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Original Article

PREPARATION AND SOLID-STATE CHARACTERIZATION OF KETOPROFEN-SUCCINIC ACID-SACCHARIN CO-CRYSTAL WITH IMPROVED SOLUBILITY

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ABSTRACT

Objective: This study aimed to improve the solubility of Ketoprofen, a non-steroidal anti-inflammatory drug (NSAID) that belongs to the Biopharmaceutical Classification System (BCS) Class II, through co-crystallization using succinic acid and saccharin coformers in a 1:1:1 and 2:1:1 molar ratio.

Methods: The slurry method was utilized to prepare the ketoprofen co-crystals, which were then subjected to various physical-chemical characterization techniques such as melting point determination, dissolution studies, differential scanning calorimetry (DSC), X-ray diffraction (XRD), and Fourier transform infrared (FTIR) spectroscopy.

Results: The results showed that the 1:1:1 molar ratio of ketoprofen-succinic acid-saccharin co-crystal (Formula 1) exhibited higher solubility than the solubility standard of Ketoprofen and the 2:1:1 molar ratio of the co-crystal (Formula 2). The dissolution profile (Q_{30}) of Formula 1, Formula 2, and standard Ketoprofen were 96.73±1.77, 93.09±1.16, and 70.22±4.72, respectively. These findings suggest that co-crystallization with succinic acid and saccharin conformers using the slurry method can significantly enhance the solubility of Ketoprofen.

Conclusion: The 1:1:1 molar ratio of ketoprofen-succinic acid-saccharin co-crystal (Formula 1) was the most effective formulation among the tested samples, demonstrating the highest solubility. This research may provide valuable insights for developing novel drug formulations with improved bioavailability and therapeutic efficacy.

Keywords: Crystal engineering, Ketoprofen, Co-crystal, Solubility

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INTRODUCTION

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) with nonselective cyclooxygenase (COX) inhibitory action, similar to ibuprofen. Based on the Biopharmaceutics Classification System (BCS), Ketoprofen belongs to BCS class II, which has low solubility in water but high permeability [1-3]. Solubility is an important physicochemical property for predicting drug absorption in the gastrointestinal tract [4, 5]. Poor solubility and limited dissolution of active pharmaceutical ingredients (APIs) are significant challenges in developing pharmaceutical preparations. According to BCS, most Class II compounds are poorly soluble but highly permeable and suitable for the pH of gastrointestinal fluid [6-8]. Despite high permeability, drugs from Class II often have low oral bioavailability due to slow and limited drug release in the gastrointestinal fluid. Therefore, efforts are being made to develop drugs with low solubility but rapid effects. Crystal modification is a technique used to develop a formulation for active ingredients with poor solubility in water [9, 10]. Co-crystallization can change the physicochemical properties of APIs, including dissolution, intrinsic solubility [11], melting point, hygroscopicity, compressibility, bulk density, and friability [12]. Co-crystals are multicomponent molecular crystals comprising two or more molecules with chemical differences, including solvents, hydrates, and stoichiometric [13] and non-stoichiometric lattice inclusion compounds [14]. Co-crystallization can alter the physicochemical properties of drugs without changing their pharmaceutical properties [15]. Co-formers can increase the dissolution rate and must be readily soluble in water, non-toxic, pharmacologically inert, capable of increasing API solubility in water, able to bind with API through hydrogen bonding [16-18], non-covalently [16, 19], chemically compatible, and not form complex bonds with API [12, 20]. Previous studies have shown that co-formers, such as organic acids or molecules with amino functional groups, can form stable co-crystals [21]. Co-crystal formation by the slurry method involves dissolving equimolar amounts of substances in a small amount of methanol at ambient temperature. The solution evaporates slowly at room temperature for 48 h to promote co-crystallization [22]. The formation of calcium co-crystal of atorvastatin and nicotinamide resulted in co-crystal atorvastatin-nicotinamide, which has higher solubility and dissolution rates than standard atorvastatin. Increased stability and dissolution rates also occurred in co-crystals of adefovir dipivoxil with saccharin co-former [23]. The physicochemical properties of the prepared Ketoprofen co-crystals were further characterized by powder x-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier transform infrared (FTIR) spectroscopy and solubility study.

