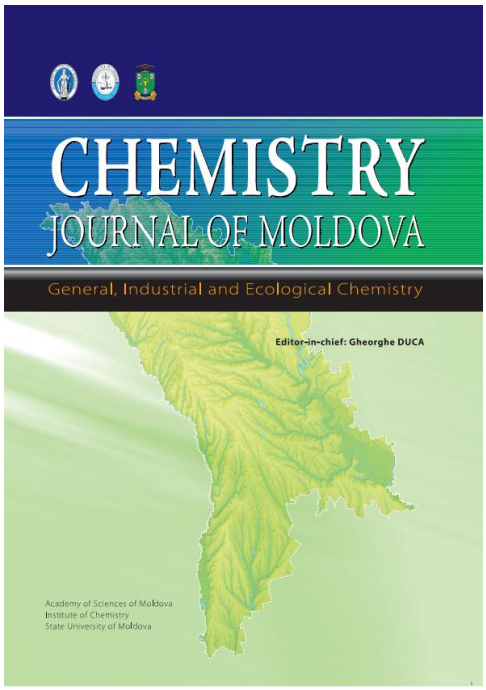

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Abstract. The purpose of this research was to improve the solubility and dissolution rate of ketoprofen by using the multicomponent crystallization approach with nicotinamide as coformer. Multicomponent crystallization of ketoprofen-nicotinamide with a 2:1 molar ratio was performed by solvent evaporation technique using 2-propanol as solvent. The characterization of the multicomponent crystal was performed using powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM). The solubility and dissolution behaviour of the multicomponent crystal in distilled water were determined by the shake-flask and standard paddle method, respectively. The results of characterization by PXRD, DSC, FTIR and SEM have confirmed the formation of a new crystalline phase of ketoprofen-nicotinamide as the multicomponent crystal. The solubility of ketoprofen-nicotinamide multicomponent crystalwas registered 1.3 times higher compared to pure ketoprofen. The multicomponent crystal dissolved about 64% within 60 minutes in comparison to the pure ketoprofen that showed a dissolution of only about 56% during the same period. The results of solubility and dissolution tests showed that the ketoprofen-nicotinamide multicomponent crystal is characterized by a solubility and dissolution rate significantly higher than those for the pure ketoprofen.

Keywords: ketoprofen, multicomponent crystallization, solvent evaporation, solubility, dissolution rate.

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Introduction

The solids of the active pharmaceutical ingredients (API) can be distinguished as crystalline and amorphous forms. API are commonly used in crystalline form, being thermodynamically more stable than the amorphous one [1,2]. A crystalline solid has three-dimensional long-range order and its physicochemical properties are strongly influenced by the molecular arrangement of components in the crystal lattice. Therefore, modification of the crystal lattice can be used to improve the physicochemical properties of crystalline API such as solubility, dissolution rate and hygroscopicity [3,4].

Currently, the modification of crystal lattice of API by the multicomponent crystallization approach is often used to improve the physicochemical properties of API [3-7]. The multicomponent crystallization approach is done by combining API with the other component called coformer [8]. In the multicomponent crystallization, the API and coformer are crystallized together in the same crystal lattice through intermolecular interactions, such as hydrogen bonds and aromatic π-π stacking [8]. The formation of the new crystal lattice from API and coformer in the multicomponent crystal changes the crystal lattice and packing arrangement of the API which induces the presence of new physicochemical properties of the API [8]. Therefore, one of the advantages of the multicomponent crystallisation approach is that it can be used to improve various physicochemical properties of API as needed by using the appropriate type of coformer.

