Farmasains: Jurnal Ilmiah Ilmu Kefarmasian
Volume 12, Number 1, 2025, 13-21
ISSN:2621-9816 (Online); 2086-6968 (Print)
Journal homepage: https://journal.uhamka.ac.id/i\ndex.php/farmasains/

Research Article

Effect of Conventional and Ultrasound-Assisted Recrystallisation of Mefenamic Acid Crystal

Pengaruh Rekristalisasi Konvensional dan Bantuan Ultrasonik terhadap Kristal Asam Mefenamat

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Received:
November 23, 2024

Reviewed:
February 4, 2025

Accepted:
March 10, 2025

Published:
April 30, 2025

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ABSTRACT
Mefenamic acid is classified as a Biopharmaceutical Classification System (BCS) Class II drug. Crystallisation techniques can significantly influence the critical properties of mefenamic acid crystals, an essential consideration in the pharmaceutical industry. This study investigates the effect of recrystallisation on the morphology and particle size of mefenamic acid crystals using ethyl acetate as the solvent. Recrystallisation was conducted using both conventional and ultrasonic-assisted methods. The yield was calculated, and characterization was performed to determine the crystal properties, shape, and particle size using polarized microscopy, X-ray Diffraction (XRD), and Fourier Transform Infrared Spectroscopy (FTIR). The results showed that conventional recrystallisation yielded 25.078%, while ultrasonic-assisted recrystallisation at 50 W, 60 W, 70 W, and 80 W yielded 43.47%, 47.71%, 51.90%, and 50.20%, respectively. Skewness and kurtosis values for the average crystal length and width indicated a normal distribution. XRD analysis revealed that the diffraction peak intensity of conventionally recrystallised crystals became narrow. In contrast, the diffraction peak intensity of ultrasonically assisted crystals broadened. FTIR results demonstrated that the recrystallisation process did not alter the fundamental chemical structure of mefenamic acid. The findings indicate that recrystallisation methods influence crystal shape and size, with ultrasonic-assisted techniques producing crystals of smaller average size than those obtained through conventional methods.

Keywords*:* Conventional, Mefenamic Acid, Recrystallisation, Ultrasonic-Assisted

ABSTRAK
Asam mefenamat merupakan obat yang termasuk dalam Sistem Klasifikasi Biofarmasetik Kelas II. Teknik kristalisasi dapat memengaruhi sifat-sifat penting kristal asam mefenamat yang perlu dipertimbangkan dalam industri farmasi. Tujuan penelitian ini adalah untuk mengetahui pengaruh rekristalisasi terhadap bentuk dan ukuran partikel kristal asam mefenamat menggunakan etil asetat sebagai pelarut. Asam mefenamat

di rekristalisasi secara konvesional dan bantuan ultrasonik, kemudian dihitung rendemen dan dilakukan karakterisasi untuk menentukan sifat, bentuk, dan ukuran partikel kristal, digunakan mikroskop polarisasi, Difraksi Sinar-X (XRD) dan Fourier Transform Infrared Spectroscopy (FTIR). Hasil menunjukan rendemen yang diperoleh dari rekristalisasi konvensional sebesar 25,078%, sedangkan rekristalisasi dengan bantuan ultrasonik pada daya 50 W (43,47%), 60 W (47,71%), 70 W (51,90%), dan 80 W (50,20%). Nilai skewness dan kurtosis dari rata-rata panjang dan lebar kristal menghasilkan distribusi normal. Hasil analisis XRD menunjukkan bahwa intensitas puncak difraksi kristal konvensional semakin menyempit, sedangkan intensitas puncak difraksi kristal yang dibantu ultrasonik semakin melebar, hasil FTIR menunjukan rekristalisasi tersebut tidak mengubah struktur kimia dasar asam mefenamat. Perbedaan metode rekristalisasi dapat memengaruhi bentuk dan ukuran kristal, terlihat pada kristal yang diperoleh dengan ultrasonik memiliki bentuk dengan ukuran rata-rata lebih kecil dibandingkan secara konvensional.

