MOLEKUL
eISSN: 2503-0310

Articles
https://doi.org/10.20884/1.jm.2023.18.3.7292

Effect of Hydrophilic Polymers on Solubility Properties of Ketoprofen-2,5-Dihydroxybenzoic Acid Multicomponent Solids

Yudi Wicaksono*, Budipratiwi Wisudyaningsih, Karina Devi Wahyu Priyadi, Aisyah Prida Laily, Salsabila Bara Putri

Active Pharmaceutical Ingredient and Excipient Research Group, Faculty of Pharmacy, University of Jember, Jember 68121, Indonesia

*Corresponding author email: yudi.farmasi@unej.ac.id

Received December 21, 2022; **Accepted** July 03, 2023; **Available online** November 20, 2023

ABSTRACT. Ketoprofen is a medicinal compound derivative of phenyl alkanoic acid that works as an anti-inflammatory, antipyretic, and analgesic. In the Biopharmaceutical Classification Systems, ketoprofen is a class II drug with high permeability but low solubility. Due to its low solubility, the absorption and bioavailability of ketoprofen are limited, which can affect its therapeutic effectiveness. This study aimed to increase ketoprofen's solubility by forming multicomponent solids using 2,5-dihydroxybenzoic acid coformer with adding hydrophilic polymers ((hydroxypropyl)methylcellulose, polyvinylpyrrolidone K90, and polyethylene glycol 4000). The results showed that ketoprofen with 2,5-dihydroxybenzoic acid coformer prepared using the solvent evaporation method formed a eutectic mixture. Adding hydrophilic polymers to the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solid decreased the crystallinity and melting point of the multicomponent solids. The multicomponent solids of ketoprofen - 2,5-dihydroxybenzoic acid with the addition of hydrophilic polymers had solubility and dissolution efficiency significantly higher ($p<0.05$) than the pure ketoprofen and ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids without hydrophilic polymers.

Keywords: Eutectic mixture, ketoprofen, multicomponent solids, solubility

INTRODUCTION

Ketoprofen is a drug derived from phenyl alkanoic acid, often used as an antipyretic and analgesic (Kuczynska & Nieradko-Iwanicka, 2021). The drug is widely used to treat muscle and joint tissue disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis. Ketoprofen has high permeability in the digestive tract but exhibits very low water solubility, which is only around 0.222 mg/mL (Fitriani et al., 2020). Therefore, ketoprofen in the biopharmaceutical classification systems is grouped as class II compounds, namely compounds that have high permeability to pass through biological membranes but have low solubility in water. The low solubility of ketoprofen can impair its bioavailability and therapeutic effectiveness (Fitriani et al., 2020; Pagano et al., 2020).

Various methods have been used to increase the solubility of the active pharmaceutical ingredient (API), one of which is through the formation of multicomponent solids (Haneef & Chadha, 2016; Wicaksono et al., 2021; Acebedo-Martínez et al., 2022). Multicomponent pharmaceutical solids are solid systems containing two or more different types of molecules, one of which is an API, and the other molecules are often referred to as coformers (Acebedo-Martínez et al., 2022). The molecules of API and coformer in multicomponent solids are linked through various types of intermolecular interactions (hydrogen bonds, π-π interactions, and van der Waals interactions) that determine the multicomponent solid (Li et al., 2021; Wathoni, 2022). API and coformers in multicomponent solid systems compose a series of crystal lattices simultaneously to change the crystalline environment of API, reducing lattice energy and increasing solubility (Yu et al., 2023). Compounds used as coformers in multicomponent solids usually have a small molecular weight, dissolve easily in water, and belong to the generally recognized as safe (GRAS) class of compounds. Compound groups commonly used as coformers in multicomponent solids include carboxylic acids, amines, and pyridines (Goswami et al., 2020; Kumar et al., 2022).

Multicomponent solids are usually classified based on the interaction between the API and the coformer (Haneef & Chadha, 2016). Cocrystals are single-phase multicomponent solids composed of two or more different molecular or ionic (generally in stoichiometric ratios) in the same crystal lattice. In cocrystal solids, API and coformer form non-covalent intermolecular interactions such as hydrogen bonds, π-π interactions, and van der Waals interactions (Yan

et al., 2020; Dutt et al., 2022). The intermolecular interactions between API and coformers in cocrystal multicomponent solids produce new crystalline structures that can change the physicochemical characteristics of API (Dutt et al., 2022).

Coamorphous solids are multicomponent solids that combine API and low molecular weight ingredients (coformers), forming a homogeneous one-phase solid. API and coformer in coamorphous systems form intermolecular interactions as in cocrystalline solids (hydrogen bonds, π-π interactions, and van der Waals interactions), but the intermolecular interactions between API and coformer do not have long-range orders, so they do not indicate the presence of a crystal lattice (Karagianni et al., 2018; Jangid et al., 2020). Coamorphous solids generally have higher physical stability than amorphous polymeric (formed by combining API with polymers) because the intermolecular interaction between API and coformer in coamorphous solids can prevent recrystallization during storage and also when in supersaturated solution (Karagianni et al., 2018).