Ketoprofen is a profen-type of non-steroidal anti-inflammatory drug, characterized by an asymmetric carbon center attached to a carboxylic acid, a methyl, and an aryl group. It is used as an analgesic and anti-pyretic agent to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea, and to alleviate moderate pain [9]. It is a weak acid of propionic acid derivative which is poorly soluble in water (0.253 mg/mL) [9]. It has been classified

as a Class II compound of the biopharmaceutical classification system, which means that its low water solubility is the limiting step for absorption and bioavailability [10]. Various methods are developed to improve the solubility of ketoprofen such as salt formation, micronization, formation of solid dispersions and re-crystallization [11-14]. However, the increased solubility of ketoprofen by using the above methods produces amorphous ketoprofen or ketoprofen with lower crystallinity, which is thermodynamically less stable.

The aim of the present study was to improve the solubility and dissolution rate of ketoprofen using the multicomponent crystallization approach. Nicotinamide was selected as coformer due to its acceptability for human consumption and it has effective functional groups to form intermolecular hydrogen bonds with various molecules [15,16]. The 2:1 ratio of ketoprofen-nicotinamide is used for the formation of the multicomponent crystal corresponding to the target stoichiometry and is commonly used for obtaining multicomponent crystals of profen-type drugs with nicotinamide as coformer [15,17,18]. The multicomponent crystallization of ketoprofen-nicotinamide was carried out by solvent evaporation technique using 2-propanol as solvent. The resulted multicomponent crystal was characterized by using PXRD, DSC, FTIR and SEM and was evaluated for solubility and dissolution behaviour by using the shake-flask and standard paddlemethod, respectively.

Experimental

Materials

Ketoprofen (purity ≥98.7%) was kindly assisted by Dexa Medica (Palembang, Indonesia). Nicotinamide (purity ≥99.6%) was purchased from Western Drugs Ltd (Udaipur, India) and 2-propanol (purity ≥99.8%) was purchased from Merck (Darmstadt, Germany).

Preparation of the multicomponent crystal

The multicomponent crystallization of ketoprofen and nicotinamide was carried out by solvent evaporation technique using 2-propanol as solvent. The mixture of ketoprofen-nicotinamide (2:1 molar ratio) was dissolved with 2-propanol in a beaker glass. The beaker glass was then covered with aluminium foil and the solution was stirred with a magnetic stirrer (Scilogex MS7-H550-Pro) for 30 minutes at room temperature. Shortly afterwards the aluminium foil was given small holes and settled at room temperature so the solvent evaporates slowly. The resulting solid was then crushed using a mortar and pestle and passed through an 80-mesh sieve. The solid powder was stored in a desiccator until testing.

Characterization methods

The *PXRD diffractograms* were collected using a powder X-ray diffractometer (Philip Xpert) with Cu Kα radiation (1.54060 Å). The measurement was carried out at 5-50° in 2θ with a step size of 0.017° and a step time of 10 s/step. The condition of divergence slit and anti-scattering slit was 0.25° with diffraction experiment on the 10-mm sample size.

The *DSC analysis* was performed using a differential scanning calorimeter (Rigaku DSC 8230). Prior to measurement, the DSC instrument was calibrated for temperature and heat flow using high purity indium standard. The sample of approximately 2.0 mg was accurately weighed in a hermetically aluminium pan and then sealed. Measurements were performed from 30 to 200°C at a heating rate of 10°C/min under a dry nitrogen atmosphere (flow rate 50 mL/min).

The *FTIR spectra* were determined using an attenuated total reflection Fourier transform infrared spectrometer (Bruker Alpha FTIR spectrometer). The measurements were performed with a resolution of 4 cm^{-1} in the range of 4000-400 cm^{-1} wavenumbers.

The *SEM analysis* was carried out using a scanning electron microscope (Hitachi TM-3000). The samples were firstly attached to a stub with double-sided carbon tape, and then coated with platinum using sputter coater ion (Hitachi E-1045) for 10 seconds. SEM analysis was performed at 15 kV accelerating voltage and 500x magnification.

Solubility and dissolution tests were determined using *UV-Vis analysis*.