MATERIALS AND METHODS

Material

This study utilized equipment such as glassware (IWAKI, Pyrex), an analytical balance (Ohaus), a pH meter (Ohaus Starter 3100), a drying cabinet, a baking sheet, an electric stove, a granule sieve with number 80, a stopwatch, a dissolution test apparatus (RC 6D, USP XXIII with paddle stirrer), a UV spectrophotometer (Milton Roy, Genesys 10), a sonicator (2510 Branson), a cuvette (Hemmet), a basin, an evaporator (Heidolph), an Ultraturax, a melting point apparatus, X-Ray Diffraction, a Spectrophotometer-Fourier Transform Infra-Red, and a Differential Scanning Calorimetry. The materials used were Ketoprofen (PT. Kalbe Farma), succinic acid (Merck p. a), saccharin (Merck p. a), 96% ethanol, 37% HCl (Merck p. a), NaOH, and distilled water.

Methods

Ketoprofen-succinic acid-saccharin blend

Coformers for co-crystal synthesis can include food additives, preservatives, pharmaceutical excipients, and other active substances that can form non-covalent bonds. Coformers reported to

form co-crystals include carboxylic acids, amides, carbohydrates, amino acids, and alcohols [24]. For this study, saccharin and succinic acid were chosen as coformers due to their excellent solubility in water. Two different formulas were prepared for the synthesis of ketoprofen co-crystals with succinic acid and saccharin, with molar ratios of 1:1:1 and 2:1:1. The materials were weighed, ground in a mortar to obtain a fine powder, and then dissolved in the appropriate solvents. In Formula 1, Ketoprofen was dissolved in 100 ml of 96% ethanol, while succinic acid and saccharin were dissolved in 100 ml of distilled water. In Formula 2, Ketoprofen was dissolved in 200 ml of 96% ethanol, while succinic acid-saccharin was dissolved in 200 ml of distilled water. The solutions were then mixed. Ethanol as a solvent could help accelerate the co-crystal formation process by increasing molecular movement and the formation of hydrogen bonds [25].

The formation of Co-crystals by slurry method

The slurry method involves mixing the active substance with the coformers and adding the appropriate solvent at room temperature to obtain a slurry-like mixture. The mixture is then evaporated until all solvent has disappeared, resulting in a solid mixture [26]. The slurry formed between the two components can lead to co-crystal formation when dried for two days at 40 °C [8]. The formed ketoprofen-succinic acid-saccharin mixture was stirred with a 300-rpm magnetic stirrer for 15 min until a homogeneous mixture was obtained. A homogenizer was then used at 2400 rpm for 10 min to obtain a homogeneous mixture with a smaller particle size. The mixture was then evaporated for 15 min to remove the ethanol solvent. After the slurry was formed, it was poured into a baking sheet and placed into a drying cabinet for 24 h at 27 °C until the co-crystal powder was obtained. The co-crystal formation is characterized by several physicochemical methods, including melting point determination, X-ray diffraction for crystallinity testing, Fourier Transform Infrared (FTIR) spectroscopy to identify functional groups in the co-crystals, thermal analysis using Differential Scanning Calorimetry (DSC), and a co-crystal solubility test.

RESULTS AND DISCUSSION

Co-crystal synthesis

A co-crystal is formed by the interaction between crystallized molecules, which involves modifying the crystal configuration of a solid material by changing the interaction between the molecules that organize the formation and breaking of non-covalent bonds, including hydrogen bond, Van der Waals bond, π bond, electrostatic bond, and halogen bond [27]. The synthesis process of Ketoprofen co-crystals with succinic acid and saccharin coformers using the slurry method resulted in a suspension (slurry) that was dried to become a white co-crystal powder. The white-colored crystals were the product of the co-crystal formation.

