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PREPARATION AND CHARACTERIZATION PHISICOCHEMICAL PROPERTIES OF MULTI COMPONENT KETOPROFEN WITH CO-FORMER GLUTAMINE

Helen Sonita[1], Erizal Zaini [1], Salman Umar [1*]
[1]Fakultas Farmasi, Universitas Andalas
Limau Manis Padang Kode Pos 25163
**Email Corresponding author: umar.salman@yahoo.com*

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ABSTRACT

Ketoprofen is a non-steroidal anti-inflammatory compound (NSAID) which has low solubility in water. This study aimed to increase the dissolution rate of ketoprofen by forming multicomponent ketoprofen-glutamine in ratios of 1:1, 1:2, and 2:1 using the solid-state grinding method. The samples were characterized using Powder X-Ray Diffractometry (PXRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR) Spectroscopy, Scanning Electron Microscope (SEM), solubility, dissolution rate, and stability tests. These results indicated the formation of a eutectic mixture of ketoprofen-glutamine. From the study of the ketoprofen–glutamine eutectic mixture, the eutectic point at a ratio of 1:1 was obtained at 95.51°C. The PXRD spectra did not show new crystal habits; the solubility test of the eutectic mixture of ketoprofen-glutamine showed increases of 2.450, 2.518, and 2.374 times, respectively. The eutectic mixture of ketoprofen–glutamine had rod-like crystal particles that formed and aggregated. The samples showed an increased dissolution rate of ketoprofen. The stability test showed that ketoprofen-glutamine was stable during storage at 75% relative humidity (RH) and 40 °C for 6 months; there was only a decrease in intensity, as seen from the PXRD spectrum.

Keywords: eutectic mixture, ketoprofen, glutamine, solubility, dissolution rate, stability

INTRODUCTION

Multicomponents can change the physicochemical properties of drugs, including increasing their solubility and dissolution rate, thereby increasing the bioavailability of poorly soluble drugs. Multicomponents consist of eutectic mixtures, amorphous solid solutions, solvates, hydrates, salts, and crystals that can be designed (Setyawan & Paramita, 2019). The formation of this multicomponent can be carried out using various methods, namely, solvent-based and solvent-free co-crystallization, also known as the solid-based method. Solvent-based methods include solvent evaporation, anti-solvent methods, cooling crystallization, reaction co-crystallization, supercritical fluid technology, and slurry conversion (Guo *et al*., 2021). Solid-based methods include contact crystallization, neat grinding, solvent drop grinding, hot-melt extrusion, spray drying, and sonocrystallization (Thayyil *et al*., 2020).

Multicomponent is a subcategory of multicomponents consisting of at least two components, namely the active substance and the coformer, which interact in the crystal lattice through non-covalent bonds, especially hydrogen bonds, and can maintain the activity of the active substance (Setyawan & Paramita, 2019). The advantage of this technique is that it does not affect the pharmacological activity of the active substance but only improves the physical properties of the substance, such as solubility, dissolution rate, and compressibility. A eutectic mixture is a multicomponent form that can be prepared by combining a drug and an inert carrier (usually a highly hydrophilic compound), or by combining two drugs with different solubilities. The melting point of the mixture of the two ingredients was lower at the eutectic point than at their respective melting points. Thermodynamic parameters, such as the melting

point, enthalpy, and entropy, affect solubility. Therefore, the solubility of the drug in the eutectic mixture increased (Bazzo *et al*., 2020).

The selection of active ingredients and coformers must be safe and non-toxic if administered to humans, which narrows the scope of selection of these coformers. Several studies have reported that organic acids or molecules with amino functional groups can be chosen as coformers because they have been proven to increase the solubility and absorption of active pharmaceutical ingredients (Nugrahani & Jessica, 2021; Fucke *et al*., 2012). Amino acids are used as coformers because they act as hydrogen-bond donors and acceptors (Song *et al*., 2019). Glutamine is an amino acid containing an amine group that can bind to the carboxylic group of ketoprofen; therefore, it is expected to form multiple components (Nugrahani & Jessica, 2021).

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) which has analgesic, antipyretic and anti-inflammatory effects. Its mechanism of action involves inhibition of prostaglandin synthesis (Shargel *et al*., 2012). This drug is widely used in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis (Sweetman, 2009). When used orally, ketoprofen has side effects, such as digestive disorders and kidney failure (Shinkai *et al*., 2008), compared to 2 hour after oral administration, which indicates the rate of absorption. The rapid onset of action is important for ketoprofen because of its analgesic activity (Shohin *et al*., 2012). The solubility of ketoprofen in water at a temperature of 22-27°C is 0.253 mg/ml; therefore, ketoprofen is practically insoluble in water (Shohin *et al*., 2012).

