 cm^{-1}. The crystal morphology was examined at various magnifications using a scanning electron microscope (Hitachi S-3400N, Tokyo).

2.5 Dissolution Rate Studies

The dissolution profiles of the ketoprofen-tromethamine multicomponent crystal, physical mixture, and pure ketoprofen were evaluated. The dissolution rate of ketoprofen and the cocrystal in CO_2-free distilled water was evaluated by using an Apparatus 2 dissolution tester (Hanson Elite 8, Hanson Virtual Instrument, USA). The test conditions were maintained at a temperature of 37±0.5 °C and stirred constantly by speed of 50 rpm. Each sample, containing 50 mg of ketoprofen, was weighed accurately and placed into 900 mL CO_2-free distilled water as the dissolution medium. Samples were taken at intervals of 5, 10, 15, 30, 45, and 60 minutes, filtered through a 0.45 μm pore filter (Whatman), and analyzed using a UV-Vis spectrophotometer (Shimadzu UV 1601, Japan) at 258 nm.

2.6 Analgesic and Anti-Inflammatory Activity Test

2.6.1 The Animal Test Group

The animals used in this study were male Wistar rats aged 2-3 months. A total of 18 rats were fasted for 18 hours. The rats were randomly divided into three treatment groups (six per group). Group I was the negative control, treated with 0.5% CMC Na suspension. Groups II and III were orally administered ketoprofen or ketoprofen-tromethamine multicomponent crystal, respectively, with the equivalent ketoprofen dose of 13 mg/kg. This study received approval from the research

ethics committee of the Faculty of Pharmacy, Universitas Andalas, under the reference number 58/UN.16.10.D.KEPK-FF/2023.

2.6.2 Analgesic Test

Analgesic activity of the samples was evaluated using the tail-flick test method. In this study, the tip of the tail of each rat was immersed in a water bath at a temperature of 50±2 °C. The time in seconds for withdrawal of the tail from the water, or the tail-flick latency, was recorded as the response of the rat to the painful stimulus. A longer reaction time was interpreted as improved analgesic activity. The cut-off time was 15 seconds as the limit to avoid tail injury by hot water. Failure to withdraw its tail within 15 seconds defined the rat as unaware of the painful stimulus. The time response to the painful stimulus was recorded before the drug administration and 15, 30, 60, and 90 minutes after administration of the drug.

The maximum possible effect (MPE) was calculated as the difference in response time between the treated and untreated groups, divided by the disparity between the cut-off point and the baseline (i.e., the untreated group), expressed as a percentage. The higher the MPE percentage, the greater the analgesic effect.

2.6.3 Anti-Inflammatory Test

The anti-inflammatory effect was assessed using a λ-carrageenan induced paw edema model. Rat paw edema was induced by injecting 0.2 ml of 0.5% w/v λ-carrageenan into the sub-plantar tissue of the left hind foot of each rat. Paw edema was measured using a plethysmometer before the λ-carrageenan injection and at intervals of 60, 120, 180, 240, and 300 minutes afterward. The anti-inflammatory activity was determined by calculating the percentage inhibition of edema in rats treated with ketoprofen and the cocrystal relative to the carrageenan control group. The inhibition of edema was quantified as the reduction in edema volume following drug administration, expressed as a percentage. A higher percentage of inhibition indicates a stronger anti-inflammatory effect.

2.6.4 Data Analysis

The data obtained in this study were the time responses to pain stimuli and paw volume, shown as mean ± SD. The data were analyzed using one-way ANOVA followed by the Duncan test at the 95% confidence level. Data were analyzed using SPSS software.

3. RESULTS AND DISCUSSION

3.1 Ketoprofen-Tromethamine Binary Phase Diagram

Selecting an appropriate drug to coformer ratio is a critical determinant in developing cocrystals to optimize their pharmaceutical properties. Drawing insights from previous research indicating the value of thermal analysis techniques for strategically selecting ratios conducive to cocrystal formation (Yamashita et al., 2013), differential scanning calorimetry (DSC) data was used to construct a binary phase diagram, providing thermal profiles of drug-coformer mixtures at varying molar ratios. DSC reveals distinct endothermic or exothermic peaks indicative of phase transitions or molecular interactions. Comparison of these thermal events between samples can identify API-coformer ratios that exhibit characteristic patterns associated with optimal cocrystal formation. This systematic approach lays the groundwork for subsequent development and characterization of cocrystals with enhanced pharmaceutical attributes.