Co-crystal physical characterization

Melting point test

Compounds characterized by elevated melting points generally exhibit reduced solubility [28-30]. The melting point test results of standard Ketoprofen were compared to those of modified co-crystal Ketoprofen. The observations of the melting point test results for Ketoprofen, coformers, and co-crystals are presented in table 1. There was a decrease in the melting point between Ketoprofen and co-crystal ketoprofen Formula 1 and Formula 2. Co-crystal Formula 1 had the lowest melting point. Factors that affect the melting point of co-crystals, such as the molecule configuration inside the crystal lattice, the degree of freedom of the molecule conformation, the molecule's symmetry, and the interaction between molecules [31, 32]. A reduction in the melting point indicates an increase in the solubility of Ketoprofen caused by the effect of succinic acid and saccharin.

Table 1: Melting point test results of ketoprofen and co-crystal formulas 1 and 2

Sample	Melting point sample experiment (°C)	Melting point reference (°C)	Reference author
Ketoprofen	96	93–96, 96.1	[1, 33]
Succinic acid	188	184-187	[34, 35]
Saccharin	230	229.63	[36, 37]
Co-crystal formula 1	76	-	
Co-crystal formula 2	77	-	

X-ray diffraction test

A co-crystal can be characterized through X-ray diffraction, where a new interaction formed in the co-crystal can give rise to new diffraction peaks compared to its pure substance [38]. Previous research has shown that a change in the XRD pattern will exhibit new peaks and peak changes that indicate the formation of a co-crystal [39]. The X-ray test results are presented in the diffractogram in fig. 1. The diffraction peak intensity from a co-crystal is lower than that of a standard compound due to a change in crystal habit. In the standard Ketoprofen and co-crystal ketoprofen diffractograms, a reduction in intensity was observed at 6.3126, 18.3094, and 22.9618 degrees, indicating a change in shape, structure, or addition in the crystal lattice [40]. The obtained diffractogram from the co-crystal synthesis process showed the formation of co-crystal Ketoprofen–succinic acid–saccharin because a new peak was found or a pattern of diffractogram between standard Ketoprofen and co-crystal ketoprofen product had changed. Based on the comparison results in table 2 among standard Ketoprofen, co-crystal Formula 1, and co-crystal Formula 2, the highest decrease in diffractogram intensity was observed in the co-crystal diffractogram ketoprofen Formula 1. This indicates that modifying Ketoprofen and succinic acid–saccharin coformers with a molar ratio of 1:1:1 caused a change in the crystal lattice, resulting in Formula 1 having the highest solubility.

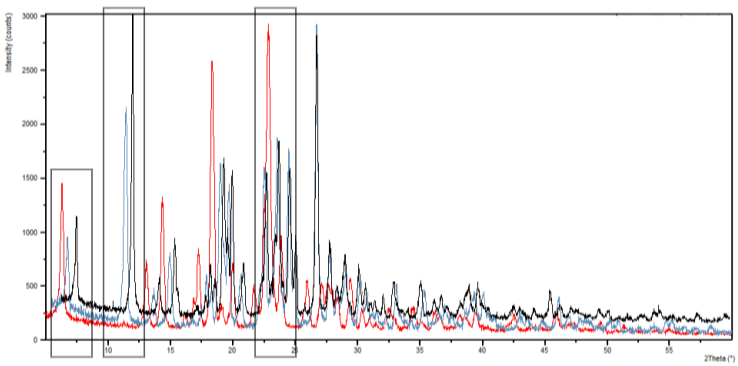

Fig. 1: XRD Diffractogram of standard ketoprofen (red), co-crystal formula 1 (blue) and co-crystal formula 2 (black)

Table 2: X-ray test results of standard Ketoprofen, co-crystals of ketoprofen formulas 1 and 2

Pos. [°2Th.]	Height standard ketoprofen	Pos. [°2Th.]	Height Co-crystal formula 1	Pos. [°2Th.]	Height Co-crystal formula 1
6.3126	1204.85	6.3457	440.25	6.3663	590.34
18.3094	2303.92	18.3295	770.69	18.3915	1170.64
22.9618	2805.07	22.9468	1063.26	22.9076	1182.49

FTIR test (Fourier transform infra-red)

