

Multicomponent crystals of mefenamic acid–tromethamine with improved dissolution rate

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ABSTRACT: Mefenamic acid (MA) is a popular nonsteroidal anti-inflammatory drug classified into BCS class II which has a low solubility and dissolution rate in an aqueous medium. The present study aimed to improve the dissolution rate of MA by preparing multicomponent crystals with tromethamine (TM) through the solvent evaporation technique. The resulting powder was characterized for its solid-state properties and evaluated for the dissolution rate. The results showed that the powder X-ray diffraction pattern of the MA–TM binary system was different from its starting materials, indicating the formation of a new crystalline phase. The differential scanning calorimetry analysis of the MA–TM binary system showed a single and sharp endothermic peak at 110 °C, which was attributed to the melting point of MA–TM multicomponent crystals. The Fourier transform infrared spectroscopy analysis showed the occurrence of solid-state interaction involving proton transfer between MA and TM. The dissolution efficiency of MA–TM multicomponent crystal was 2.5-fold higher than the intact MA. The study concludes that the MA–TM binary system forms a salt-type multicomponent crystal. The multicomponent crystals can significantly increase its dissolution rate and is an alternative technique for modifying the physicochemical properties of active pharmaceutical ingredients.

KEYWORDS: Mefenamic acid; tromethamine; multicomponent crystal; dissolution rate.

1. INTRODUCTION

Mefenamic acid (MA) is an active pharmaceutical ingredient that has anti-inflammatory and analgesic activities. It is used clinically to relieve mild to moderate pain and in the treatment of rheumatoid arthritis [1]. In addition, MA is also reported to exhibit a neuroprotective effect [2]. This drug is classified into BCS class II, according to the biopharmaceutical classification system which is a drug with low solubility and high permeability [3,4]. Low drug solubility in water will cause low absorption of drugs in the gastrointestinal fluid. To optimize the absorption and, thus, the bioavailability of MA in the systemic circulation, it is critical to improving its dissolution rate in aqueous medium [5,6]. Several studies have been carried out to improve the solubility and dissolution rate of MA, including reduction of particle size, formation of solid dispersion, complexes inclusion, self-emulsifying formulation, molecular complexes, nanocrystals formation, the addition of surfactants, spray drying and freeze drying technique [4,7–14].

Solid-state properties of drug compounds significantly influence their physicochemical properties and bioavailability [15,16]. One of the interesting strategies to change the solid-state properties to improve solubility and dissolution rate is the formation of a multicomponent phase by crystal engineering techniques [17]. Multicomponent crystals of pharmaceutical materials consist of co-crystal, salt, hydrate and solvate. Modification of physicochemical properties of an active pharmaceutical ingredient (API) via crystal engineering has become a popular approach because this approach can improve solubility, dissolution rate, compressibility, physical and chemical stability and pharmacological effectiveness [18–22].

Our previous finding has shown that MA can form salt type multicomponent crystal with N-Methyl-D-Glucamine with improved the dissolution rate and physical stability [22]. In the current study, we prepared multicomponent crystals of MA (Fig. 1A) with tromethamine (TM) (Fig. 1B) by the solvent evaporation technique. TM is a GRAS (generally recognized as safe) excipient according to FDA (the US Food and Drug Administration) and is widely used as an alkalizer and biological buffer. Moreover, TM is also used as a salt co-former for some weak acid drugs to improve the physicochemical properties [23,24]. To our knowledge,

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there is no report on the formation of the multicomponent crystal of MA-TM so far. The present study aimed to improve the dissolution rate of MA through crystal engineering technique and characterize the solid-state properties of the multicomponent crystal of MA-TM by scanning electron microscopy (SEM), powder X-ray diffraction analysis (PXRD), differential scanning calorimetry (DSC) thermal analysis, and Fourier transform infrared (FT-IR) spectroscopy.

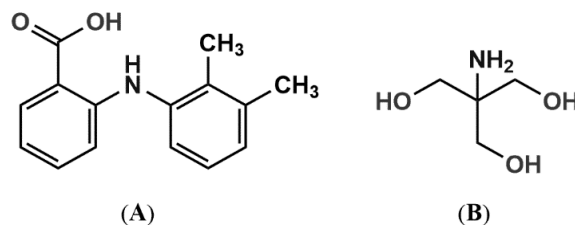


Figure 1. Molecular structures of (A) Mefenamic acid and (B) Tromethamine.