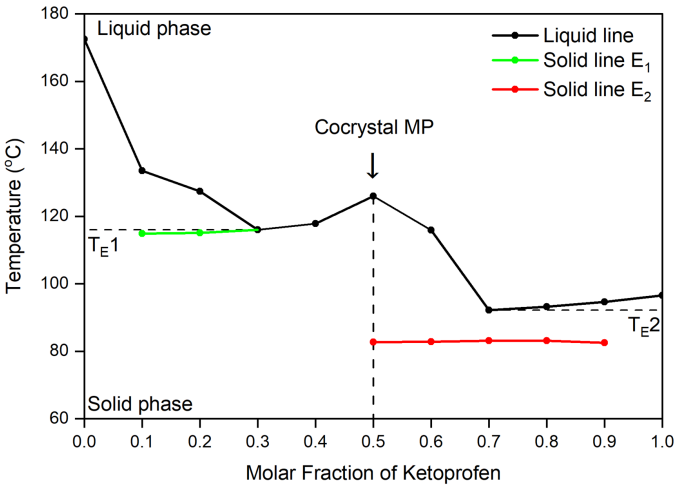

Figure 2. Binary Phase Diagram of Ketoprofen-Tromethamine

Figure 2 represents the binary phase diagram of ketoprofen and tromethamine in various molar ratios. The diagram pattern shows the W form usually indicating the possibility of cocrystal formation. The two lowest melting points are eutectic temperatures where the two solids melt together. In diagrams showing the W shape, the drug-coformer ratio likely to form a cocrystal is indicated by the highest melting point between these two eutectic points (Zaini et al., 2010).

3.2 Ketoprofen-Tromethamine Multicomponent Crystal Characterization

The ketoprofen DSC thermogram revealed a single, well-defined endothermic peak at 96.53 °C representing the melting point. Tromethamine exhibited two endothermic peaks at 141.45 and 172.53 °C. Based on the binary phase diagram (Figure 2), the 5:5 (1:1) molar ratio sample confers the highest melting point at 126.02 °C, so this ratio was selected to formulate the crystal using the solvent drop grinding method. The DSC thermogram of the cocrystal powder (Figure 3) indicates a reduction in intensity and a shift to a lower temperature of the melting point peak, indicating a decrease in crystallinity.

X-Ray diffraction analysis was performed to assess alterations in the pattern and degree of crystallinity of ketoprofen in the resulting multicomponent crystal. Figure 4 depicts an overlay of diffractograms for the cocrystal and its individual components. Ketoprofen and tromethamine exhibit a high degree of crystallinity characterized by distinct interference peaks.

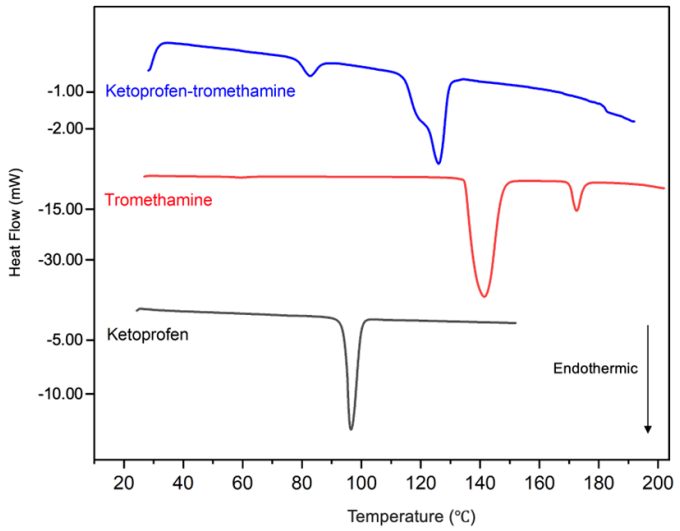

Figure 3. Overlay of Ketoprofen, Tromethamine, and Ketoprofen-Tromethamine Cocrystal Thermogram

Specifically, ketoprofen displays high-intensity peaks at angles of 2θ = 14.3551°, 18.6711°, and 24.1831°, and tromethamine displays peaks at 2θ = 14.2251°, 18.6971°, and 24.1311°. The cocrystal exhibits new peaks that differ from each component at angles of 15.3721°, 20.3915°, 26.7001°, 28.5338°, and 34.5954°, describing a new crystalline phase.