FTIR analysis can be used to identify functional groups in a substance, and in a co-crystal, it can identify a new bond that forms. The FTIR test in this study aimed to identify a chemical interaction between medicine with a coformer produced from the co-crystal synthesis process. A new group detected in the infrared spectrum, such as OH-groups, indicates such an interaction [41]. The FTIR spectrum showed an interaction, such as a hydrogen bond between Ketoprofen and succinic acid. This is shown by a shift of the wavenumber in ketone C=O groups to a higher frequency in co-crystal Formula 1 and 2 compared to Ketoprofen. Forming a co-crystal generally involves weak bonds, especially hydrogen bonds in functional groups (4000–1000 cm-1). In that area, a water molecule or solvent to form a crystal lattice was observed through a shift from peak vibration [42]. It indicates that a hydrogen bond has formed between ketoprofen-succinic acid-saccharin. The results of the FTIR test are presented in the spectrum in fig. 2.

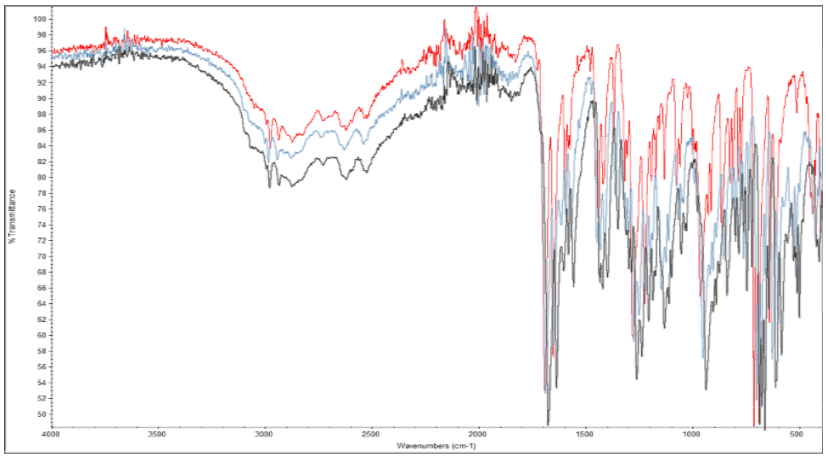

Fig. 2: FTIR spectrum ketoprofen (red), co-crystal formula 1 (blue) and co-crystal formula 2 (black)

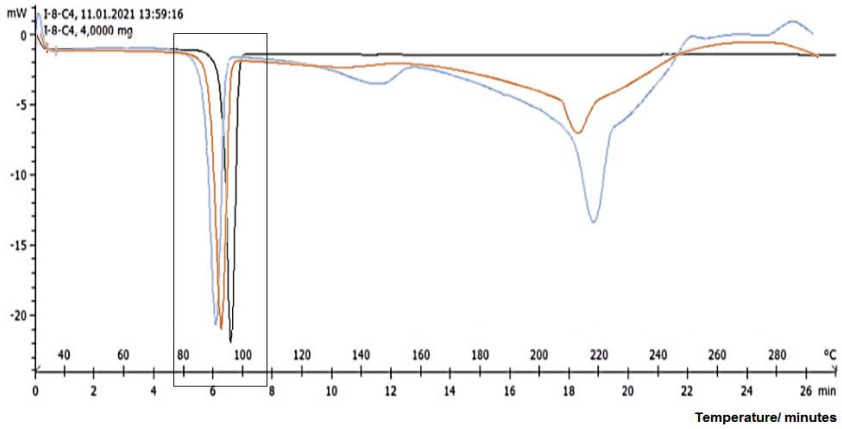

Fig. 3: DCS thermogram of standard ketoprofen (black), co-crystal formula 1 (blue) and co-crystal formula 2 (red)

DSC thermal analysis

DSC thermal analysis testing provides an endothermic or exothermic peak result that indicates a change in the formation of medicinal crystals. Such changes include melting, evaporation, decomposition, or polymorphic transition [43]. The parameter measured by this instrument is the melting point and enthalpy energy from the co-crystal. In our study, thermal analysis using DSC was conducted by heating at 100 °C/minute at temperatures between 30 °C and 250 °C, which revealed a shifting temperature of the endothermic peak in standard Ketoprofen. The thermogram for the DSC analysis is shown in fig. 3.