Another form of multicomponent solid resulting from the combination of API and coformer is a eutectic mixture, namely a mixture of two components (API and coformer) that are immiscible in the solid state but completely miscible in the liquid state (Haneef & Chadha, 2016). API and coformer in the eutectic composition show a lower melting point than the melting point of its constituent components. The solids of the eutectic mixture are stabilized by stronger cohesive interactions and weaker adhesive interactions (Haneef et al., 2021). Structurally, the multicomponent solids of eutectic mixtures are non-isomorphous (having a mismatch in size and shape) with weak intermolecular interactions, so their crystal structure adopts that of the constituent materials. Eutectic mixtures are known to increase the solubility of APIs due to a thermodynamic function (lowering the melting point) and because the component molecules in a binary mixture system are assembled with weak interactions (Haneef et al., 2021).

Modifying the physicochemical properties of API through the formation of multicomponent solids (cocrystal, coamorphous, and eutectic) has the advantage that the type of interaction between API and coformers in multicomponent solids is non-covalent interactions (hydrogen bonds, π-π interactions, and van der Walls interactions) which does not change the molecular structure of API (Haneef & Chadha, 2016; Haneef et al., 2021; Dutt et al., 2022). Thus, the formation of multicomponent solids does not change the pharmacological activity of the API and only changes physicochemical properties such as solubility, dissolution rate, and compressibility (Dutt et al., 2022; Acebedo-Martínez et al., 2022).

The use of hydrophilic polymers in multicomponent solid systems is known to increase the effectiveness of increasing the solubility of insoluble active pharmaceutical ingredients (Mummidi & Jayanthi, 2013; Mehta et al., 2013). Hydrophilic polymers in multicomponent solid systems can change the environment of the functional groups of the constituent molecules, thus affecting the crystallization and solubilization processes of solids (Chaturvedi et al., 2020; Sahoo et al., 2021). The use of hydrophilic polymers in multicomponent solids isradipine - hydroxypropyl-cyclodextrin and cefixime – β-cyclodextrin has been shown to increase the solubility and dissolution rate of the drug significantly (Mummidi & Jayanthi, 2013; Mehta et al., 2013).

This study aims to increase ketoprofen's solubility by forming multicomponent solids, using the 2,5-dihydroxybenzoic acid coformer, and adding hydrophilic polymers. The choice of 2,5-dihydroxybenzoic acid as a coformer was because previous in silico studies showed that ketoprofen could form a non-covalent intermolecular interaction with the benzoic acid compounds and does not change the molecular structure of ketoprofen (Siswandi et al., 2015). The formation of multicomponent solids through non-covalent interactions that do not change the molecular structure of API is known not to cause changes in the pharmacological activity of API (Haneef & Chadha, 2016; Haneef et al., 2021; Dutt et al., 2022; Acebedo-Martínez et al., 2022). The hydrophilic polymers used are hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP) K90, and polyethylene glycol (PEG) 4000. The three polymers are highly soluble in water, so they can form an environment where the functional groups of the API in multicomponent solids become more easily solubilized by water molecules (Chaturvedi et al., 2020; Sahoo et al., 2021). In addition, they are biologically safe, so they are often used to develop active pharmaceutical ingredients (Mummidi & Jayanthi, 2013; Mehta et al., 2013; Zhang et al., 2022).

EXPERIMENTAL SECTION

Materials

The materials used were ketoprofen (Tokyo Chemical Industry, Japan), 2,5-dihydroxybenzoic acid (Merck KGaA, Darmstadt, Germany), HPMC Mn 10,000 (Merck KGaA, Darmstadt, Germany), PVP K90 (JH Nanhang Life Science, Zhejiang, China), PEG 4000 (Merck KGaA, Darmstadt, Germany), KH_2PO_4 (Merck KGaA, Darmstadt, Germany), NaOH (Merck KGaA, Darmstadt, Germany), methanol for analysis (Smart-Lab Indonesia, Tangerang, Indonesia), and distilled water.

Equipment

The main tools used are a UV-Vis spectrophotometer, differential scanning calorimeter (DSC), powder X-ray diffractometer (PXRD), Fourier transform infrared (FTIR) spectrophotometer, dissolution tester, orbital shaker, and SPSS 22.0 software for windows.

Methods

Preparation of multicomponent solids

Multicomponent solids were prepared by the solvent evaporation method. Ketoprofen and 2,5-dihydroxybenzoic acid were used in a stoichiometric ratio of 1:1, while the hydrophilic polymer added was 2% (w/w) of the total weight of ketoprofen and 2,5-dihydroxybenzoic acid. The description of the preparation carried out is as follows: ketoprofen (311 mg), 2,5-dihydroxybenzoic acid (189 mg), and hydrophilic polymer (10 mg) are put into a beaker glass, then 5 ml of methanol is added and stirred with a magnetic stirrer (25 °C) for 30 minutes until all the solids dissolve. The beaker glass is then covered with an aluminum sheet that has been given small holes, and then the beaker glass is left at room temperature so that all the solvent evaporates. The multicomponent solids in the beaker were reduced with mortar and then sieved using an 80-mesh sieve. The dry powder of the multicomponent solid was put into a brown bottle container and stored in a desiccator until further testing.

Characterization with PXRD

The characterization was carried out with an x-ray diffractometer instrument (Panalytical X'Pert Pro) using a CuKα radiation source (1.54060 Å). Measurements were made at an angle range of 2θ at 5-50° with a step size of 0.017° and a step time of 10 s/step. The conditions for the anti-scattering and the divergence slit were set at 0.25° with a sample size of 10 mm (Wicaksono et al., 2018).