Solubility and dissolution tests

Calibration curve. Ketoprofen stock solution (100 ppm) was prepared by dissolving 10 mg of pure ketoprofen in distilled water of 100 mL volumetric flask up to the mark. Ketoprofen standard solutions of concentration of 10, 20, 25, 40, 50 and 100 ppm were prepared by dilution of the stock solution with distilled water. The absorbance of the standard solutions was measured on a UV-Vis spectrophotometer (Hitachi U-2900) at 300 nm using 10 mm quartz quvette. The measurements were carried out at 300 nm because nicotinamide had no absorbance at this wavelength and posed no interference to ketoprofen. The resulting calibration curve of ketoprofen in distilled water has the linear regression equation $y= 0.008x+0.007$ with square correlation coefficient (R^2) of 0.9999 (Figure 1).

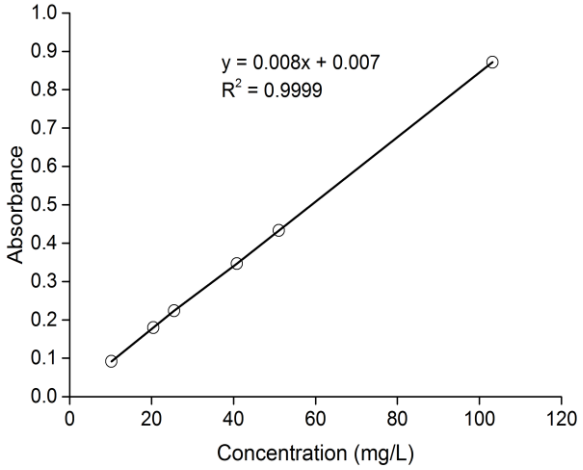

Figure 1. Calibration curve of ketoprofen in distilled water at λ= 300 nm.

Solubility test. The sample was tested for solubility in distilled water by the shake-flask method. An excess sample (about 50 mg) was fed into a 250-mL Erlenmeyer flask containing 50 mL of distilled water. Erlenmeyer flask was shaken using an incubator orbital (Stuart S1600) with a stirring speed of 150 rpm and a temperature of 37±0.5°C for 12 hours. In the filtered solutions (0.45 µm filters) the ketoprofen concentration was determined from the calibration curve. Testing was conducted with three repetitions.

Dissolution test. The dissolution test was performed by paddle method using a dissolution apparatus (Logan UDT-804) in 900 mL of distilled water medium. The sample used was equivalent to 50 mg ketoprofen, while the stirring rate and the test temperature were 100 rpm and 37±0.5°C, respectively. At each time interval, 5 mL of the solution was withdrawn from the instrument and replaced by equal volume of distilled water. In the filtered solutions (0.45 µm filters) the ketoprofen concentration was determined from the calibration curve. Testing was repeated three times.

Statistical analysis

The statistical analysis of obtained data was conducted using one way analysis of variant (ANOVA) of SPSS version 16.0 for Windows. The test average values were considered significantly different at $p<0.05$.

Results and discussion

Powder X-ray diffraction analysis

PXRD is a very important method in characterization of crystalline properties of solid-state samples. The formation of the new crystalline phase can be confirmed based on the unique fingerprint of the diffractogram [19]. The characteristic diffraction of multicomponent crystals is characterized by the appearance of new diffraction peaks and the absence of some diffraction peaks of individual components [20,21]. The overlay of powder X-ray diffractograms of ketoprofen, nicotinamide and ketoprofen-nicotinamide is shown in Figure 2. The diffractogram of ketoprofen has specific peaks of 2θ at 6.3, 14.3, 18.3, and 22.8°, while nicotinamide has 2θ specific peaks at 14.6, 14.8, 25.8, and 27.4°. The diffractogram of both materials indicated conformity with reports in previous studies [14,22,23].