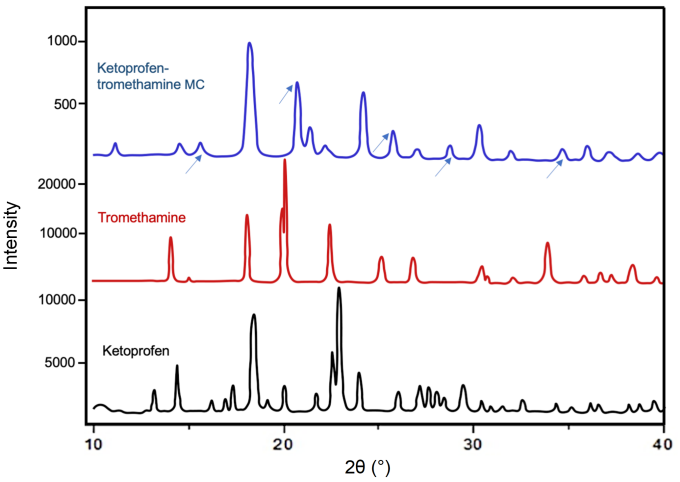

Figure 4. Overlay Diffractogram of Ketoprofen, Tromethamine, and Ketoprofen-Tromethamine Cocrystal

According to theory, differences in pKa values can be employed to predict the type of multicomponent crystal that will be formed. Salts are expected for pKa differences greater than 2 or 3. The pKa value of ketoprofen is 4.45, whereas that of tromethamine is 8.95, indicating the potential for the two substances to form a salt (Grothe et al., 2016; Yuliandra et al., 2019; Zaini et al., 2019).

FT-IR analysis is valuable for an initial examination of intermolecular interactions between two solid components. FT-IR spectra can reveal transmission band shifts, providing insights into functional group interactions and whether they involve a salt or cocrystal. The FT-IR spectra overlay for the cocrystal, intact ketoprofen, and coformer are illustrated in Figure 5. The strong, precise band at 1693.53 cm^{-1} for ketoprofen represents the stretching vibration of the carboxylate (COOH) function. For the multicomponent crystal, this stretching band shifts to higher wavenumber at 1824.69 cm^{-1}. Furthermore, a considerable shift is observed in the O−H stretching band from 2979.11 to 3155.60 cm^{-1}, suggesting an intermolecular hydrogen bond between ketoprofen and tromethamine (Fulias et al., 2015) and suggestive of a cocrystal.

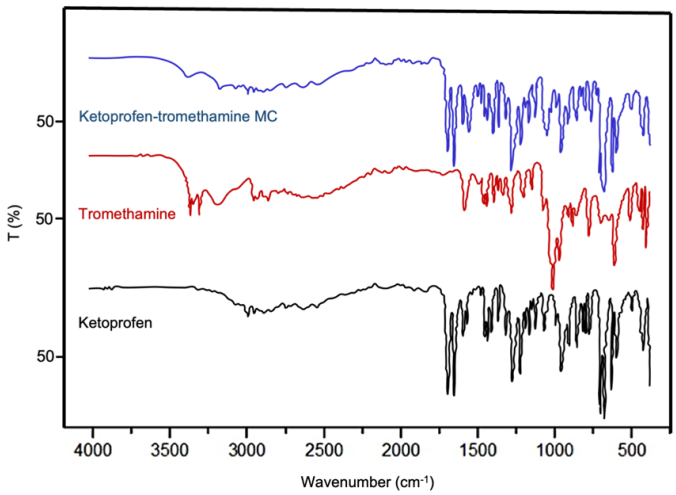

Figure 5. Overlay of FT-IR Spectra of Ketoprofen, Tromethamine, and Ketoprofen-Tromethamine Cocrystal

Scanning electron microscopy (SEM) was applied to elucidate the morphological changes in the materials before and after the cocrystal formation. At magnifications of 500× and 1000×, SEM revealed ketoprofen to be an irregular, porous crystalline solid (Figures 6A and 6B), while tromethamine exhibited block-like crystals with a slightly uneven surface (Figures 6C and 6D). The ketoprofen-tromethamine cocrystal exhibited a distinct crystal morphology, differing from those of its individual components (Figures 6E and 6F), and supporting a physical interaction between ketoprofen and tromethamine, not a physical mixture.