Kata Kunci: *Konvensional, Asam Mefenamat, Rekristalisasi, Bantuan Ultrasonik*

INTRODUCTION

Mefenamic acid, a non-steroidal anti-inflammatory drug (NSAID), is widely used for its analgesic and antipyretic properties (1). Despite its broad therapeutic benefits, mefenamic acid faces a significant challenge in terms of solubility, as it falls under class II of the Biopharmaceutics Classification System (BCS), compounds characterised by low solubility but high permeability (2). Its poor solubility can affect the drug's bioavailability, thereby necessitating efforts to enhance the physicochemical properties of mefenamic acid, particularly through modification of the crystallisation process (3). Recrystallisation is a commonly employed technique to address this issue, as it can significantly influence particle size, morphology, and crystal distribution, ultimately affecting drug performance (4).

Conventional recrystallisation, frequently applied in the pharmaceutical industry, relies on temperature changes and solvent evaporation to produce crystals with specific purity and size characteristics (4). However, this method presents limitations in precisely controlling particle size and distribution. In contrast, ultrasound-assisted recrystallisation offers a more modern approach by utilising high-frequency sound waves to generate cavitation effects (5). These effects can initiate nucleation and promote more controlled crystal growth, thus potentially producing crystals with smaller, more uniformly distributed particles (6).

The primary advantage of ultrasound-assisted recrystallisation lies in its ability to yield crystals with superior characteristics compared to the conventional method (6). Ultrasound can generate high mechanical energy through cavitation, which facilitates the breakdown of larger particles into smaller, more uniform forms. Additionally, this method can reduce the crystallisation time and enhance production efficiency (7,8). These advantages position ultrasound as an appealing alternative within the pharmaceutical industry, especially for compounds such as mefenamic acid that require physicochemical modification. Ethyl acetate was chosen as the solvent in this study due to its clear appearance, low toxicity, and volatility. It has also been shown to effectively enhance the solubility and modify polymorphic crystal forms of various pharmaceutical compounds (9). By comparing the results of conventional and ultrasound-assisted recrystallisation, this study aims to evaluate the effects of both methods on the crystal characteristics of mefenamic acid, particularly in terms of morphology, particle size, and size distribution. These characteristics are important, as they can influence pharmacokinetic and pharmacodynamic properties, including dissolution rate, stability, and bioavailability (10). A study by Iyer *et al*. (2016) demonstrated that ultrasound not only increases yield but also reduces

crystallisation induction time compared to conventional cooling crystallisation techniques. Ultrasound may thus serve as an effective method to improve both the quality and efficiency of the crystallisation process (5).

The novelty of this research lies in the comparative approach of conventional and ultrasound-assisted recrystallisation methods, which has not been extensively explored, particularly for mefenamic acid using ethyl acetate as a solvent. Furthermore, this study investigates the influence of ultrasonic parameters, such as power and sonication time, on the morphological and dimensional characteristics of the resulting crystals. Hence, the present research deepens the understanding of the recrystallisation process and offers a practical solution to enhance the quality of mefenamic acid crystals. This study has the potential to significantly advance the development of more efficient and higher-quality pharmaceutical formulations. By optimising the recrystallisation process, it is expected that mefenamic acid crystals with improved physicochemical properties can be obtained, thereby enhancing their therapeutic efficacy. Moreover, this study may serve as a foundational reference for further development of pharmaceutical technologies, particularly in applying ultrasound to modify the crystal characteristics of drug compounds. Therefore, this study aims to determine the effect of recrystallisation on the morphology and particle size of mefenamic acid crystals, using ethyl acetate as the solvent.

Materials and Methods

Materials

Mefenamic acid was obtained from PT. Phapros (Indonesia). Ethyl acetate (analytical grade) was purchased from Merck (Germany). Whatman filter paper No. 40 was used for filtration (GE Healthcare, United Kingdom).