2. RESULTS AND DISCUSSION

The initial evaluation of the multicomponent crystal phase is the crystal habit using an SEM microscope apparatus. The crystallization process of the API from various solvents can produce different crystal habit, polymorphs and particle sizes. Crystal habit is one of the essential physicochemical properties in the manufacturing process. The crystal habit will affect the flowability, compressibility, dissolution rate and bulk density of the API particles [25,26]. In most cases, the solid-state interaction of the binary system API with excipients often produces a new crystal habit that is different from its forming compounds [27,28]. Fig. 2 demonstrates a crystal habit of mefenamic acid (MA), tromethamine (TM) and multicomponent crystals of MA-TM. MA is irregularly shaped solid particles, and TM shows large spherical particles. Meanwhile, the multicomponent crystals of MA-TA indicate a new crystal habit as fine needle-shaped particles.

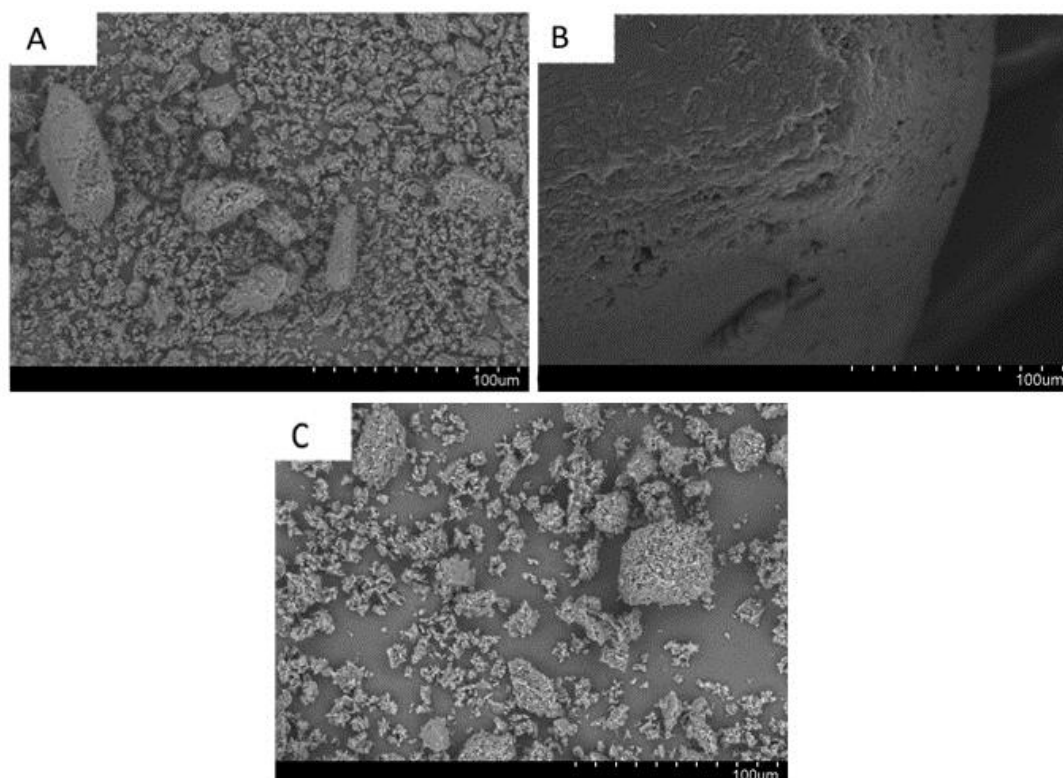


Figure 2. Scanning electron micrographs of (A) mefenamic acid; (B) tromethamine; and (C) Multicomponent crystal of mefenamic acid–tromethamine (all images at 500 x magnification).