Several previous studies have been carried out to increase the solubility of ketoprofen, including the formation of multicomponent ketoprofen with nicotinamide using the solvent evaporation technique which shows an increase in solubility 1.3 times higher than pure ketoprofen (Wicaksono *et al*., 2018) using the Co Grinding technique using the polymer Hydroxypropyl Methylcellulose E6 with a solubility increase of 6.5 times (Hilaliyati *et al*., 2017), an increase in solubility with a solid dispersion of ketoprofen-macrogol 6000-KLHT is 3.8 times (Jachowicz *et al*., 2000), an increase in solubility with a solid dispersion of ketoprofen-polyvinylpyrrolidone (PVP) is a ratio of 1:1.5 providing a faster dissolution rate of ketoprofen than the physical mixture (Patil *et al*., 2010) with the ketoprofen fusion technique with the coformer used p-amino-salicylate, showing a 14-fold increase in solubility in water (Vaghela *et al*., 2014) where it can be interpreted that multicomponents can improve physicochemical properties, especially the solubility of ketoprofen.

In this study, the multicomponent preparation of ketoprofen was carried out using glutamine as a coformer using the solid-state grinding method. The advantages of multicomponent preparation of eutectic mixtures can be achieved using simple and cost-effective methods. In addition, this method allows the combination of active pharmaceutical ingredients to be thermally relevant (in the case of mixtures of eutectic drugs) and has a more stable form than the amorphous form (Bazzo *et al*., 2020). The results of this study showed that the solubility of ketoprofen improved, thereby increasing its bioavailability. The resulting multicomponents will be characterized including solubility test, dissolution test, differential scanning calorimetry (DSC) analysis, X-Ray Diffractometry (XRD), Fourier Transform Infra-red (FTIR) spectroscopy, microscopy with Scanning Electron Microscopy (SEM) and continued with stability test for multicomponents.

RESEARCH METHODS

Equipment and Materials

The equipment used in this study were digital scales (Shimadzu-AUX 220, Japan), Differential Scanning Calorimetry (Shimadzu DSC-60 Plus, Japan), powder X-ray diffraction (PANalytical X'Pert Pro), Scanning Electron Microscopy (Hitachi Flexsem 1000), IR spectrophotometer (Shimadzu IRTracer-100 AH), dissolution rate test equipment (SR8 Plus Dissolution Test Station Hanson Virtual Instrument), Orbital Shaker, High Performance Liquid Chromatography 1220 Infinity II LC System (Agilent, USA), climatic chamber, desiccator and other standard laboratory glassware.

The materials used included: Ketoprofen (Boc Sciences, New York), Glutamine (TCI-EP), methanol grade liquid chromatography (Merck, Germany), aqua pro injection, aquabides (Ikapharmindo Putramas, Indonesia), reagent: Potassium dihydrogen phosphate (KH_2PO_4) pro analysis (Merck), Sodium Hydroxide (NaOH) pro analysis (Merck).

Research Procedure

1. **Preparation of Multicomponent Ketoprofen**

   Three multicomponent formulations were prepared with active substance ratios of 1:2, 1:1, and 2:1 (w/w). Each ketoprofen-glutamine was weighed based on the molar ratio using the solvent drop grinding method, and the weighed material was placed in a mortar, mixed with two drops of methanol, and crushed for 30 minutes until a dry powder was formed.

2. **X-Ray Diffraction (XRD)**

   The analysis was performed using pure ketoprofen and ketoprofen-glutamine as multicomponents. X-ray diffraction (XRD) analysis of the sample powders was performed at room temperature using an X-ray diffractometer (PANalytical XPert Pro) with Cu K radiation (λ = 1.54178 Å) at a voltage of 45 kV and a current of 40 mA. Samples were measured in reflection mode at 0.05 theta with an angle range of 5 °to 45º theta at a scanning speed of 5°/minute. The analysis was performed for pure ketoprofen and pure glutamine and the results of the multicomponent ketoprofen and glutamine (Zaini *et al*., 2019).

3. **Differential Scanning Calorimeter (DSC)**

   The DSC analysis procedure began by weighing approximately 5 mg of the sample and placing it on a closed aluminum plate. The DSC device was programmed at a temperature range of 30–250 °C with a heating speed of 10 °C per minute and nitrogen gas flow of 20 mL/minute, and the endothermic and exothermic processes were recorded on the recorder. Analysis was performed for pure ketoprofen and ketoprofen-glutamine (Zaini *et al*. 2019).

4. **Fourier Transformation-Infrared Spectrophotometer (FT-IR)**

   The pure ketoprofen and ketoprofen-glutamine levels were measured using an infrared spectrophotometer. The sample powder (1 – 2 mg) was mixed with 10 mg of KBr in a mortar, crushed until well blended, transferred to a mold, and then compressed at a pressure of 800 kPa in an airtight disc. The absorbance of the samples was measured at 4000 nm-1-600 nm-1. This analysis shows the spectrum of the functional groups of each sample (Zaini *et al*., 2019).