Characterization with DSC

Characterization was carried out using a differential scanning calorimeter (Rigaku DSC 8230), calibrated using the indium standard. A sample powder of about 2 mg was put in an airtight aluminum container. Measurements were carried out at a temperature of 30-250°C with a heating rate of 10°C/min under dry nitrogen gas flow conditions with a flow rate of 50 mL/min (Wicaksono et al., 2018).

Characterization with FTIR spectrophotometer

This characterization aims to identify the functional groups of molecules and intermolecular interactions in solid samples. The FTIR spectra were recorded using a Fourier transform infrared spectrometer (Bruker FTIR Alpha II). Measurements were made with a resolution of 4 cm^{-1} in the wavenumber range of 4000-400 cm^{-1}.

Solubility test

The solubility test was carried out using the shaking method. The excess sample to produce a saturated solution (about 15 mg) was put into a 100 mL Erlenmeyer, then 15 mL of distilled water was added. Erlenmeyer was tightly closed with aluminum foil, placed in an orbital shaker (Thermo Scientific), and shaken for 24 hours at 25°C. The supernatant was filtered using a 0.45-micron cellulose nitrate filter membrane, and the ketoprofen content was determined using a UV-Vis spectrophotometer (Thermo Scientific Genesys) (Wicaksono et al., 2018). The absorption measurement of the test solution was carried out at λ 260 nm where 2,5-dihydroxybenzoic acid, HPMC, PVP K90, and PEG 4000 did not provide absorption, so the measured absorption only correlated with ketoprofen concentration.

Dissolution test

The dissolution test using a paddle-type dissolution apparatus (Logan UDT-804) was carried out in 900 ml phosphate buffer pH 7.4. The sample used was equivalent to 50 mg of ketoprofen, and the test was carried out at 37±0.5 °C with a stirring speed of 100 rpm. 5 mL of dissolution media was taken at 15, 30, 45, 60, 75, and 90 minutes and always replaced with the same volume of new dissolution media. Samples from the dissolution medium were filtered using a 0.45-micron filter membrane, and the ketoprofen content was determined by a UV-Vis spectrophotometer at λ 260 nm (Thermo Scientific Genesys) (Wicaksono et al., 2018).

Statistical analysis

The data obtained were tested for statistical significance using the ANOVA test using SPSS 22.0 software for Windows. The difference in sample data is considered significant if the value of $p<0.05$.

RESULTS AND DISCUSSION

PXRD Diffractogram

Characterization using PXRD aims to identify the phase and changes in the crystalline structure of solid samples. The results of characterization with PXRD are shown in **Figure 1**. The ketoprofen diffractogram has prominent peaks at 6.35, 13.07, 14.32, 17.30, 18.33, 20.01, 22.59, 22.85, 23.87, 25.98, and 28.37°, whereas the 2,5-dihydroxybenzoic acid diffractogram has the prominent diffraction peaks at 7.35, 15.92, 19.67, 23.42, 25.03, 26.78, 30.29, and 44.49°. The diffractograms have shown the presence of sharp diffraction peaks with very high intensity indicating that the two materials are crystalline solids (Sapkal et al., 2020; Wicaksono et al., 2021).

The ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids showed a diffractogram with diffraction peaks which were a combination of diffraction peaks from the individual diffractogram of ketoprofen and 2,5-dihydroxybenzoic acid. The diffractogram of the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids have shown a decrease in the intensity of the diffraction peaks when compared to the diffractogram of its constituent materials, but no new diffraction peaks were seen. This phenomenon has indicated that in the solid system of ketoprofen – 2,5-dihydroxybenzoic acid does not form a new solid phase with a different crystalline structure, but only defects in the molecular arrangement in the crystal lattice of the unit cell of the constituent materials (Sahoo et al., 2021).

The ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids added with a hydrophilic

polymer, the overall diffractogram showed a pattern of diffraction peaks similar to the diffractogram of the ketoprofen-2,5-dihydroxybenzoic acid multicomponent solids without the hydrophilic polymer. However, the diffractogram of multicomponent solids added with hydrophilic polymers shows diffraction peaks with lower intensities when compared to the diffraction peaks of multicomponent solids without adding hydrophilic polymers. Hydrophilic polymers in multicomponent solid systems are known to affect the environment in multicomponent systems so that they can cause defects in the molecular arrangement in the unit cell of the crystal lattice of ketoprofen and 2,5-dihydroxybenzoic acid (Sahoo et al., 2021).

The intensity of the diffractogram diffraction peaks of the solid materials is related to the degree of crystallinity. Thus, adding a hydrophilic polymer to the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids reduce the crystallinity of the solids. Decreased crystallinity of multicomponent solids is associated with increased solubility of poorly water-soluble drugs (Choi et al., 2022).