PXRD analysis is a reliable technique for determining the degree of crystallinity and the formation of new crystalline phases. Each solid crystalline phase has a distinctive diffraction pattern which can be used as a fingerprint for each crystalline phase [29]. The PXRD patterns of MA, TM and multicomponent crystals MA-TM are presented in Fig. 3. MA is a crystalline solid with sharp diffraction peaks at $2\theta = 13.84, 15.03, 15.65, 20.02, 21.21, 26.03, 27.67, 31.24$ and 31.87° . The MA diffractogram shows the polymorph I as reported by a previous study [30]. TM also has a high degree of crystallinity, with typical diffraction peaks at $2\theta = 14.01, 18.09, 20.13, 22.40, 25.06, 26.76$ and 33.79° . On the other hand, the diffractogram of the physical mixture of MA-TM is only a superimposition of the interference peaks of MA and TM. Furthermore, the diffractogram of MC shows a distinct pattern which is different from intact MA and TM. Some new diffraction peaks appear at $2\theta = 11.85, 17.52, 19.56, 21.60, 23.42$ and 29.37° . This result proves that a multicomponent crystal phase is formed between MA and TM in the equimolar ratio (1:1). The multicomponent crystals include cocrystals, salt, solvate and hydrate. The pK_a rule can be one of the guidelines for predicting whether the interactions between the two solid phases (active pharmaceutical ingredients and excipients) form either a cocrystalline phase or salt. The cocrystalline phase is likely to be formed if the pK_a difference between the API and the excipient <2 . Whereas, if the pK_a difference >3 , then it can form a salt-type multicomponent crystal [31,32]. The pK_a s of MA and TM are reported as 4.2 and 8.07, respectively [11,33]. In the present study, the difference in pK_a between these two solid phases is 3.87 (>3). Based on the ΔpK_a rule it can be assumed that the interaction between MA and TM is through the formation of salt-type multicomponent crystals.

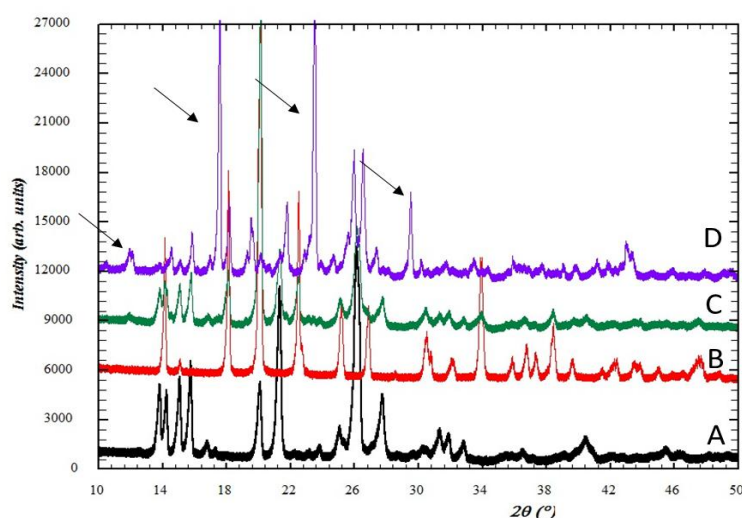


Figure 3. PXRD pattern of (A) mefenamic acid, (B) tromethamine, (C) physical mixture of mefenamic acid-tromethamine, and (D) multicomponent crystal of mefenamic acid-tromethamine.

The DSC thermal analysis was applied to characterize the solid-phase thermodynamic properties. Thermal analysis is also used to screen for the multicomponent crystal phase formation [34]. Herein, MA shows a sharp endothermic peak at 232.8°C , which is the melting point of MA. Meanwhile, TM shows two endothermic peaks, at 137.1°C and 170.5°C (Fig. 4). The endothermic peak at 170.5°C , is the melting point of TM, whereas at 137.1°C is a temperature of a solid-state transition [24]. The multicomponent crystal shows a single endothermic peak (110°C) which is different from the two constituent components. The melting point of the multicomponent crystal of MA-TM was lower than intact MA. The melting point of the molecular crystal of active pharmaceutical ingredients is correlated with the lattice energy of its crystalline phase. In general, the lower the melting point of a solid phase, the lower the lattice energy. The low lattice energy of a crystalline phase would allow it to dissolve faster in aqueous medium [35,36].