The diffractogram of ketoprofen-nicotinamide exhibits new peaks at position 2θ 18.6° and 26.0°, which were absent in both the ketoprofen and the nicotinamide. The peaks at positions 11.2° and 27.2° present in the individual components were absent in the ketoprofen-nicotinamide. The powder X-ray diffractogram of ketoprofen-nicotinamide showed diffraction peaks different from those of the constituents. The diffraction peaks of ketoprofen-nicotinamide indicated the difference of its crystal lattice compared to the individual components. This indicated that the ketoprofen-nicotinamide was not a mechanical mixture, but had formed a multicomponent crystal with new solid crystalline phase [21,24].

DSC analysis

The DSC curves and the data of the melting temperature-enthalpy of fusion (ΔH) are shown in Figure 3 and Table 1, respectively. The DSC curve of ketoprofen showed a single endothermic peak at 96.2°C (ΔH= 94.8 J/g), while the nicotinamide showed a single endothermic peak at 129.9°C (ΔH= 208.6 J/g). These endothermic peaks were attributed to the melting points of the two ingredients. The melting points of the ketoprofen and nicotinamide are in good agreement with literature [22,25].

One indication of formation of a new crystalline phase is the emergence of different melting points with the initial components [26,27]. Ketoprofen-nicotinamide has a lower melting point than the melting point of both the individual components. The DSC curve of ketoprofen-nicotinamide has a melting endothermic peak at 72.4°C (ΔH= 27.6 J/g) markedly different from the endothermic melting peak of ketoprofen and nicotinamide.