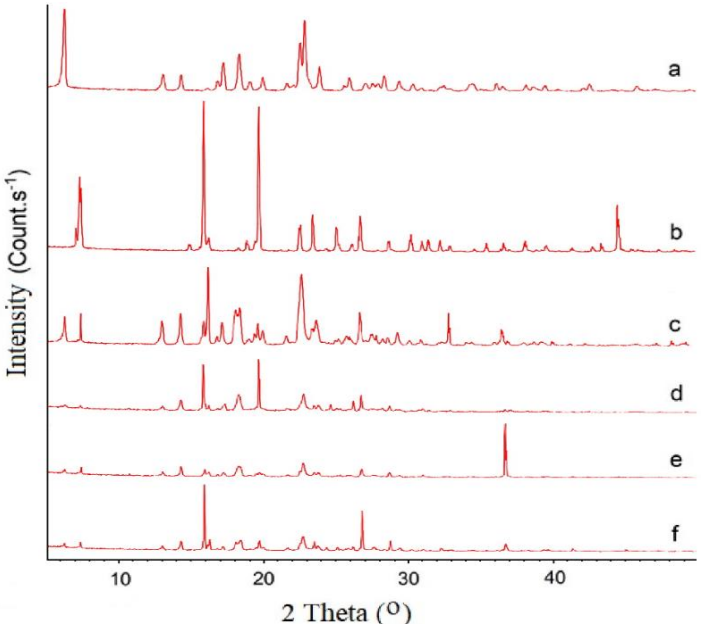

Figure 1. PXRD diffractogram of (**a**) ketoprofen, (**b**) 2,5-dihydroxybenzoic acid, (**c**) ketoprofen – 2,5-dihydroxybenzoic acid, (**d**) ketoprofen – 2,5-dihydroxybenzoic acid - HPMC, (**e**) ketoprofen - 2,5-dihydroxybenzoic acid - PVP K90, and (**f**) ketoprofen - 2,5-dihydroxybenzoic acid - PEG 4000

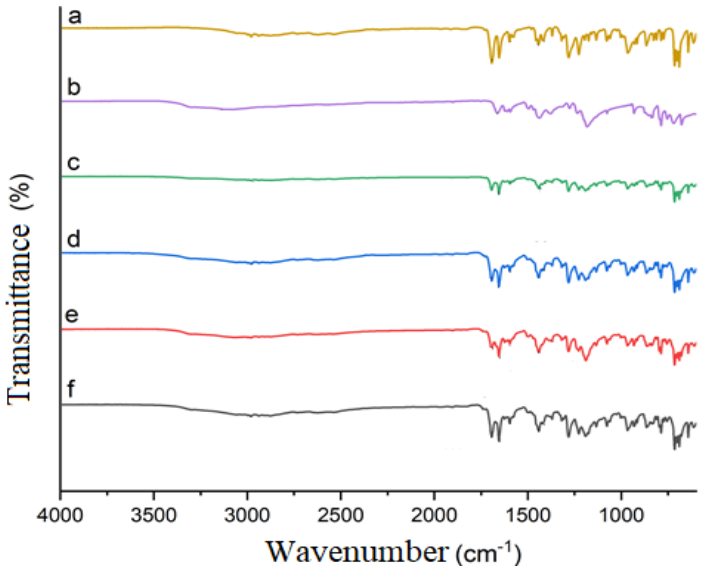

Figure 2. FTIR spectrum of (**a**) ketoprofen, (**b**) 2,5-dihydroxybenzoic acid, (**c**) ketoprofen – 2,5-dihydroxybenzoic acid, (**d**) ketoprofen – 2,5-dihydroxybenzoic acid - HPMC, (**e**) ketoprofen - 2,5-dihydroxybenzoic acid - PVP K90, and (**f**) ketoprofen - 2,5-dihydroxybenzoic acid - PEG 4000

FTIR Spectrum

FTIR characterization is used to identify the functional groups of molecules and detect intermolecular interactions in multicomponent solid systems. The FTIR spectrum of ketoprofen (**Figure 2**) has specific absorption peaks at 1440 and 1597 cm^{-1} (C=C aromatic ring stretching), 1654 cm^{-1} (C=O ketone stretching), 1694 cm^{-1} (C=O carboxylic acid stretching) and 3400-2400 cm^{-1} (OH stretching) which are generally in agreement with the literature (Wicaksono et al., 2020a). The 2,5-dihydroxybenzoic acid on FTIR characterization showed a spectrum with specific absorption peaks at 1656 cm^{-1} (C=O carboxylic acid stretching) and broad peak at 3073 cm^{-1} (OH and NH stretching) (Félix-Sonda et al., 2014).

The FTIR spectrum of ketoprofen - 2,5-dihydroxybenzoic acid has shown absorption peaks, a combination of absorption peaks from the individual spectrum of ketoprofen and 2,5-dihydroxybenzoic acid. The absorption peaks of the individual spectrum in the multicomponent solid spectrum have not shown a shift in the wavenumber of absorption peaks of proton donor/acceptor groups in hydrogen bonds. The absence of shifts in the absorption peaks of proton donor/acceptor groups in hydrogen bonds indicated that the constituent molecules in the multicomponent solids do not form hydrogen bond interactions with each other (Parhi & Suresh, 2015; Inam et al., 2022).

The spectrum of the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids with added hydrophilic polymer also showed absorption peaks at the exact wavenumber compared to the individual spectrum of ketoprofen and 2,5-dihydroxybenzoic acid. The spectrum indicates that the molecules of ketoprofen and 2,5-dihydroxybenzoic acid in the multicomponent solids with added hydrophilic polymer also do not form hydrogen bond interactions. Thus, it was concluded that the addition of hydrophilic polymers (HPMC, PVP K90, and PEG 4000) in the amount of 2% (w/w) to the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids did not cause the formation of hydrogen bond interactions between the molecules of ketoprofen and 2,5-dihydroxybenzoic acid.