Methods

1. Conventional Recrystallisation of Mefenamic Acid

Two grams of mefenamic acid were dissolved in 50 mL of ethyl acetate. The solution was heated and stirred at 300 rpm at a temperature of 60°C until the solute completely dissolved. The solution was filtered using a Büchner funnel under a vacuum and then cooled in a refrigerator for 15 minutes until the solution reached a supersaturated state, followed by nucleation. The crystals were then observed forming near the walls and bottom of the beaker. The resulting crystals were filtered using filter paper to separate them from the solvent. They were dried in an oven at 70°C and stored in a tightly closed container at room temperature. Crystal yield was then calculated (5,11).

2. Ultrasonically Assisted Recrystallisation of Mefenamic Acid

Two grams of mefenamic acid were dissolved in 50 mL of ethyl acetate. The solution was sonicated in an ultrasonic bath at 41°C with a power of 50-80 W for 10 minutes until the mefenamic acid dissolved. The solution was filtered using a Büchner funnel under a vacuum and then cooled in a refrigerator for 15 minutes until the solution reached a supersaturated state, followed by nucleation. Crystals were observed forming near the walls and bottom of the beaker. The resulting crystals were filtered using filter paper to separate them from the solvent. The crystals were dried in an oven at 70°C and stored in a tightly closed container at room temperature. The crystal yield was then calculated (5).

3. Characterisation

a. Polarising Microscopy

A small quantity of the recrystallised crystals was placed on a microscope slide and positioned on the microscope stage. A 400x magnification was used to observe the crystal structure. Data collected included measurements of particle length and width. Particle size distribution was obtained by analysing data from 100 crystal particles in each sample. Sample observations were conducted via a computer-connected camera mounted on the microscope's eyepiece, and particle diameter measurements were performed using an integrated micrometre (5).

b. X-Ray Diffraction (XRD)

A 100-200 mg sample of mefenamic acid crystals from conventional and ultrasonically assisted recrystallisation methods was placed in a glass sample holder and levelled to avoid particle orientation

during sample preparation. Analysis was performed over a diffraction angle (theta) range of 5-45° using Cu radiation, a Kα filter, a voltage of 40 kV, and a current of 40 mA (4,12).

c. Fourier Transform Infrared Spectroscopy (FTIR) Analysis

FTIR analysis was performed on both the raw material and the recrystallised samples. Samples were compressed into KBr pellets and measured over a wavenumber range of 4000 to 400 cm^{-1} (5,11).

Data Analysis

The dried crystals were observed under a polarizing microscope to determine their morphology and dimensions. ImageJ software was used to analyze particle size. A polarising microscope with a magnification of 400x was employed to observe the crystals. The data obtained included the length and width of the particles. Particle size distribution was determined by collecting data from 100 crystal particles per sample. The data were then generalised for the entire sample based on skewness and kurtosis as statistical indicators (5).

RESULTS AND DISCUSSION

The yield of mefenamic acid crystals obtained through conventional and ultrasound-assisted recrystallisation methods is presented in **Table 1.**

Table 1. Yield of Mefenamic Acid Crystals using Conventional and Ultrasound-Assisted Recrystallisation Methods

No	Method	Yield (%)
1.	Conventional	25.08±0.12
2.	Ultrasonic 50 W	43.47±0.10
3.	Ultrasonic 60 W	47.71±0.09
4.	Ultrasonic 70 W	51.90±0.69
5.	Ultrasonic 80 W	50.20±0.35

These results indicate that crystals produced using ultrasonic treatment at 70 W power yielded the highest recovery, while those obtained through conventional methods resulted in the lowest yield. This outcome is attributed to the significant influence of temperature and stirring speed on the crystallisation process (13). A decrease in temperature acts as a trigger to accelerate crystal formation, while an increase in stirring speed contributes to the growth rate of crystals. Combining these two factors produces a relatively uniform distribution of crystals (5,13). The higher yield at 70 W ultrasonic power compared to 80 W is due to the energy at 70 W being more optimal for crystal formation without causing fragmentation or disruption. At 80 W, excessive energy can lead to turbulence, increased solution temperature, and uneven particle size distribution, ultimately reducing the yield (7). The 70 W setting provides stable and controlled conditions for crystallisation, resulting in maximum yield (14,15). Therefore, 70 W power was used to represent ultrasonic recrystallization to be compared with the conventional recrystallisation method.