5. **Scanning Electron Microscopy (SEM)**

   Scanning electron microscopy (SEM) analysis was performed on pure ketoprofen and ketoprofen-glutamine. Prior to analysis, the samples were coated with a thin layer of palladium-gold with a thickness of 10 nm. The voltage was regulated at 15 – 20 kV, with a current of 12 Ma. The samples were observed at various magnifications by SEM (Zaini *et al*., 2019).

6. **Solubility Test**

   A solubility test was carried out on ketoprofen and its multicomponents, which were made into a saturated solution. Each equivalent of 75 mg of ketoprofen was weighed and then placed into a 100 mL Erlenmeyer and supplemented with 100 mL of aquabidest. The test was performed for 1 day using an orbital shaker at a temperature of 25°C and a speed of 100 rpm (Zaini *et al*., 2019). The sample was then filtered using a 0.45 µm membrane filter (whatman) and analyzed using HPLC. The test was repeated 3 times.

7. **Dissolution Test**

   The dissolution profiles of ketoprofen and its components were also determined. The dissolution flask was filled with 900 mL of phosphate buffer (pH 6.8). The temperature was set at 37±0.5 °C at a speed of 50 rpm. The sample was then placed in the dissolution medium. The dissolution solution (5 mL) was pipetted at 5 minutes intervals:10, 15, 30, 45, and 60. Each pipette was replaced with dissolution medium, which was maintained at the same temperature so that the volume of the dissolution medium remained constant

(Saafrida *et al*., 2023). Each solution was filtered using a 0.45 µm membrane filter (whatman) and analyzed using HPLC under the same conditions as the retention time of ketoprofen was determined. The percentage dissolution was determined by comparing the area of the sample with the area of the standard ketoprofen of known concentration. The test was repeated 3 times.

8. Stability Test

The multicomponent ketoprofen prepared by the solid-state grinding method was placed in a brown glass bottle and stored for 6 months in a climatic chamber at 75% Relative Humidity (RH) at 40±2 °C. After storage for 6 months, testing was carried out using XRD. Multicomponent diffractograms were compared to diffractograms after storage under certain conditions (Zaini *et al*., 2019).

Data analysis

The data analysis used in this study was one-way and two-way analysis of variance (ANOVA) using SPSS 26.

RESULTS AND DISCUSSION

From the thermogram results of the multicomponent ketoprofen-glutamine, it can be seen that it has a slightly lower melting point than the original compound, 95.51°C in the 1:1 formula. The eutectic mixture had a lower melting point than the original compound, resulting in a decrease in the lattice energy. Thus, the energy required to break the crystal-forming interactions is also smaller, resulting in an increase in solubility (Chadha *et al*., 2017). In addition, the increase in the solubility of the eutectic mixture was due to the smaller particle size and better wettability, which contributed to a faster dissolution rate (Sekiguchi & Obi, 1961). Thus, it can be concluded that the multicomponent ketoprofen-glutamine was a eutectic mixture. This result is supported by the data obtained from the X-ray diffraction analysis, where the higher the amount of glutamine used, the lower the degree of crystallinity.

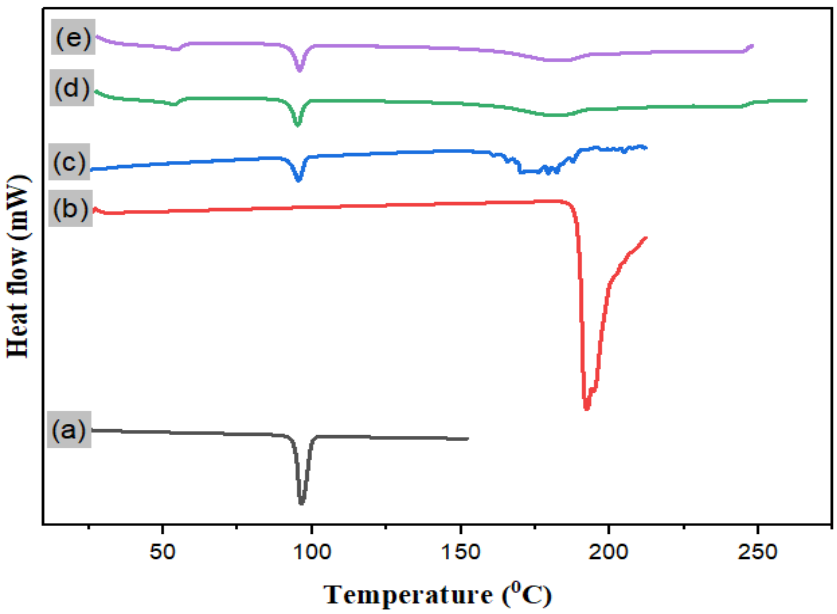

Figure 1. Thermogram (a) ketoprofen (b) glutamine (c) keto-glu 1:1, (d) keto-glu 1:2 (e) keto-glu 2:1

Table I. Comparison of The Melting Point and Enthalpy Values of Ketoprofen, Glutamine, and The Multicomponent Ketoprofen-Glutamine