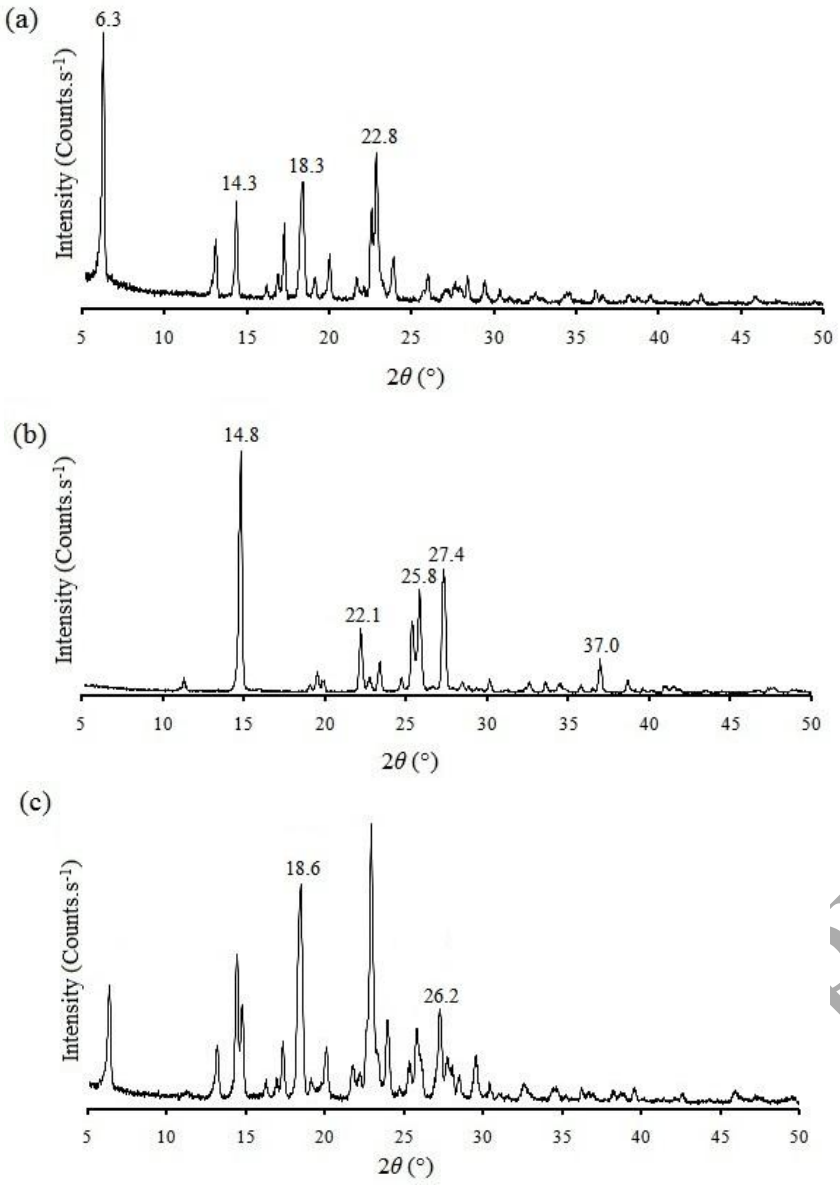

Figure 2. Powder X-ray diffractogramsof pure ketoprofen *(a)*, nicotinamide *(b)* and ketoprofen-nicotinamide *(c)*.

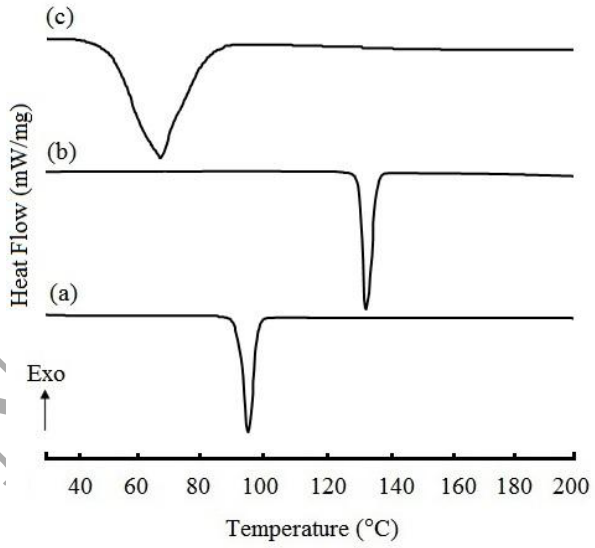

Figure 3. DSC curves of ketoprofen *(a)*, nicotinamide *(b)* and ketoprofen-nicotinamide *(c)*.

Table 1.

Melting temperature and enthalpy of fusion of ketoprofen, nicotinamide and ketoprofen-nicotinamide.

Samples	*Melting temperature(℃)*	*Enthalpy of fusion (ΔH) (J/g)*
Ketoprofen	96.2	94.8
Nicotinamide	129.9	208.6
Ketoprofen-nicotinamide	72.4	27.6

These results indicated that ketoprofen and nicotinamide completely transformed into a multicomponent crystal as a new crystalline phase. In addition, ketoprofen-nicotinamide has a single endothermic peak indicated the absence of unbound component due to the mixture complete transformation into the crystalline phase of the multicomponent crystal [28].

FTIR analysis

FTIR spectroscopy is a technique commonly used to characterize intermolecular interactions in multicomponent crystals [27,29,30]. The obtained FTIR spectra of ketoprofen, nicotinamide and ketoprofen-nicotinamide are shown in Figure 4. The FTIR spectrum of ketoprofen has absorption peaks at 2979 and 2938 cm^{-1} (corresponding to a carboxylic -O-H stretching), 1695 cm^{-1} (-C=O acid stretching), 1654 cm^{-1} (-C=O ketone stretching) and 1599 and 1451 cm^{-1} (aromatic ring -C=C- stretching). This is in agreement with previously reported research [23]. The FTIR spectra of nicotinamide has specific peaks at 3363 and 3166 cm^{-1} (-NH_2 stretching), 1676 cm^{-1} (-C=O amide stretching), 1397 cm^{-1} (-CN stretching), and 1340 cm^{-1} (ring stretching), which was also in accordance with previous research reports [31].

The spectra of ketoprofen-nicotinamide showed a shift of the absorption peaks compared to the spectra of individual components. The shift of the absorption peaks occurred in the -O-H and -C=C- stretching of ketoprofen (from 1451 cm^{-1} to 1445 cm^{-1}) and -NH_2 stretching (from 3166 cm^{-1} to 3177 cm^{-1}), -C=O amide stretching (from 1676 to 1695 cm^{-1}), -CN stretching (from 1397 to 1400 cm^{-1}) and pyridine ring stretching (from 1340 to 1371 cm^{-1}) of nicotinamide.