The morphology and size of mefenamic acid crystals recrystallised using ethyl acetate solvent were observed using a polarising microscope at 400x magnification, as shown in **Figure 1**. The observations revealed that crystals formed via conventional recrystallisation had a needle-like shape, whereas those obtained through ultrasonic-assisted recrystallisation displayed a more symmetrical form. This result is supported by studies indicating that ultrasonic-assisted recrystallisation produces smaller crystals with a more uniform size distribution due to cavitation effects and shock waves generated by ultrasound, which break down larger particles into smaller ones, thereby enabling better thermal stability and superior physical properties (5,16,17). Thus, the crystal shape and size differences between conventional and ultrasonic methods are evident. Additionally, the particle size and shape of the resulting crystals can be controlled through the ultrasonic power level. Ultrasonic treatment can also

produce crystals that are shorter and thicker in structure, enhancing their handling and formulation potential.

(a) (b)

Figure 1. Morphology of mefenamic acid crystals observed under a microscope at 400x magnification: (a) conventional recrystallisation (b) ultrasound-assisted recrystallisation

The morphological differences between crystals produced with and without ultrasonic assistance reveal that the ultrasound-assisted process produces smaller crystals compared to those generated through conventional methods. It occurs because the sonication time and ultrasonic wave frequency can affect the shape and size of the crystals (18). The more cavitation bubbles that are formed, and the more they collapse, the greater the reduction in solid surface area, accompanied by the generation of shock waves. The dissolved molecules collide with one another, and the resulting crystal shape depends on the growth rate at each crystal surface. Collisions between these particles lead to significant changes in surface morphology, composition, and crystal reactivity (7,8). Therefore, throughout the recrystallisation process, mefenamic acid crystals subjected to ultrasonic treatment experience continuous inter-particle collisions, reducing crystal size (19).