DSC Thermogram

Characterization using DSC aims to determine the thermal characteristics of a solid material when it is heat treated (Wicaksono et al., 2020b). Ketoprofen and 2,5-dihydroxybenzoic acid have shown thermograms with sharp endothermic peaks at 96.3 and 206.2°C, respectively, indicating their melting temperatures. Meanwhile, the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids showed an endothermic peak at 86.0°C, indicating the melting point of the binary mixture of the two materials. The thermogram indicates that the binary mixture between ketoprofen and 2,5-dihydroxybenzoic acid melts simultaneously at a single temperature, where the melting point is lower than the melting point of the constituent components (Haneef & Chadha, 2016; Bazzo et al., 2020).

The PXRD diffractogram indicates that ketoprofen and 2,5-dihydroxybenzoic acid do not form a new solid phase with a different crystalline structure but only defects in the molecular arrangement in each crystal lattice. Meanwhile, the FTIR spectrum did not show any shift in the absorption peaks of the proton donor/acceptor groups in the hydrogen bonds of ketoprofen and 2,5-dihydroxybenzoic acid, indicating no hydrogen bonds between components. Therefore, based on DSC, PXRD, and FTIR analysis, overall, it can be concluded that ketoprofen and 2,5-dihydroxybenzoic acid in multicomponent solids form a binary eutectic mixture (Haneef & Chadha, 2016). The eutectic mixture or eutectic solid is a mixture of two materials that produces a solid in which the liquid phase of the constituent materials is miscible, and the melting point is lower than the melting point of the constituent components (Bazzo et al., 2020).

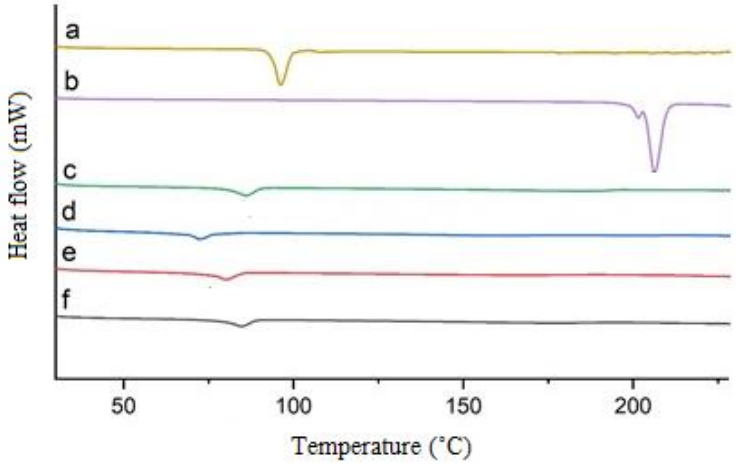

Figure 3. DSC thermogram of (**a**) ketoprofen, (**b**) 2,5-dihydroxybenzoic acid, (**c**) ketoprofen – 2,5-dihydroxybenzoic acid, (**d**) ketoprofen – 2,5-dihydroxybenzoic acid - HPMC, (**e**) ketoprofen - 2,5-dihydroxybenzoic acid - PVP K90, and (**f**) ketoprofen - 2,5-dihydroxybenzoic acid - PEG 4000

A eutectic mixture is composed of weakly bound molecules or has no chemical interactions, making them immiscible in their solid form. However, at specific ratios, it is completely miscible in the liquid state and inhibits the crystallization of each component resulting in a system with a lower melting point (Chaturvedi et al., 2020).

The ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids with added hydrophilic polymer showed a thermogram with one endothermic peak indicating the melting point of each multicomponent solids. Each ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids with added HPMC, PVP K90, and PEG 4000 had melting points of 72.5, 80.0, and 84.7°C, respectively. The ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solid with added hydrophilic polymers showed a lower melting point than the multicomponent solids without hydrophilic polymer. The effect of decreasing the melting point of the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids due to adding a hydrophilic polymer, namely HPMC>PVP K90>PEG 4000. The decrease in the melting point of the multicomponent solids added with hydrophilic polymer was confirmed by the PXRD diffractogram, namely a decrease in crystallinity, where the solid with lower crystallinity has a lower melting point (Aldeeb et al., 2022).

Solubility

The solubility of ketoprofen from the sample solid in distilled water is shown in **Figure 4**. Pure ketoprofen has a solubility of 171.12±6.29 mg/L, while the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solid has a solubility of 194.91±2, 88 mg/L. The formation of multicomponent solids showed a significant increase in solubility ($p<0.05$) compared to the solubility of pure ketoprofen. The multicomponent solids with added hydrophilic polymers, ketoprofen - 2,5-dihydroxybenzoic acid - HPMC, ketoprofen - 2,5-dihydroxybenzoic acid - PVP K90, and ketoprofen - 2,5-dihydroxybenzoic acid - PEG 4000, showed solubility of 210.72±3.83, 235.85±2.88, and 214.64±1.02 mg/L, respectively.

The solubility test showed that adding a hydrophilic polymer to the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids increased the solubility of ketoprofen significantly ($p<0.05$) compared to the solubility of ketoprofen in the multicomponent solids without hydrophilic polymer. The increase in solubility of ketoprofen from the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids with added hydrophilic polymers is thought to be due to a decrease in crystallinity so that the crystal lattice energy becomes lower than multicomponent solids without hydrophilic polymer (Wicaksono et al., 2020b). The lower crystal lattice energy of a solid material causes the molecules in the solid to be more easily solved by solvent molecules so that their solubility increases (Chaturvedi et al., 2020).