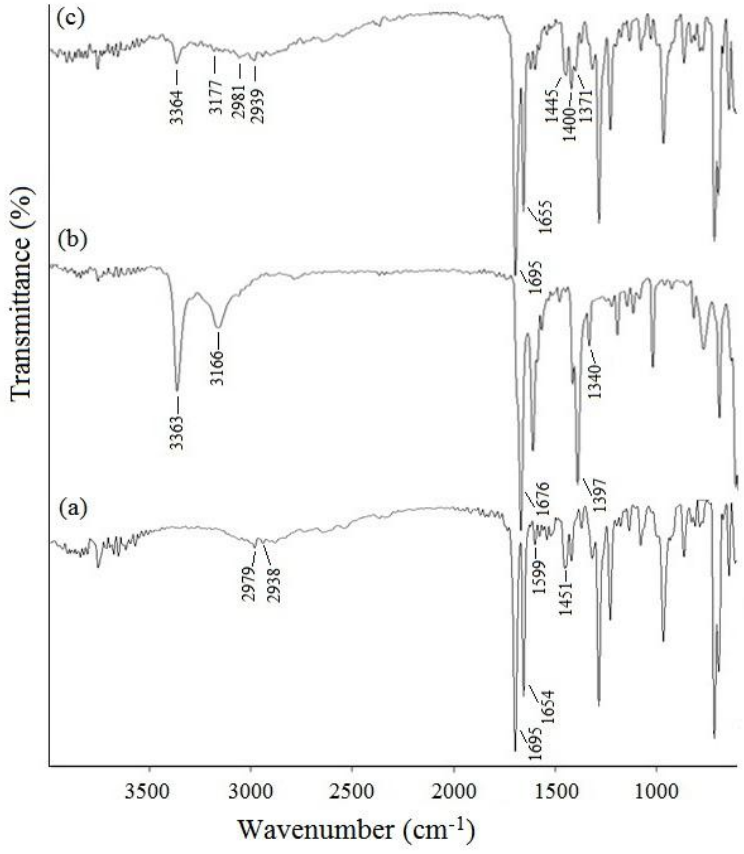

Figure 4. FTIR spectra of ketoprofen *(a)*, nicotinamide *(b)* and ketoprofen-nicotinamide *(c)*.

The shift of the absorption peaks of ketoprofen-nicotinamide indicated the formation of intermolecular interactions between ketoprofen and nicotinamide. Based on the shift of the absorption peaks, ketoprofen and nicotinamide formed a multicomponent crystal through intermolecular hydrogen bonds and π stacking interaction between the-O-H and the aromatic ring of ketoprofen with the -NH_2, -C=O, -CN, and the ring of nicotinamide [29,30,32-34].

Morphological analysis

The SEM images of ketoprofen, nicotinamide and the ketoprofen-nicotinamide multicomponent crystal are presented in Figure 5. The morphological changes of individual components in the ketoprofen-nicotinamide indicated the formation of a multicomponent crystal between ketoprofen and nicotinamide [7].