Compounds	Endoterms Peak	Entalphi (ΔH)
Ketoprofen (a)	96.53°C	-299.87 mJ/g
Glutamine (b)	192,3°C	54,97 J/g
MK Keto-Glu 1:1 (c)	95,51°C	-27,08 J/g
MK Keto-Glu 1:2 (d)	96,13°C	29,29 J/g
MK Keto-Glu 2:1 (e)	95,89°C	44,399 J/g

The ketoprofen diffractogram shows a crystalline solid owing to the presence of a characteristic sharp interference peak with a high degree of crystallinity at diffraction angles of 2θ = 14.3731, 18.3771, and 22.8751. The ketoprofen–glutamine multicomponent diffractogram still showed ketoprofen peaks; however, the peak intensity of the crystalline solids decreased. The peak intensity of the 1:2 formula was the lowest among those of the other formulas. A decrease in the intensity of this peak indicated a change in the degree of crystallinity. This shows that the greater the number of amino acids used, the lower the intensity of the interference peak and the lower the degree of crystallinity (Patel *et al*., 2019).

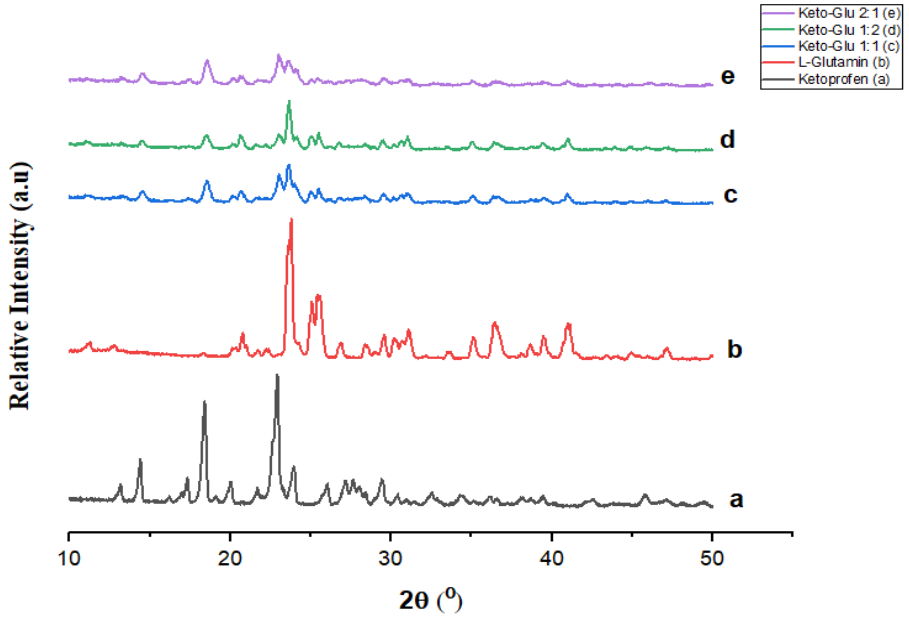

Figure 2. X-ray diffractogram (a) ketoprofen (b) glutamine (c) keto-glu 1:1 (d) keto-glu 1:2, (e) keto-glu 2:1

Table II. The Results of Diffraction Peak Diffractogram Measurements at an Angle of 2θ (⁰) and The Intensity of The Ketoprofen, Glutamine and Ketoprofen-Glutamine Multicomponent Formulas 1:1, 1:2, and 2:1

Ketoprofen (a)		Glutamine (b)		Diffraction Peak Sudut 2θ (⁰)	Keto-Glu 1:1 (c)	Keto-Glu 1:2 (d)	Keto-Glu 2:1 (e)
Angle 2θ (⁰)	Intensity	Sudut 2θ (⁰)	Intensity		Intensity		
13,1576	760,4071	6,3716	1305,042	6,4171	443,7432	388,0303	456,1727
14,3666	1346,755	13,1706	777,0056	13,2031	297,1064	286,466	278,5041
18,3836	2961,917	20,8276	276,9454	14,3731	316,4006	238,8576	322,2989
22,8686	3404,095	23,7916	936,9804	18,3771	521,9023	376,8009	523,4018
23,9476	1248,776	25,3971	284,3510	22,8751	581,9127	334,5962	592,1956