3.3 Dissolution Rate Studies

Dissolution rate tests of pure ketoprofen and the ketoprofen-tromethamine cocrystal were carried out in CO_2-free distilled water, and the dissolution profiles are presented in Figure 7. The rate of dissolution of ketoprofen in the cocrystal was significantly higher than that of pure ketoprofen, an increase attributed to the hydrophilic nature of tromethamine (Yuliandra et al., 2019). After 30 minutes, 97.53% of the cocrystal was dissolved, compared to only 36.09% of pure ketoprofen.

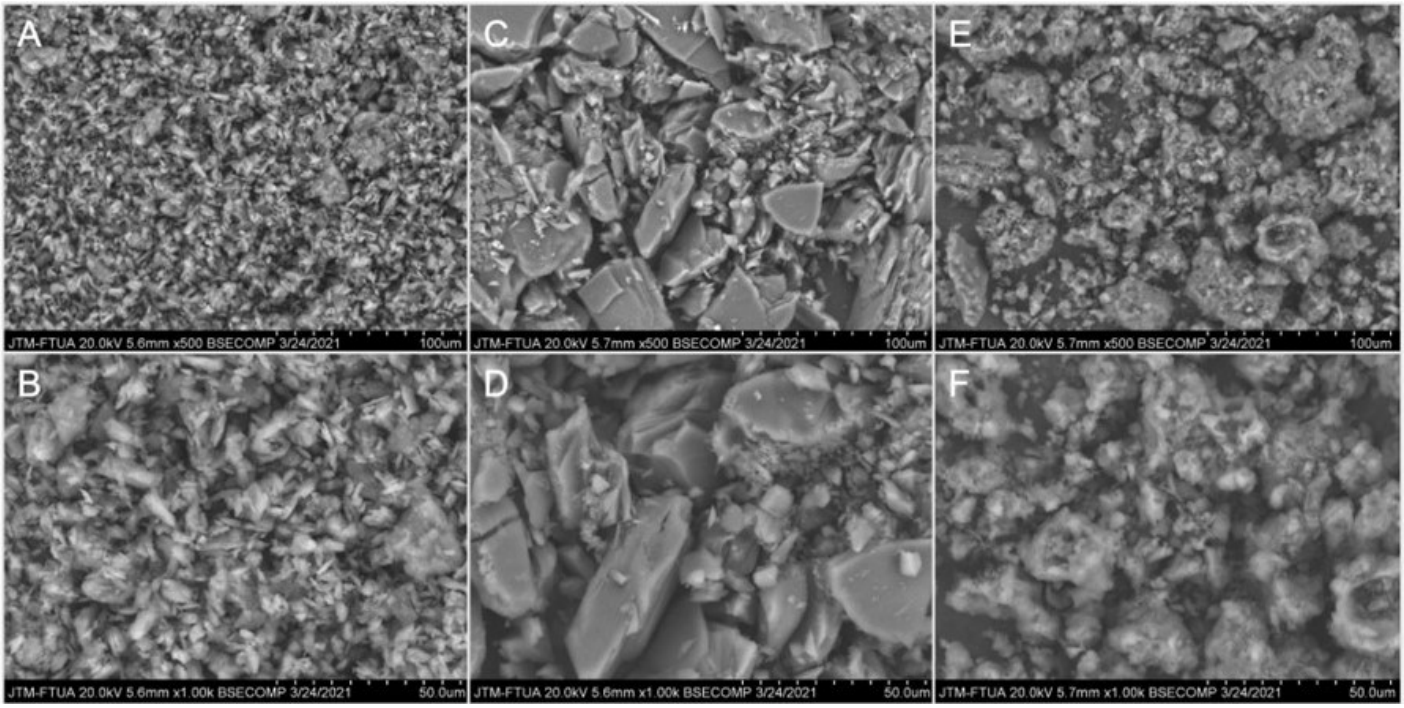

Figure 6. SEM Micrograph of Ketoprofen (A and B), Tromethamine (C and D), and Cocrystal 1:1 (E and F)