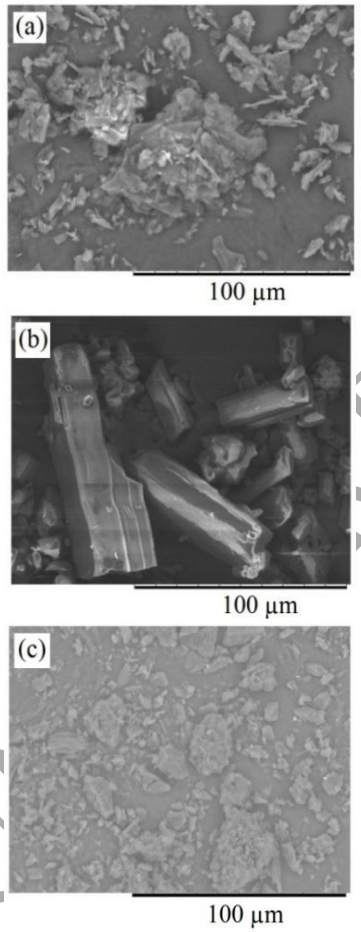

Figure 5. SEM images of ketoprofen *(a)*, nicotinamide *(b)* and ketoprofen-nicotinamide *(c)*.

Solubility assessment

The solubility of ketoprofen and ketoprofen-nicotinamide multicomponent crystal in distilled water was 181±15 and 241±21 mg/mL, respectively. The ketoprofen-nicotinamide multicomponent crystal showed a significant increase in solubility (p<0.05) of about 1.3 times higher compared to the solubility of ketoprofen. The increase of solubility of the multicomponent crystal is often associated with a decrease of its melting point. A multicomponent crystal with a lower melting point tends to have higher solubility than the initial ingredient [35,36]. The DSC experiment showed that the ketoprofen-nicotinamide multicomponent crystal has a melting point at 72.46°C, which is lower by 24°C than ketoprofen. So it can be expected that the increased solubility of the ketoprofen-nicotinamide multicomponent crystal may be caused by the decrease of the melting point.

Dissolution behaviour

The dissolution behaviour of ketoprofen and ketoprofen-nicotinamide multicomponent crystal in distilled water was shown in Figure 6. The amount of ketoprofen released from the ketoprofen-nicotinamide multicomponent crystal within the first 30 minutes increased rapidly and subsequently formed a plateau profile indicating a saturation kinetics process [37]. The multicomponent crystal showed higher dissolution rate compared to ketoprofen with a cumulative amount released 64±5% at 60 minutes. The dissolution profile in distilled water indicated that the amount of ketoprofen released from the ketoprofen-nicotinamide multicomponent crystal was higher than the pure ketoprofen (only about 56%).

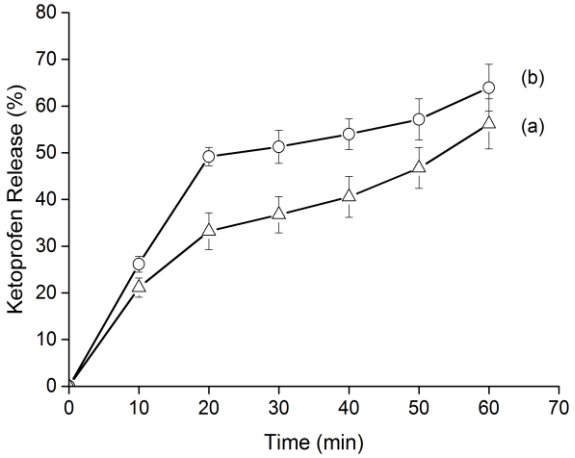

Figure 6. Dissolution profile of ketoprofen *(a)* and ketoprofen-nicotinamide *(b)* in distilled water.

Conclusions

In the present study, the solubility and dissolution rate of ketoprofen was improved by the multicomponent crystallization approach using nicotinamide as a coformer in a 2:1 molar ratio. The formation of the multicomponent crystal of ketoprofen and nicotinamide was

confirmed using PXRD, DSC, FTIR, and SEM methods.

The result of solubility and dissolution tests showed that the ketoprofen-nicotinamide multicomponent crystal has higher solubility and dissolution rate than the pure ketoprofen. The multicomponent crystal showed a significant increasing in solubility (p<0.05) of about 1.3 times higher compared to the solubility of ketoprofen (241±21 mg/mL and 181±15 mg/mL, respectively). The dissolution of the multicomponent crystal was about 64% within 60 minutes; however the pure ketoprofen showed a dissolution of only about 56% during the same period.

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