The observed bonds were O-H with a wavenumber range of 3300-2500 cm-1 and C=O with a wavenumber range of 1900-1650 cm-1. Based on the ketoprofen FTIR spectrum obtained, the wavenumber was 1693.32 (carbonyl –C=O); and 2875.44 (carboxylate –C=O) shows the presence of C-O, carbonyl, and hydroxyl bonds, indicating the presence of a carboxylic group in ketoprofen. Glutamine showed wave numbers of 1623.11 (carbonyl –C=O) and 3407.72 (-CN), indicating the presence of hydroxyl, carbonyl, and C-O bonds, indicating the presence of the NH2 group in glutamine. In the multicomponent ketoprofen-glutamine 1:1, the spectrum results showed peaks at wave numbers 3407.53 (carboxylates –C=O) and 1655.35 (carbonyl –C=O), which showed the presence of hydroxyl, carbonyl, and C-O bonds, indicating the presence of groups carboxylates and ketone groups. In the 1:2 ketoprofen-glutamine multicomponent, the spectrum results showed peaks at wave numbers 3407.47 (carboxylates –C=O) and 1655.21 (carbonyl –C=O), which showed the presence of hydroxyl, carbonyl, and C-O bonds, indicating the presence of groups carboxylates and ketone groups. In the multicomponent ketoprofen-glutamine 2:1, the spectrum results showed peaks at wave numbers 3408.69 (carboxylates –C=O) and 1655.30 (carbonyl –C=O), which showed the presence of hydroxyl, carbonyl, and C-O bonds, indicating the presence of carboxylic groups and ketones.

Based on the results of the multicomponent FTIR spectrum of ketoprofen-glutamine (1:1, 1:2, and 2:1), no significant new spectrum was formed compared to the ketoprofen-glutamine spectrum. The interaction that occurs is an intramolecular interaction characterized by a decrease in the intensity of the spectrum, but the bond that is formed is a weak bond or is easily released again. The peaks that appeared were still similar to those of ketoprofen-glutamine, indicating that the multicomponent ketoprofen-glutamine formed a eutectic mixture. The bonds formed are non-covalent bonds, namely hydrogen bonds due to the interaction between hydrogen atoms and electronegative atoms. It is possible that interactions occur between the carboxylic acid groups in ketoprofen and the amine groups in proline or bonds between carboxylic acid groups in ketoprofen and glutamine (Jeffrey & Saenger, 1994; Bazzo *et al.*, 2020; Patel *et al.*, 2019).

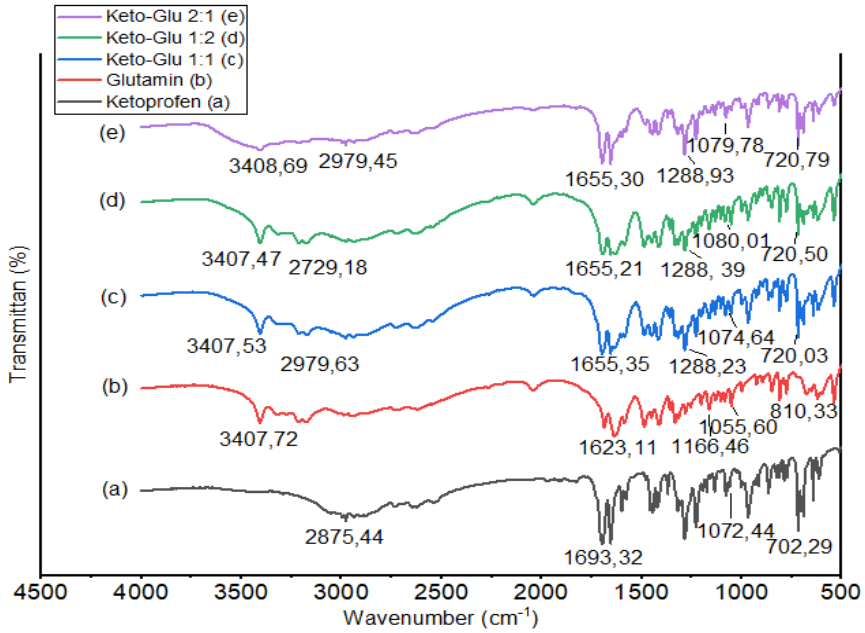

Figure 3. FTIR Spectra (a) ketoprofen, (b) glutamine, (c) keto-glu 1:1, (d) keto-glu 1:2, (e) keto-glu 2:1

Table III. Comparison of FTIR Wave Numbers for Ketoprofen, Glutamine and Multicomponent Ketoprofen-Glutamine Formulas 1:1, 1:2 and 2:1

No	Functional groups	Wave Number (cm^{-1})				
		Ketoprofen (a)	Glutamine (b)	Keto-Glu		
				1:1 (c)	1:2 (d)	2:1 (e)
1	O – H	2875,44	3407,72	3407,53	3407,47	3408,69
2	C = O	1693,32	1623,11	1655,35	1655,21	1655,30

Scanning electron microscopy (SEM) been used in several studies to identify and compare the shapes of the surfaces of eutectic mixtures (Araya-Sibaja *et al.*, 2019; Haneef & Chadha, 2018; Patel *et al.*, 2019). Scanning electron microscope (SEM) was performed at a magnification of 4000 times. The results of the analysis revealed the shape of the surface of ketoprofen and glutamine. Ketoprofen exhibited aggregate morphology. Glutamine exhibits a single rod-like morphology. At keto-Glu 1:1 (figure 13C), an aggregate between ketoprofen and glutamine was formed, which was characterized by the morphological forms of ketoprofen and glutamine still visible. The 1:2 keto-glue sample (figure 13D) showed similar aggregates to the 1:1 keto-glue sample, but based on the morphological observations, glutamine appeared to be more significant than ketoprofen, showing that the morphology of ketoprofen and glutamine was no longer visible. For the 2:1 keto-glue sample (Fig. 13E), the aggregate morphology of ketoprofen was no longer visible, because it was evenly dispersed on the surface of the particles. Scanning electron microscope (SEM) analysis has been carried out in several previous studies where this eutectic mixture was observed based on its morphology, and changes in particle shape and size resulted in an even distribution of particles on the surface of the particles (Emami *et al.*, 2018).