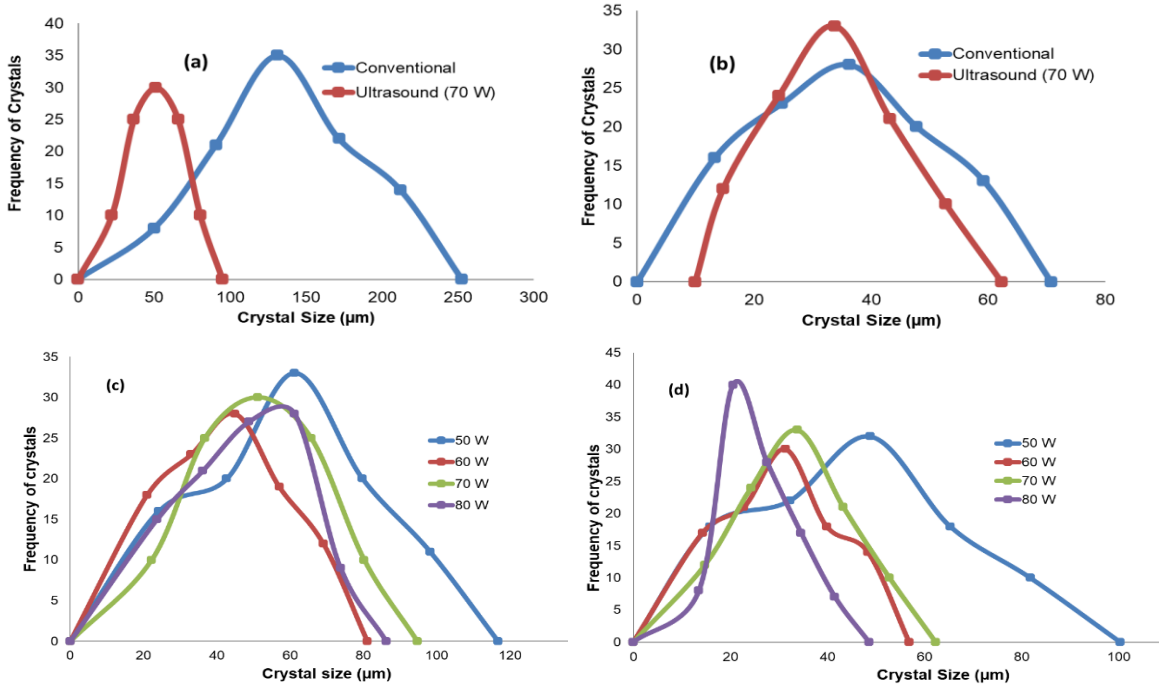

Figure 2. Crystal size distribution of conventional and ultrasonic recrystallisation (a) crystal length (b) crystal width. Particle size distribution of ultrasonic recrystallisation (c) crystal length (d) crystal width

The analysis of the crystal size distribution of mefenamic acid based on length and width observed under a microscope, aims to understand the physical characteristics and crystal morphology, as well as to evaluate the effect of the method or process conditions (such as ultrasonic application or power variation) on the size and shape of the crystals produced conventionally or through modified methods like the use of ultrasonics (20). **Figure 2** (a) and (b) show the crystal particle size distribution based on length and width. Ultrasonic recrystallisation at a power of 70 W was used as a reference for comparing with conventional recrystallisation results. Meanwhile, **Figure 2** (c) and (d) show the differences in crystal particle size distribution based on length and width at varying ultrasonic power levels ranging from 50 W to 80 W.

Skewness and kurtosis values were analysed to determine whether the data were normally distributed. Skewness quantifies the asymmetry of the distribution, whereas kurtosis indicates the sharpness or flatness of the data peak (5,20). A negative skewness-kurtosis value indicates a left-skewed distribution, whereas a positive value indicates a distribution with a high peak (20).

Table 2. Crystal Size Analysis of Mefenamic Acid via Conventional and Ultrasound-Assisted Recrystallisation Based on Microscopic Observation

Method	Length		Width	
	Skewness	Kurtosis	Skewness	Kurtosis
Conventional	0.633	0.323	0.297	-0.412
Ultrasonic 50 W	1.182	1.000	0.641	0.697
Ultrasonic 60 W	0.038	0.111	1.490	1.064
Ultrasonic 70 W	-0.418	-1.449	0.418	-0.496
Ultrasonic 80 W	-0.523	-0.780	0.756	-0.545

The crystal size analysis results (**Table 2**) showed that data with skewness and kurtosis values close to zero, or within the range of -2 to +2 are normally distributed. Therefore, the crystal size distribution of mefenamic acid, both from conventional recrystallisation and ultrasound-assisted recrystallisation, is regarded as normal (12). These findings strengthen the validity of the data and indicate that the recrystallisation process produced a consistent and orderly particle size distribution.