FT-IR spectroscopy analysis is widely used to evaluate the solid-state interaction within multicomponent crystal systems. The changes and shifts of absorption bands in the FT-IR spectra indicate an inter-intramolecular bonding and interaction between drug and co-former in the crystal lattice [37]. FT-IR spectra of MA and MA-TM are presented in Fig. 5. MA demonstrates some characteristic absorption peaks for at wavenumbers 3306.45 cm^{-1} ($-\text{NH}$), 2859.20 cm^{-1} ($-\text{CH}_3$), 1643.81 and 1576.66 cm^{-1} ($-\text{COOH}$), and $1436.90, 1243.77,$ and 1160.69 cm^{-1} (symmetric deformation vibrations of $-\text{CH}_3$ group) [38]. Interestingly, the spectrum shows that the stretching vibration of the carbonyl group of COOH previously seen in MA at 1643.81 cm^{-1} is

shifted to a lower wavenumber in the multicomponent crystal (1558 cm⁻¹). This change shows a stretching vibration of the carboxylate anion (COO⁻). Therefore, according to the data, it is assumed that solid-state interactions of MA–TM might involve proton transfer from MA molecules to TM molecules. This phenomenon is very reasonable because the pK_a difference between MA and TM is quite significant (3.87) [11,32].

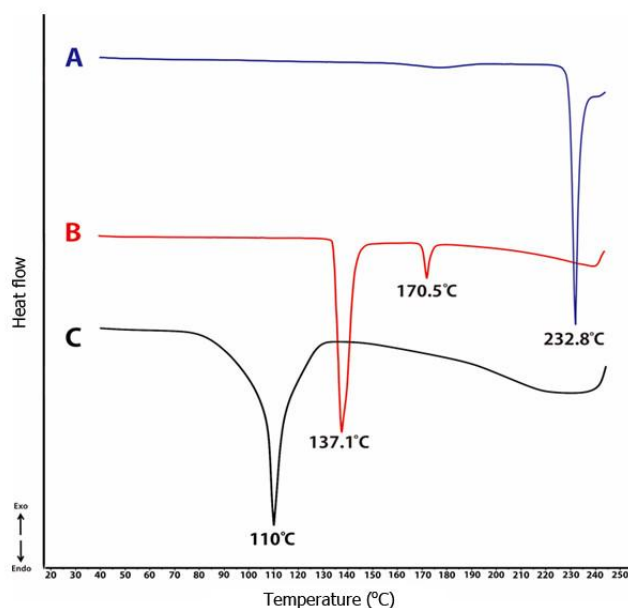


Figure 4. DSC thermogram of (A) mefenamic acid, (B) tromethamine, and (C) multicomponent crystal of mefenamic acid–tromethamine.

In general, there are two approaches to enhance the solubility and dissolution rate of poorly soluble drugs: 1) physicochemical properties modification of solid drug substances, and 2) manufacturing process and formulation strategies [39]. The formation of multicomponent crystals of MA–TM is an interesting approach to improving the dissolution rate of MA, which is a poorly soluble drug. Dissolution rate and bioavailability of the solid dosage form of MA are influenced by solid-state properties such as polymorphic properties, hydrophobicity and its particle size [40,41]. In addition, MA undergoes a phase transition due to mechanical stress and high relative humidity. This causes a transformation of form II of MA to form I which is less soluble [42,43]. In the current study, we report the formation of a new salt-type multicomponent crystal of MA–TM with an increased dissolution rate and dissolution efficiency. The dissolution rates of MA–TM and intact MA are demonstrated in Fig. 6, while the dissolution efficiency is presented in Table 1. The dissolution efficiency of salt-type multicomponent crystal MA–TM was 2.5-fold higher than intact MA. Furthermore, the dissolution efficiency was also significantly enhanced. The salt formation is proven to improve the physicochemical properties of APIs, especially the solubility and dissolution rate. Previous studies have reported an increase in solubility and dissolution rate of MA via multicomponent crystal phase with some excipients such as nicotinamide, cytosine, pyridine derivative [44–46].