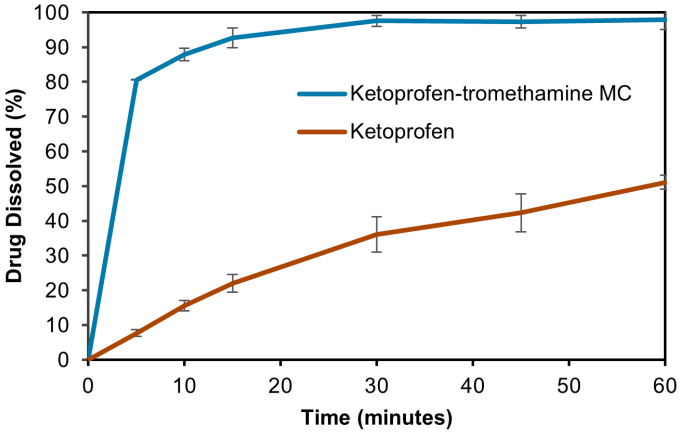

Figure 7. Dissolution Profile of Intact Ketoprofen and Cocrystal in CO_2-Free Distilled Water

Another parameter used to evaluate solubility is dissolution efficiency, a measure of the quantity dissolved over time, represented as the area under the curve (AUC). The average dissolution efficiency is calculated by comparing the area under the dissolution curve to time (t) with the area of a square when the active substance is 100% dissolved (Chatzizaharia and Hatziavramidis, 2015). Dissolution efficiencies of 31.56% for pure ketoprofen and 92.42% for the ketoprofen-tromethamine cocrystal again indicate the positive effect of the hydrophilic coformer on the solubilization of ketoprofen in aqueous media.

3.4 Analgesic and Anti-Inflammatory Activity Test

To compare the analgesic effects of ketoprofen and the cocrystal, the rat tail-flick method was applied. Animals used in this study were acclimated for 7 days to their new environment to reduce stress. The tail-flick test has been used to determine drug anti-nociceptive properties in response to pain from high intensity phasic stimulus (Dzoyem et al., 2017). The tail flick is a product of polysynaptic reflexes in the spine, regulated by the supraspinal structures. Administration of heat, cold, and mechanical or electrical stimuli can activate this reflex (Gregory et al., 2013). Temperatures above 48 °C can cause strong stimulation of pain receptors resulting in intense pain sensations (Green and Akirav, 2010). Acute pain induces the release of peripheral mediator caused by the inflammation of the damaged tissue (Santenna et al., 2019).

In the tail-flick test used in this study, the reflex involves withdrawing the tail from hot water at a temperature of 50±2 °C (Goyal et al., 2013). Induction was the same for each animal, dipping 3-5 cm of the tail into hot water. The tail-flick time was determined before and 15, 30, 60, and 90 minutes after the administration of the drug preparation. ANOVA followed with Duncan's test were used to analyzed the data. Based on the analysis, there were significant differences between groups (p <0.05), indicating that the average time required for rats to flick their tails between groups was different (Table 1).

The results showed that the normal time of response to the pain stimulus was in the range of 3.0-3.5 seconds. In the negative control group, the treatment failed to significantly increase the response time (p >0.05), although there was a slight

Table 1. Results of Average Rat Response Time to Pain Stimulus in Seconds in Tail Flick Test

Group	Response Time to Pain Stimulus in Seconds (mean ± SD)				
	0 minute	After 15 minutes	After 30 minutes	After 60 minutes	After 90 minutes
Control	3.0 ± 0.00	2.3 ± 0.51	3.6 ± 0.51	4.0 ± 1.26	4.1 ± 1.16
Ketoprofen	3.5 ± 0.54	5.8 ± 0.75[ab]	6.8 ± 1.32[ab]	6.0 ± 0.63[ab]	5.5 ± 1.04[ab]
Ketoprofen-tromethamine	3.3 ± 0.51	8.2 ± 0.75[ab]	8.3 ± 1.50[ab]	7.3 ± 0.81[ab]	6.8 ± 0.75[ab]