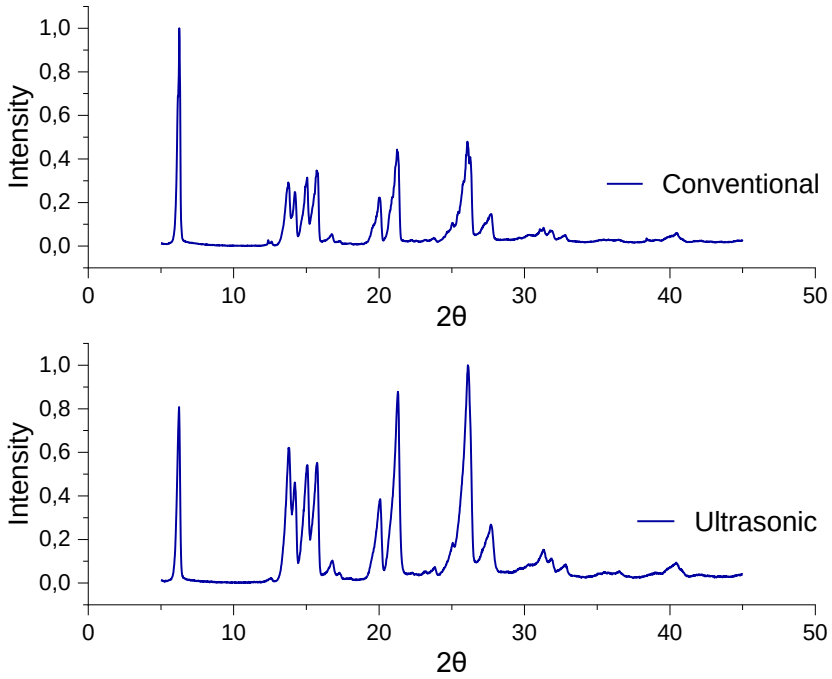

Figure 3. XRD analysis results of mefenamic acid crystals via conventional and ultrasound-assisted recrystallisation

XRD is a technique used to determine the crystal system, crystal quality, and symmetry, identify crystal defects, andobtain crystal parameters for mixture identification and chemical analysis (21). **Figure 3** presents the XRD analysis results in the form of a diffractogram. Based on the diffractogram observations, the 2θ peak angles from conventional recrystallisation ranged from 6.298° to 31.889°, while those from ultrasound-assisted recrystallisation ranged from 6.265° to 31.313°.

The mefenamic acid crystals obtained from conventional recrystallisation showed less uniform crystal shapes and tended to be larger with rougher surfaces. The diffraction pattern displayed broadened peaks due to the larger crystal size and imperfections in the crystal structure. In contrast, the ultrasound-assisted recrystallisation produced crystals that were more uniform in shape and had smoother surfaces due to the intensive ultrasonic process. The diffraction pattern tended to exhibit sharper peaks and higher intensities, indicating that the formed crystals were smaller and had a more ordered crystal structure. These findings are supported by studies conducted by Mudalip *et al*. (2019) and Xiang *et al*. (2024), which confirmed that ultrasound resulted in smaller crystal sizes, more uniform distribution, and smoother morphology. Additionally, the XRD patterns showed sharper peaks and higher intensities, indicating a more ordered crystal structure and better purity (14,22).