Dissolution

The dissolution of ketoprofen from the sample solid in phosphate buffer pH 7.4 is shown in **Figure 5**. Pure ketoprofen at 15 minutes showed a release of 35.74±1.98% and at subsequent times showed a release profile at a slow rate. At the end of the dissolution test (90 minutes), the total release of pure ketoprofen was only 49.38±0.60%. At 15 minutes, the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids without hydrophilic polymer showed a release of 67.09±0.10%, a significant increase ($p<0.05$) compared to the release of pure ketoprofen.

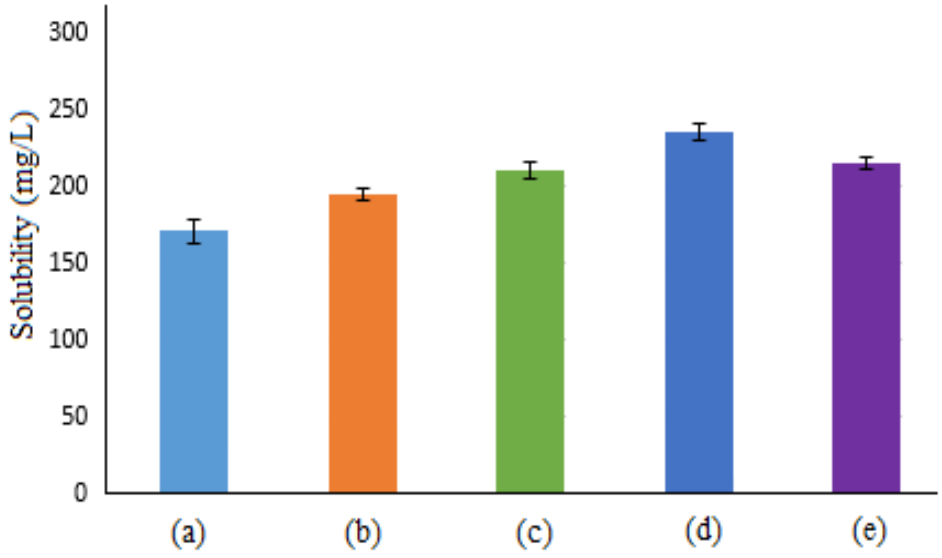

Figure 4. Solubility in distilled water of (**a**) ketoprofen, (**b**) ketoprofen – 2,5-dihydroxybenzoic acid, (**c**) ketoprofen – 2,5-dihydroxybenzoic acid - HPMC, (**d**) ketoprofen - 2,5-dihydroxybenzoic acid - PVP K90, and (**e**) ketoprofen - 2,5-dihydroxybenzoic acid - PEG 4000

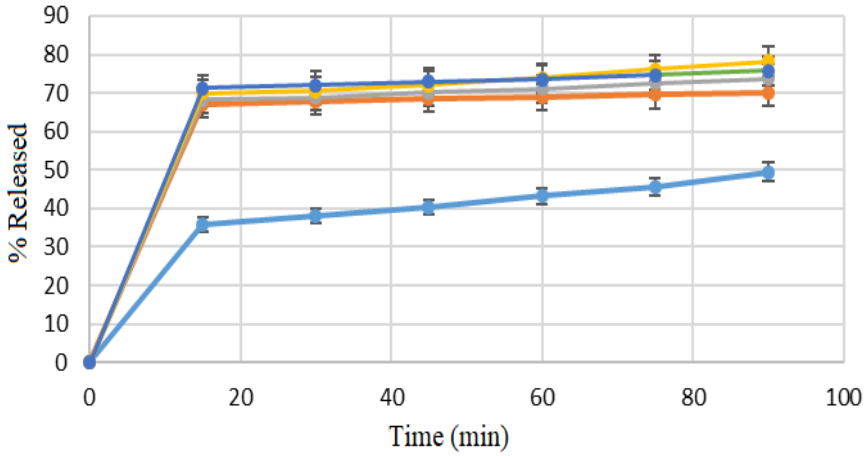

Figure 5. Dissolution profiles in phosphate buffer pH 7.4 of ketoprofen (—●—), ketoprofen – 2,5-dihydroxybenzoic acid (—●—), ketoprofen – 2,5-dihydroxybenzoic acid – HPMC (—●—), ketoprofen - 2,5-dihydroxybenzoic acid - PVP K90 (—●—), and ketoprofen - 2,5-dihydroxybenzoic acid - PEG 4000 (—●—)

Table 1. Dissolution efficiency in phosphate buffer pH 7.4

Solids	Dissolution efficiency (%)
Ketoprofen	37.90±0.56
Ketoprofen - 2,5-dihydroxybenzoic acid	62.80±0.17
Ketoprofen - 2,5-dihydroxybenzoic acid - HPMC	64.59±0.36
Ketoprofen - 2,5-dihydroxybenzoic acid - PVP K90	66.95±0.76
Ketoprofen - 2,5-dihydroxybenzoic acid - PEG 4000	67.04±0.17

The multicomponent solid ketoprofen - 2,5-dihydroxybenzoic acid with the addition of a hydrophilic polymer at 15 minutes showed releases of 68.23±0.21% (HPMC), 70.00±0.30% (PVP K90), and 71.17± 0.30% (PEG 4000). The amount of release at 15 minutes from the multicomponent solid of ketoprofen - 2,5-dihydroxybenzoic acid with the addition of a hydrophilic polymer showed a significant increase ($p<0.05$) compared to the release of the multicomponent solid of ketoprofen- 2,5-dihydroxybenzoic acid without a hydrophilic polymer. At the end of the dissolution test (90 minutes), the multicomponent solid of ketoprofen - 2,5-dihydroxybenzoic acid without the addition of a hydrophilic polymer showed a release of 70.17 ± 0.30, while the multicomponent solid of ketoprofen - 2,5-dihydroxybenzoic acid with the addition of a hydrophilic polymer showed releases were 73.72±1.52% (HPMC), 78.21±1.13% (PVP K90), and 75.80±0.84% (PEG 4000).