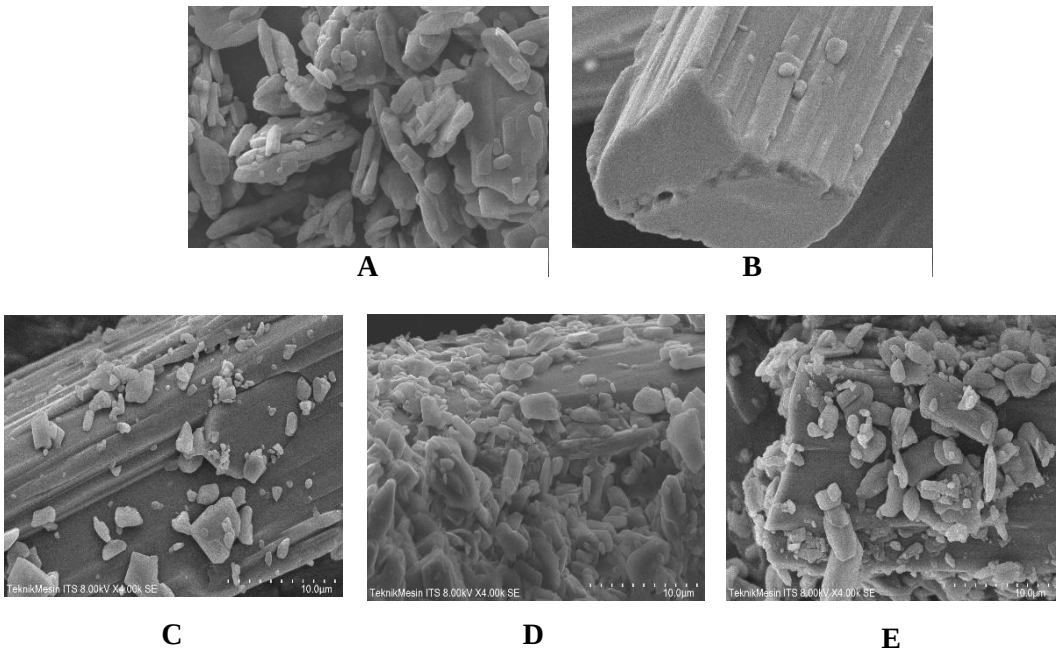

Figure 4. SEM microphotographs (A) ketoprofen, (B) glutamine, (C) keto-glu 1:1, (D) keto-glu 1:2, (E) keto-glu 2:1 magnification 4000 times

The 1:2 ketoprofen-glutamine eutectic mixture formula had the highest solubility compared to the other samples, while pure ketoprofen had the lowest solubility. The solubility of ketoprofen in the eutectic mixture of ketoprofen-glutamine 1:2 increased more than 2 times compared to that of pure ketoprofen. This is supported by the results of DSC, XRD, and FTIR analyses,

which showed that there was a change in the melting point, a decrease in the degree of crystallinity, and interactions between the functional groups in all samples.

Table IV. The Results of The Solubility Test of Ketoprofen, L Multicomponent Ketoprofen-Glutamine in Formulas 1:1, 1:2, and 2:1

Sample	Average level of dissolved Ketoprofen (mg/100mL) ± SD	Solubility Enhancement
Ketoprofen	10,17 ± 0,045	-
Keto-Glu 1:1	24,92 ± 0,41	2,450 times
Keto-Glu 1:2	25,61 ± 0,28	2,518 times
Keto-Glu 2:1	24,15 ± 0,12	2,374 times