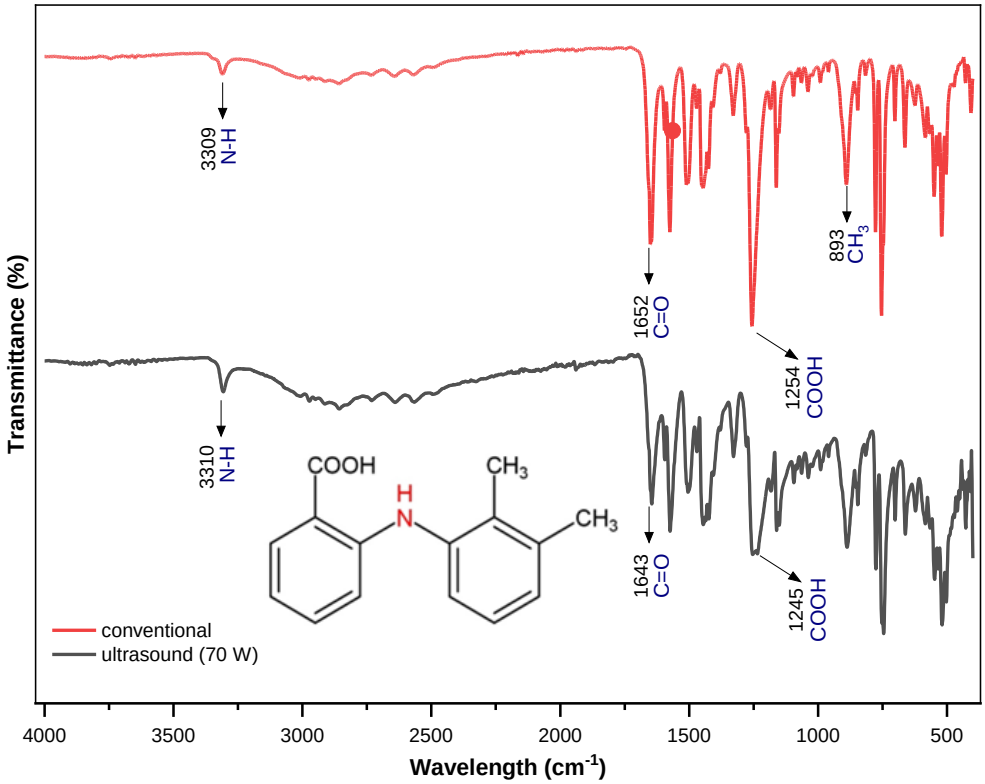

Figure 4. FTIR analysis results of mefenamic acid crystals via conventional and ultrasound-assisted recrystallisation

The analysis of the FTIR spectrum patterns (**Figure 4**) showed the presence of specific functional groups. The mefenamic acid crystals obtained from both conventional and ultrasound-assisted recrystallisation exhibited slight shifts in the wavenumbers of the NH, C=O, and COOH groups (23,24). Shifts in the FTIR spectrum may reflect changes in the crystal structure of mefenamic acid (25). The use of ultrasound can lead to a more ordered or altered crystal structure than the conventional method.

The FTIR analysis results (**Table 3**) also indicate no changes in the structure of mefenamic acid. It was proven by the similarity in peak positions, intensities, and FTIR spectral shapes between the two samples. This similarity suggests that the mefenamic acid molecules' functional groups and chemical bonds remained stable and were not modified during the recrystallisation process (25). Therefore, it can be concluded that the conventional or ultrasound-assisted recrystallization did not alter the chemical structure of mefenamic acid.

Table 3. FTIR Analysis of Mefenamic Acid Crystals via Conventional and Ultrasound-Assisted Recrystallisation

Functional Group	Wavenumber (cm^{-1})	
	Conventional	Ultrasonic
N-H	3309	3310
C=O	1652	1643
N-H Stretching	1574	1567
Benzene Ring Stretching	1504	1496
COOH	1254	1245
CH_3	893	890

CONCLUSION

Ultrasound-assisted recrystallisation produced mefenamic acid crystals with the highest yield, more symmetrical shape, smaller particle size, and a more uniform size distribution compared to the conventional method. XRD and FTIR analyses confirmed that the crystals obtained through ultrasound-assisted recrystallisation possessed a more ordered structure and higher purity without altering the basic chemical structure of mefenamic acid. The ultrasound-assisted recrystallisation method has proven superior in producing mefenamic acid crystals with improved physical characteristics, potentially enhancing the quality and effectiveness of pharmaceutical formulations, making it a promising option for future pharmaceutical applications.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to the Direktorat Riset, Teknologi, dan Pengabdian kepada Masyarakat (DRTPM) of the Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia for funding the research grant through the Beginner Lecturer Scheme in 2021. This financial support has facilitated the optimal implementation of the research, contributing to the advancement of scientific knowledge, particularly in the pharmacy field. The authors also hope that the results of this study will be beneficial for the development of science and the broader community. Special thanks are also extended to the Faculty of Pharmacy, Universitas Muhammadiyah A.R. Fachruddin, for their support, facilities, and contributions throughout the research process.

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