[a] denotes p value <0.05 of standard and test drug compared to control group;
[b] denotes p value <0.05 of test drug compared to standard drug; One-way ANOVA with post hoc Duncan's test was used to difference the between group.

increase in response time after 30, 60 and 90 minutes. This can be attributed to the body's natural adaptation to pain mediated by natural analgesics, endogenous morphine or endorphins, that increase the ability to endure pain.

The ketoprofen and cocrystal groups showed a significant difference in response time to painful stimuli with p value <0.05 compared to the control group. The tail flick latency was found to be higher in these two groups and this increased response time was observable 10 minutes after treatment. The maximum analgesic activity of both the ketoprofen and cocrystal test drug was seen at 30 minutes after treatment, when the average response times were 6.8 and 8.3 seconds, respectively (Table 1, Figure 8). The percentage of MPE was 62.35% for ketoprofen and 99.41% for cocrystal ketoprofen. Furthermore, the cocrystal ketoprofen also showed a significant longer response time to the stimuli compared to the pure ketoprofen (p <0.05).

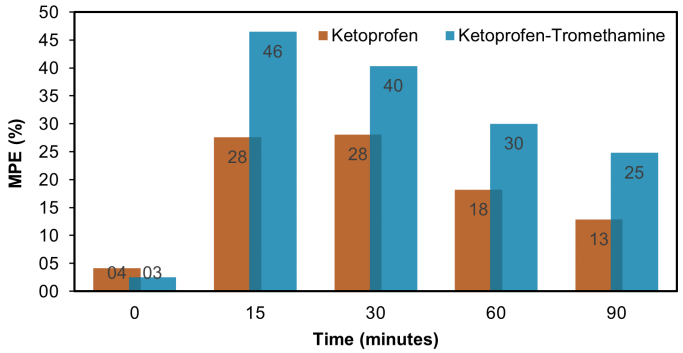

Figure 8. MPE (%) Comparison of Intact Ketoprofen and Ketoprofen-Tromethamine Multicomponent Crystal Using the Tail-Flick Method

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) widely used in the treatment of pain, inflammation, and arthritis and is reported to have rapid and effective analgesic activity. This study was aimed to evaluate the analgesic activities of the standard ketoprofen and the test multicomponent ketoprofen. Ketoprofen works by non-specifically inhibiting the COX-1 and COX-2 enzymes, thereby reducing the production of prostaglandins (PGE2) and prostacyclin (PGI2) which are mediators of inflammation (Kuczyńska and Nieradko-Iwanicka, 2021). Because of its high lipo-solubility, ketoprofen can easily cross the blood brain barrier within 15 minutes to affect the central nervous system (Pereira-Leite et al., 2017). Based on the results of this study, the ketoprofen cocrystal showed better analgesic activity than intact ketoprofen, and the difference was significant (p <0.05).

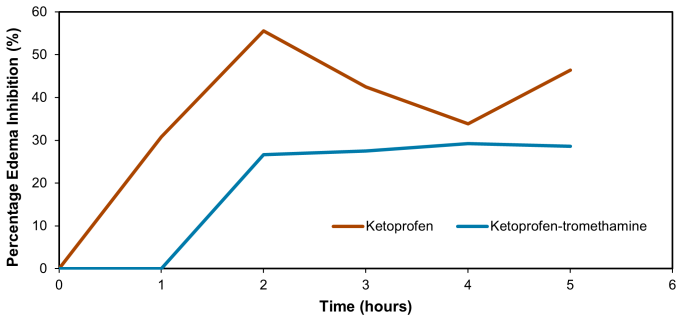

Figure 9. Edema Inhibition (%) Comparison of Intact Ketoprofen and Ketoprofen-Tromethamine Multicomponent Crystal Using the Carrageenan-Induced Paw Edema

In Figure 9, the effects of administering ketoprofen and ketoprofen cocrystal to the edema inhibition was presented, meanwhile the comparison to a control at different time points are detailed in Table 2. The drug formulations were administered orally at a dose of 13 mg/kg bw. Significant changes in paw volume were observed at 4 hours, indicating a meaningful difference between the test group and the control group, with p <0.05. Figure 10 shows that the edema inhibition of multicomponent ketoprofen was stronger than that of ketoprofen at each sampling time.