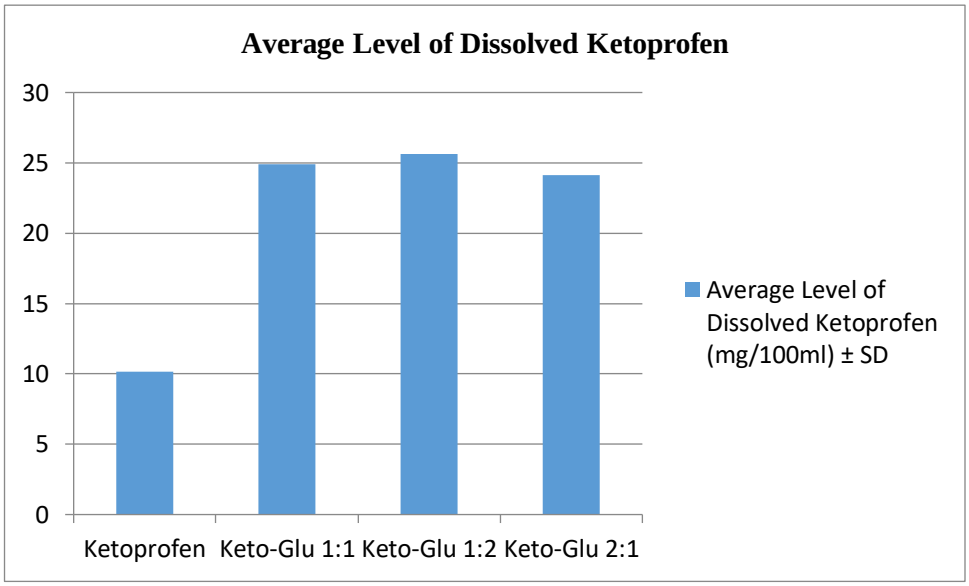

Figure 5. Bar Diagram of The Solubility of Pure Ketoprofen and Multicomponent Ketoprofen-Glutamine Formulas 1:1, 1:2, and 2:1

Dissolution test results of pure ketoprofen and multicomponent ketoprofen-glutamine at 1:1, 1:2, and 2:1 ratios were carried out using the basket method. The medium used was 900 mL of phosphate buffer pH 6.8 at 37 ± 0.5 °C and 50 rpm for 60 minutes. The test was carried out by taking samples at the 5th minute; 10, 15, 30, 45, and 60 (Saafrida *et al*., 2023). The average % dissolved in the 60th minute of ketoprofen and multicomponent ketoprofen-glutamine in formulas 1:1, 1:2, and 2:1 were 31.03 ± 0.11; 43.06±0.08; 54.56 ± 0.32 and 34.56 ± 0.02%, respectively. The sample of the 1:2 ketoprofen-glutamine eutectic mixture had a fast dissolution rate because of its high internal energy, making it easier for the particles to interact with water molecules, causing it to increase its solubility in water (Dengale *et al*., 2016). Preparations with a high level of solubility and speed of dissolution of the active substance from the dosage form will be faster; conversely, preparations with low solubility and speed of dissolution of the active substance from the dosage form will be slower (Abdou, 1989). The increase in the dissolution rate of the multicomponent samples was also affected by the reduction in particle size. The increase in the dissolution rate is proportional to the increase in the surface area of the substance in contact with the dissolution medium, and inversely proportional to the particle size of the substance (Bazzo *et al*., 2020). This is supported by the results of DSC, XRD, and FTIR analyses, which showed that there was a change in the melting point, a decrease in the degree of crystallinity, and interactions between functional groups in all samples.

Table V. Percent Results of Dissolved Ketoprofen, Multicomponent Ketoprofen-Glutamine Formula 1:1, 1:2, and 2:1

Time (minute)	Mean percent dissolved (%) ± Standard Deviation (SD)			
	Ketoprofen	Keto-Glu 1:1	Keto-Glu 1:2	Keto Glu 2:1
5	26,98 ±0,06	32,07±0,13	44,20±0,09	21,93±0,05
10	27,31±0,04	42,39±0,18	51,23±0,16	32,17±0,13
15	27,55±0,08	42,46±0,08	51,73±0,13	35,20±0,27
30	28,67±0,94	46,13±0,09	56,86±0,19	35,78±0,13
45	29,07±0,04	43,79±0,29	54,61±0,03	34,87±0,04
60	31,03±0,11	43,06±0,08	54,56±0,32	34,56±0,02
Average (Sample)	28,43±1,51	41,65±4,89	52,20±4,43	32,42±5,28