Table 1. Comparative analysis of dissolution efficiency between multicomponent crystal of MA–TM and intact MA.

| Materials | Dissolution efficiency (%) | Average | t-value | p-value |
|--|----------------------------|---------------|---------|---------|
| Intact mefenamic acid (MA) | 28.37 | 28.75 ± 0.666 | -46.314 | 0.000 |
| | 28.37 | | | |
| | 29.52 | | | |
| Multicomponent crystal of mefenamic acid with tromethamine (MA–TM) | 74.41 | 75.99 ± 1.636 | | |
| | 75.90 | | | |
| | 77.67 | | | |

Average data are presented as mean ± standard deviation, statistical analysis was conducted by independent t-test (95% confidence interval).

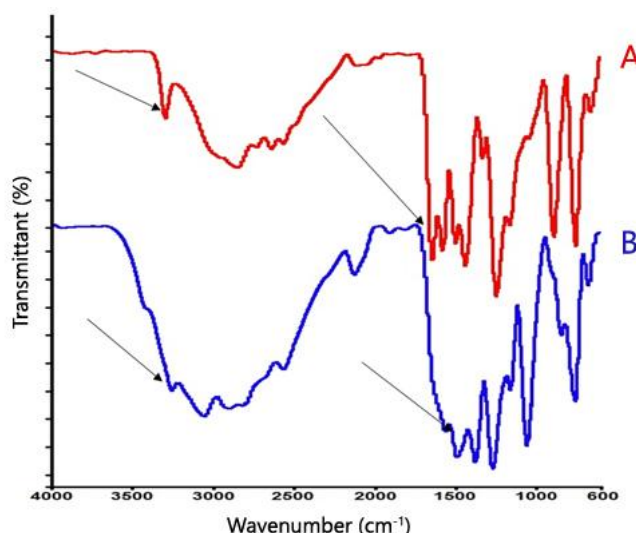


Figure 5. FT-IR spectra of (A) mefenamic acid, and (B) multicomponent crystal of mefenamic acid-tromethamine.

There are several factors that might contribute to increasing the dissolution rate of a multicomponent crystal of MA-TM. First, salt type multicomponent crystal of MA-TM has a better affinity for the aqueous medium because the solid phase is more hydrophilic. When in contact with the aqueous medium, the salt form will dissociate into cationic and anionic ions. Second, from a solid-state properties point of view, there were changes in the crystal structure and the melting point of the crystalline phase. The melting point of a crystalline solid is influenced by the lattice energy, which binds molecules in the unit cell. The lower the melting point of the solid phase, the weaker the lattice energy of the crystalline phase. Hence, the dissolution rate is faster [18,24,33,36].

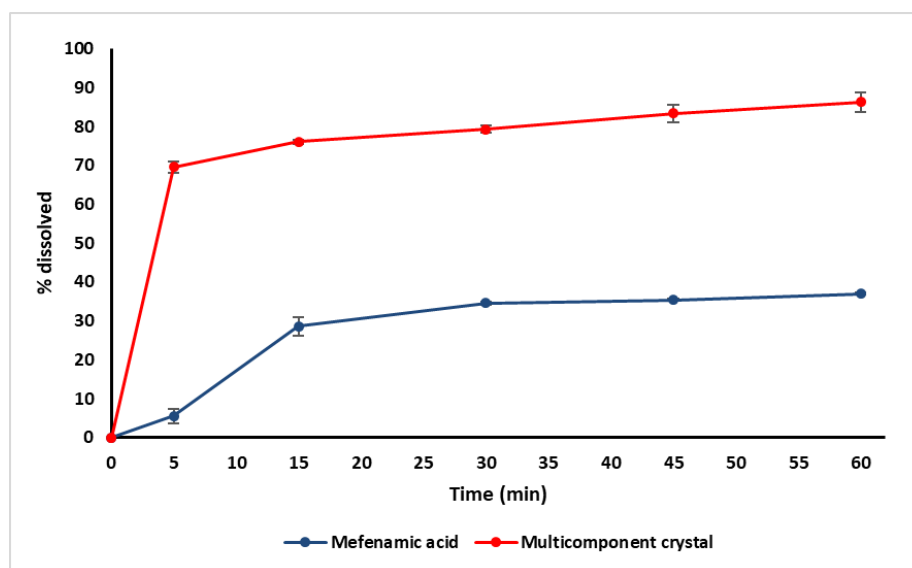


Figure 6. In vitro dissolution rate profile mefenamic acid and multicomponent crystal of mefenamic acid-tromethamine.