The thermogram for Ketoprofen and co-crystals Formula 1 and 2 revealed decreased peak temperature. The peak endothermic temperature for Ketoprofen was 95.08 °C; for co-crystal Formula 1 (92.41 °C) and co-crystal Formula 2 (93.04 °C). A crystal lattice and size change caused This melting point reduction [44]. The energy required to melt the co-crystal was smaller than that required to melt standard Ketoprofen. The thermogram also showed a reduction in enthalpy energy between standard Ketoprofen, co-crystal formula 1, and formula 2. The most significant reduction of enthalpy energy occurred in co-crystal Formula 1, with ΔH = 50.72 J/g compared to standard Ketoprofen with ΔH = 113.49. Therefore, we can conclude that the decrease in melting point and enthalpy of fusion was caused by a change in co-crystal size and a decrease in the number of crystal lattices produced from co-crystallization compared to standard Ketoprofen, which also required less energy to melt those crystals

[45]. Based on DSC thermal analysis, the change in the crystal lattice product resulting from co-crystallization confirmed the formation of a new crystalline phase (co-crystal). The thermogram for co-crystal formula 1 showed three peaks, while that for co-crystal formula 2 showed only two. This suggests that in co-crystal formula 1, the crystal phase was more pronounced.

Co-crystal chemical characterization

Dissolution test

This test determines the amount of standard Ketoprofen and Ketoprofen in the co-crystal. The dissolution profiles of standard Ketoprofen compared to Ketoprofen co-crystal Formula 1 and 2 are presented in fig. 4 and table 3. The highest Q_{30} value was obtained in Ketoprofen co-crystal Formula 1, 96.73%. In contrast, the Q_{30} value in Ketoprofen co-crystal Formula 2 was 93.09%. Furthermore, the Q_{30} value of standard Ketoprofen was 70.22%.

The dissolution profile showed a significant increase in the dissolution of Ketoprofen in the modified co-crystal compared to standard Ketoprofen. The dissolution results are presented in the table and fig. below. Based on the dissolution profile graph, it can be seen that co-crystal formula 1 has a larger area under the curve (AUC) value than co-crystal formula 2 and standard Ketoprofen. A more significant AUC value indicates that co-crystal formula 1 has a higher dissolution profile.

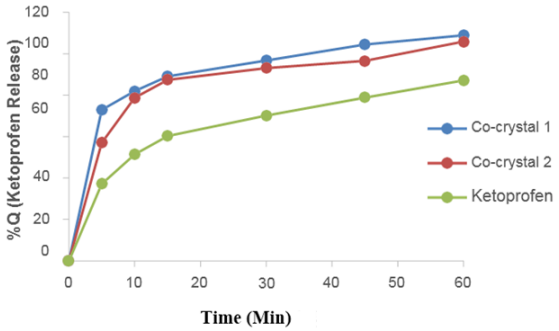

Fig. 4: The dissolution profile of standard Ketoprofen, co-crystal formula 1 and co-crystal formula 2

Table 3: Dissolution parameters of standard Ketoprofen, co-crystal formula 1 and co-crystal formula 2

Parameters	Co-crystal formula 1	Co-crystal formula 1	Standard ketoprofen
Q30 (%)	96.73±1.77	93.09±1.16	70.22±4.72
AUC (µg. h/ml)	5500.70±139.59	5192.45±167.3	3936.54±107.4

All data showed mean±SD (n=4); n is the number of observations.

CONCLUSION

This study concludes that synthesizing ketoprofen co-crystal using succinic acid and saccharin coformers can enhance the solubility of Ketoprofen. The comparison of molar ratios between co-crystal ketoprofen Formula 1 (1:1:1) and Ketoprofen co-crystal Formula 2 (2:1:1) showed that Formula 1 with a molar ratio of 1:1:1 exhibited a higher increase in dissolution value than Formula 2. The addition of succinic acid and saccharin coformers affected the physicochemical profile of Ketoprofen, as indicated by the changes in crystallinity profile observed in the PXRD test, thermal profile observed in the DSC test and melting point apparatus, the formation of OH groups detected in the FTIR test, and the solubility profile observed in the dissolution test using phosphate buffer media at pH 7.4.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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