The paw edema test was conducted to assess the anti-inflammatory properties of ketoprofen and the multicomponent ketoprofen. Rat paws were injected with the inflammatory agent carrageenan, which induced paw swelling, a characteristic marker of inflammation. Both ketoprofen and the cocrystal reduced paw volume, indicative of their anti-inflammatory effects.

Inflammation is a local response of tissues to injury, serving as one of the body's defense mechanisms to inhibit the spread of harmful agents (Mahat and Patil, 2007). Several reactions are associated with the onset of inflammatory symptoms and tissue damage, including edema, leukocyte infiltration, and

Table 2. The Effects of Ketoprofen and Ketoprofen Multicomponent Compared to the Control Group at Different Time Points in the Carrageenan-Induced Paw Edema Model

Group	Change in Paw Volume (mL) ± SD				
	1 hour	2 hours	3 hours	4 hours	5 hours
Control	0.26 ± 0.13	0.45 ± 0.13	0.80 ± 0.15	0.65 ± 0.10	0.56 ± 0.10
Ketoprofen	0.18 ± 0.04	0.20 ± 0.06	0.46 ± 0.15	0.43 ± 0.12[a]	0.30 ± 0.08[a]
Ketoprofen-tromethamine	0.33 ± 0.21	0.33 ± 0.21	0.58 ± 0.13	0.46 ± 0.05[a]	0.40 ± 0.16

[a] indicates p-value < 0.05 compared to the control group for both standard and test drugs.

granuloma formation. Inflammation is a highly complex reaction involving numerous mediators (Amdekar et al., 2012).

Acute carrageenan-induced inflammation is a procedure suitable for determining the anti-inflammatory activity of a formulation. The development of paw edema in the carrageenan-induced paw edema model in rats can be depicted with a biphasic curve. The first phase of inflammation occurs within one hour after carrageenan injection, primarily due to injection trauma and the production of various compounds (Singh and Newman, 2011), including anti-inflammatory and proinflammatory mediators (such as prostaglandins, leukotrienes, histamine, bradykinin, and TNF-α) (Amdekar et al., 2012). The carrageenan-induced paw edema model in rats is sensitive to compounds with cyclooxygenase inhibition as a mechanism of action, making it suitable for evaluating the anti-inflammatory effects of NSAIDS like ketoprofen (Singh and Newman, 2011). Ketoprofen works by non-specifically inhibiting COX-1 and COX-2 involved in prostaglandin synthesis, which is evident from the inhibition of the inflammatory response after 4 hours. A significant difference is observed between the test drug group and the control group.

These findings reinforce the well-established anti-inflammatory properties of ketoprofen in the context of NSAIDs. It is particularly noteworthy that the ketoprofen-tromethamine cocrystal can potentially enhance the anti-inflammatory effects. Continued investigation must be conducted to gain a full understanding of the therapeutic efficacy of this multicomponent system in addressing inflammation, as its anti-inflammatory effect cannot solely be attributed to the cyclooxygenase pathway.

The pharmacological assessments in this study indicate that the ketoprofen-tromethamine cocrystal exhibits a promising analgesic effect, suggesting its potential therapeutic utility in pain management. The crystal's enhanced dissolution rate and potential for improved bioavailability make it an intriguing candidate for further exploration in pharmaceutical formulations. However, further studies, including clinical trials, are needed to validate its safety and efficacy for human use.

4. CONCLUSIONS

The ketoprofen-tromethamine cocrystal, synthesized through the solvent drop grinding method in a 1:1 molar ratio, demonstrates improved dissolution characteristics. Additionally, its superior analgesic properties, as evidenced by pharmacological assessments, hold promise for applications in pain management.

5. ACKNOWLEDGMENT

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