The dissolution efficiency values (**Table 1**) show that the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids with added hydrophilic polymer each has a dissolution efficiency of 64.59±0.36% (HPMC), 66.95±0.76 (PVP K90), and 67.04±0.17% (PEG 4000). The dissolution efficiency values indicated that the addition of hydrophilic polymers significantly increased ($p<0.05$) the dissolution efficiency of the ketoprofen - 2,5-dihydroxybenzoic acid compared to the ketoprofen – 2,5-dihydroxybenzoic acid multicomponent solids without hydrophilic polymer. Ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids with added a hydrophilic polymer have higher dissolution efficiency are thought to be due to their higher solubility and also the solubilization effect of the hydrophilic polymers (Chaturvedi et al., 2020).

CONCLUSIONS

Ketoprofen and 2,5-dihydroxybenzoic acid using solvent evaporation method formed multicomponent solids, which is a eutectic mixture. Adding hydrophilic polymers to the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids lowered the melting point and significantly increased ($p<0.05$) the solubility compared to the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solid without hydrophilic polymers. The ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solids with added a hydrophilic polymer showed a significantly higher ($p<0.05$) dissolution efficiency than the ketoprofen - 2,5-dihydroxybenzoic acid multicomponent solid of without a hydrophilic polymer.

ACKNOWLEDGMENTS

This publication is supported by the Skripsi/Thesis Reworking Grant 2022 of the University of Jember (Contract Number: 6320/UN25.3.1/LT/2022).

REFERENCES

Acebedo-Martínez, F.J., Alarcón-Payer, C., Barrales-Ruiz, H.M., Niclós-Gutiérrez, J., Domínguez-

Martín, A., & Choquesillo-Lazarte, D. (2022). Towards the development of novel diclofenac multicomponent pharmaceutical solids. *Crystals, 12*(1038).

Aldeeb, R.A., El-Miligi, M.F., El-Nabarawi, M.A., Tag, R., Amin, H.M., & Taha, A.A. (2022). Enhancement of the solubility and dissolution rate of telmisartan by surface solid dispersions employing superdisintegrants, hydrophilic polymers and combined carriers. *Scientia Pharmaceutica, 90*(71).

Bazzo, G. C., Pezzini, B. R., & Stulzer, H. K. (2020). Eutectic mixtures as an approach to enhance solubility, dissolution rate and oral bioavailability of poorly water-soluble drugs. *International Journal of Pharmaceutics, 588*(119741).

Chaturvedi, K., Shah, H. S., Nahar, K., Dave, R., & Morris, K. R. (2020). Contribution of crystal lattice energy on the dissolution behavior of eutectic solid dispersions. *ACS Omega, 5*(17), 9690–9701.

Choi, M., Woo, M.R., Choi, H., & Jin, S.G. (2022). Effects of polymers on the drug solubility and dissolution enhancement of poorly water-soluble rivaroxaban. *International Journal of Molecular Sciences, 23*(9491).

Dutt, B., Choudhary, M., & Budhwar, V. (2022). A brief discussion of multicomponent organic solids: key emphasis on Co-crystallization. *Turkish journal of pharmaceutical sciences, 19*(2), 220-231.

Félix-Sonda, B. C., Rivera-Islas, J., Herrera-Ruiz, D., Morales-Rojas, H., & Höpfl, H. (2014). Nitazoxanide cocrystals in combination with succinic, glutaric, and 2,5-dihydroxybenzoic acid. *Crystal Growth & Design, 14*(3), 1086–1102.

Fitriani, L., Firdaus, W.A., Sidadang, W., Rosaini, H., Putra, O.D., Oyama, H., Uekusa, H., & Zaini, E. (2022). Improved solubility and dissolution rate of ketoprofen by the formation of multicomponent crystals with tromethamine. *Crystals, 12*(275).

Goswami, P. K., Kumar, V., & Ramanan, A. (2020). Multicomponent solids of diclofenac with pyridine based coformers. *Journal of Molecular Structure, 1210*(128066).

Haneef, J., & Chadha, R. (2016). Drug-drug multicomponent solid forms: cocrystal, coamorphous and eutectic of three poorly soluble antihypertensive drugs using mechanochemical approach. *AAPS PharmSciTech, 18*, 2279-2290.

Haneef, J., Ali, S., & Chadha, R. (2021). Emerging multi-drug eutectics: opportunities and challenges. *AAPS PharmSciTech, 22*(66).

Inam, S., Irfan, M., Lali, N. ul ain, Khalid Syed, H., Asghar, S., Khan, I. U., Khan, S.-U.-D., Iqbal, M. S., Zaheer, I., Khames, A., Abou-Taleb, H. A., & Abourehab, M. A. S. (2022). Development and characterization of eudragit® EPO-based solid dispersion of rosuvastatin calcium to foresee the impact on solubility, dissolution and antihyperlipidemic activity. *Pharmaceuticals, 15*(492).