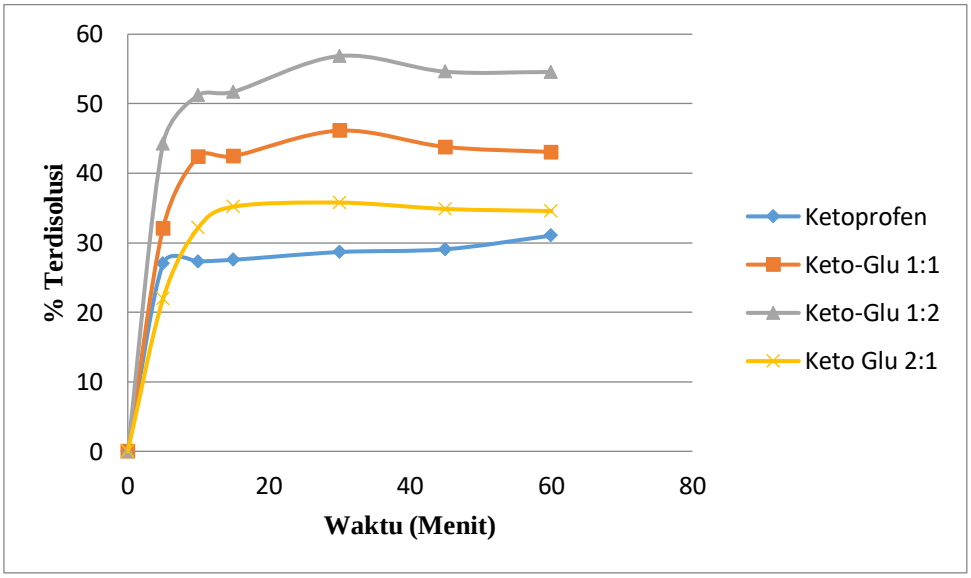

Figure 6. Dissolution Percentage Curves of Ketoprofen, a Multicomponent Ketoprofen-Glutamine Formula 1:1, 1:2, and 2:1

Stability tests according to ICH guidelines are carried out at 40 °C RH 75% within 6 months or more. Analysis of the stability test results using an XRD apparatus was used to evaluate the stability of the multicomponent ketoprofen-glutamine crystals. The stability test results obtained with this tool show the same diffractogram pattern, which indicates that the accelerated stability does not affect the crystal structure. There was a change in the intensities of several peaks, indicating a change in the degree of crystallinity. The low intensity is most likely due to the low rearrangement or orderliness of the crystal lattice due to the thermodynamic activity (Ainurofiq *et al*., 2018).

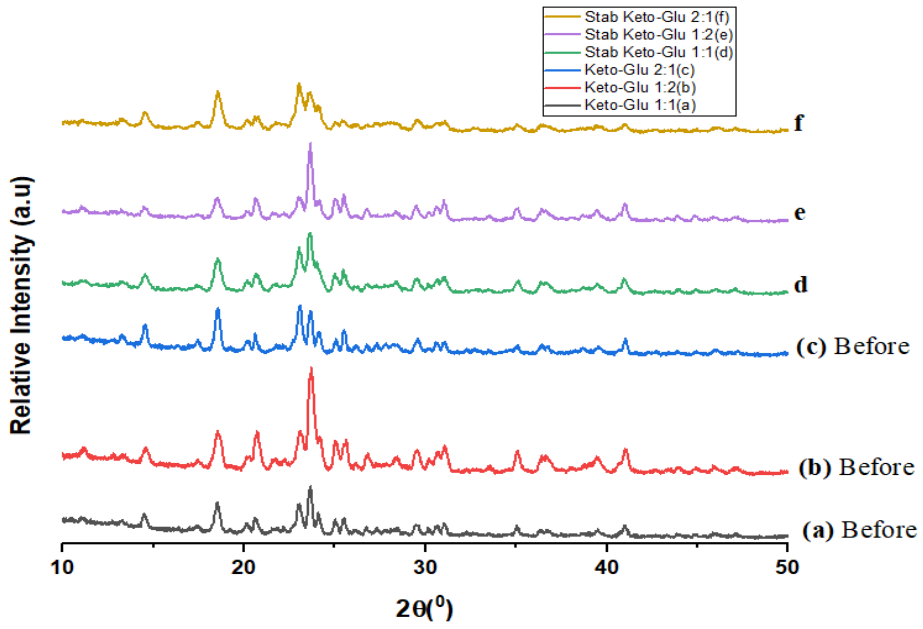

Figure 7. Keto-Glu PXRD diffractograms before and after storage at 75% RH for 6 months

Table VI. Comparison of Diffraction Peak Intensities of The Multicomponent Ketoprofen-Glutamine Formula 1:1, 1:2, and 2:1

Diffraction Peak 2θ (0)	Intensity					
	Keto-Glu 1:1 (a)	Keto-Glu 1:2 (b)	Keto-Glu 2:1 (c)	Keto-Glu 1:1 (d)	Keto-Glu 1:2 (e)	Keto-Glu 2:1 (f)
	Before			After		
6,4171	628,3601	692,852	694,931	443,7432	388,0303	456,1727
13,2031	368,871	422,1324	455,5181	297,1064	286,466	278,5041
14,3731	404,3071	441,6952	415,3832	316,4006	238,8576	322,2989
18,3771	550,0469	690,8446	635,9458	521,9023	376,8009	523,4018
22,8751	596,3051	547,371	687,6661	581,9127	334,5962	592,1956

CONCLUSION

Multicomponent ketoprofen- forms a eutectic mixture using the solid-state grinding method at a 1:1 formula with a slightly lower eutectic point than the original compound at 95.51°C. The increased solubility of multicomponent ketoprofen-glutamine was 2,450, 2.518, and 2.374 times higher than that of pure ketoprofen. Dissolution at 60 minutes of pure ketoprofen and multicomponent ketoprofen-glutamine were 31.03 ± 0.11, 43.06 ± 0.08, 54.56 ± 0.32, 34.56 ± 0.02, respectively. There was a decrease in intensity, indicating that the stability test did not affect the ketoprofen-glutamine preparation, based on the XRD results before and after the stability test.

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