3. CONCLUSION

A new salt-type multicomponent crystal of mefenamic acid-tromethamine is successfully prepared using the solvent co-evaporation technique. This multicomponent crystal shows remarkable changes in thermodynamic and crystallographic properties. Notably, the dissolution rate and dissolution efficiency of the salt-type multicomponent crystals of mefenamic acid-tromethamine are significantly higher than intact mefenamic acid.

4. MATERIALS AND METHODS

4.1. Materials

Mefenamic acid was kindly provided by Indofarma Ltd. (Indonesia). Tromethamine was purchased from Merck (Germany). Organic solvents and chemicals were of analytical grade and used without further purification.

4.2. Experimental Methods

4.2.1. Preparation of multicomponent crystal of MA–TM

An equimolar amount of the multicomponent crystals of MA–TM was prepared by the solvent co-evaporation technique. MA was dissolved in ethanol, while TM was dissolved in distilled water. Both were mixed and stirred until clear. The solution was evaporated at room temperature for 48 hours. Fine needle crystals were collected and stored in a desiccator for further characterization. As a comparator for PXRD analysis, an equimolar physical mixture of MA–TM was also prepared through a gentle mixing by spatula for 10 minutes.

4.2.2. Scanning Electron Microscopy Analysis

SEM microphotos were obtained by using an SEM apparatus (HITACHI type S-3400N, Japan). Sample powders were placed on an aluminum sample holder and all samples were sputtered with a thin film of gold–palladium. The measurements were obtained with the following conditions: 10 kV voltage and 12 mA current.

4.2.3. Powder X-ray Diffraction (PXRD) Analysis

PXRD analysis was performed at room temperature with a PANanalytical PW 30/40 X-ray diffractometer (the Netherlands). The diffractogram was recorded from $2\theta = 10^\circ$ to 50° . The X-ray diffractometer was programmed as follow; target metal Cu, K α filter, voltage 45 kV and current 40 mA.

4.2.4. Differential Scanning Calorimetry (DSC) Analysis

DSC thermal analyses of MA, TM and MA–TM were conducted using a DSC apparatus (SETARAM Type EVO-131, France) which was calibrated using indium. Approximately 5 mg of each sample was placed in an aluminum pan, and the temperature of measurement was set from 40 to 250 °C with a heat flow of 10 °C/minute. Nitrogen was used with a flow rate of 10–20 mL/min.

4.2.5. Fourier Transform Infrared (FT-IR) Spectroscopy Analysis

The FT-IR spectra of MA and MA–TM were generated by an FT-IR spectrophotometer (Perkin Elmer FT-IR, USA). The sample was mixed with potassium bromide in a weight ratio of 1:100. The mixture was then compressed into pellets. The absorption of samples was recorded at wavenumbers 4000–600 cm⁻¹. The analysis was performed for MA and MA–TM.

4.2.6. In vitro Dissolution Rate Study

In vitro dissolution rate profiles of MA and MA–TM was determined by using dissolution testing equipment type I USP (Copley Scientific NE4-COPD, UK). The equipment was adjusted at a speed of 50 rpm in 900 mL dissolution medium of phosphate buffer solution (pH 7.4) containing 0.5% sodium lauryl sulfate. The temperature was maintained at 37 ± 0.5 °C. At predetermined times (0, 5, 15, 30, 45 and 60 minutes), approximately 5 mL of the aliquot was withdrawn and filtered. The concentration of MA in the medium was determined using a UV-vis spectrophotometer at a maximum absorption wavelength of 238.5 nm. The experiment was run in triplicate. The data were presented in a chart (time vs percent of dissolved MA). The dissolution efficiency was calculated in accordance with an equation proposed by Khan in 1975 [47] and analyzed statistically by using independent *t* test with 95% confidence interval.

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