Jangid, A. K., Jain, P., Medicherla, K., Pooja, D., & Kulhari, H. (2020). Solid-state properties, solubility, stability and dissolution behaviour of co-amorphous solid dispersions of baicalin. *CrystEngComm, 22*(37), 6128–6136.

Karagianni, A., Kachrimanis, K., & Nikolakakis, I. (2018). Co-amorphous solid dispersions for solubility and absorption improvement of drugs: composition, preparation, characterization and formulations for oral delivery. *Pharmaceutics, 10*(98).

Kuczyńska, J., & Nieradko-Iwanicka, B. (2021). The effect of ketoprofen lysine salt on mucosa of rat stomach after ethyl alcohol intoxication. *Biomedicine & Pharmacotherapy, 141*(111938).

Kumar, V., Goswami, P. K., Balendra, Tewari, S., & Ramanan, A. (2022). Multicomponent solids of niflumic and mefenamic acids based on acid-pyridine synthon. *Frontiers in Chemistry, 10*(729608).

Li, L., Pang, Z., Ma, K., Gao, Y., Zheng, D., Wei, Y., Zhang, J., & Qian, S. (2021). Effect of coformer selection on in vitro and in vivo performance of adefovir dipivoxil cocrystals. *Pharmaceutical Research, 38*, 1777-1791.

Mehta, P., More, A.S., & Kulkarni, A. (2013). Effect of hydrophilic polymers on cefixime complexation with β-cyclodextrin, *International Journal of Current Pharmaceutical Research, 5*(3), 66-70.

Mummidi, V., & Jayanthi, V.R. (2013). Effect of hydrophilic polymers on isradipine complexation with hydroxypropyl β-cyclodextrin. *Drug Development and Industrial Pharmacy, 39*(7), 970-977.

Pagano, C., Latterini, L., di Michele, A., Luzi, F.D., Puglia, D., Ricci, M., Antonio Viseras Iborra, C., & Perioli, L. (2020). Polymeric bioadhesive patch based on ketoprofen-hydrotalcite hybrid for local treatments. *Pharmaceutics, 12*(733).

Parhi, R., & Suresh, P. (2015). Alginate-poloxamer beads for controlled release of metoprolol succinate. *Turkish Journal of Pharmaceutical Sciences, 12*(1), 59-66.

Sahoo, R. N., Satapathy, B. S., Ray, J., Dash, R., & Mallick, S. (2021). Celecoxib crystallized from hydrophilic polymeric solutions showed modified crystalline behavior with an improved dissolution profile. *ASSAY and Drug Development Technologies, 19*(4), 237–245.

Sapkal, S. B., Adhao, V. S., Thenge, R. R., Darakhe, R. A., Shinde, S. A., & Shrikhande, V. N. (2020). Formulation and characterization of solid

dispersions of etoricoxib using natural polymers. *Turkish Journal of Pharmaceutical Sciences, 17*(1), 7–19.

Siswandi, S., Rusdiana, T., & Levita, J. (2015). Virtual screening of co-formers for ketoprofen co-crystallization and the molecular properties of the cocrystal. *Journal of Applied Pharmaceutical Science, 5*(6), 78–82.

Wathoni, N., Sari, W.A., Elamin, K.M., Mohammed, A.F., & Suharyani, I. (2022). A review of coformer utilization in multicomponent crystal formation. *Molecules, 27*(8693).

Wicaksono, Y., Rosidi, V. A., Saragih, S. Y., Fauziah, L. S., & Setyawan, D. (2021). Preparation of spray dried coamorphous solids to improve the solubility and dissolution rate of atorvastatin calcium. *Jurnal Teknologi, 83*(2), 77–83.

Wicaksono, Y., Setyawan, D., & Siswandono, S. (2018). Multicomponent crystallization of ketoprofen-nicotinamide for improving the solubility and dissolution rate. *Chemistry Journal of Moldova*, *13*(2), 74–81.

Wicaksono, Y., Setyawan, D., & Siswandono, S. (2020)a. Analysis of solid-state interactions of ketoprofen-coformer binary mixtures by DSC and hot stage microscopy. *Molekul, 15*(2), 121-129.

Wicaksono, Y., Setyawan, D., Nugraha, A. S., & Siswandono, S. (2020)b. Thermal behavior of cocrystal: a case study of ketoprofen-malonic acid and ketoprofen-nicotinamide cocrystals. *Sains Malaysiana, 49*(11), 2679–2687.

Yan, Y., Kariuki, B.M., Hughes, C.E., Logsdail, A.J., & Harris, K.D. (2020). Polymorphism in a multicomponent crystal system of trimesic acid and t-butylamine. *Crystal Growth & Design, 20*(9), 5736–5744.

Yu, M., Liang, M., An, Q., Wang, W., Zhang, B., Yang, S., Zhou, J., Yang, X., Yang, D., Zhang, L., Du, G., & Lu, Y. (2023). Versatile solid modifications of multicomponent pharmaceutical salts: novel metformin–rhein salts based on advantage complementary strategy design. *Pharmaceutics, 15*(1196).

Zhang, S., Zhang, X., Meng, J., Lu, L., Du, S., Xu, H., & Wu, S. (2022). Study on the effect of polymer excipients on the dispersibility, interaction, solubility, and scavenging reactive oxygen species of myricetin solid dispersion: experiment and molecular simulation. *ACS omega, 7*(1), 1514-1526.