Effect of ultrasonic waves on polymorphism and crystal size distributions of mefenamic acid

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Abstract. Crystallization of pharmaceutical compound that have different polymorphic forms and broad crystal size distributions remain major challenge in industry. In this present work, the potential of ultrasonic intensifications on crystallization of mefenamic acid polymorph is investigated. The effect of sonication times (5 min – 30 min) and ultrasonic powers (153.3 – 766.7 Watt) at frequency of 65 kHz on polymorphic form and crystals size distributions (CSDs) of mefenamic acid crystals during cooling crystallization were investigated using One-Factor-At-a-Time method (OFAT). The polymorphic form, CSD and shape were determined using Fourier transform infrared spectroscopy (FTIR), Malvern Mastersizer, optical microscope and X-ray diffractometry, respectively. It was found that ultrasonic power of 766.7 Watt and 30 min of sonication time produce plate-shaped crystals with the narrow CSD. The polymorph was consistent with Form I. The findings justify the suitability of ultrasonic waves to produced plate-like mefenamic acid Form I crystals with narrow CSD.

1. Introduction

Crystallization is a widely used separation and purification process to obtain solid crystalline form in pharmaceutical industries [1-3]. It was reported approximately 80% of the active pharmaceutical ingredients (APIs) are produced using crystallization process [4]. Crystallization can be considered as the first step in the formulation stage; and therefore, it must be controlled to attain desired product properties such as a consistent polymorphic form, shape and size [5, 6]. Moreover, about 85 % of active pharmaceutical ingredients (APIs) exhibit polymorphism and 50 % of it have more than one polymorphic forms [7]. Failure to produce crystals with desired properties would eventually affect the downstream processes such as filtration and drying, products therapeutic performances, as well as shelf-life [2].

2-(2,3-dimethylphenyl)aminobenzoic known as mefenamic acid is one of the commercial APIs produced using crystallization process. This API is commercially used to treat mild to moderate pain, including menstrual pain and prevent migraines associated with menstruation [8]. Mefenamic acid was reported to have three polymorphic forms namely Forms I, II and III [9, 10]. Form I was reported to be more thermodynamically stable as compared to Forms II and III thus, make it more desirable in the pharmaceutical industries. In addition to the polymorphism, the solid crystalline powder of this API and can be found in different size and shape such as plate or needle-like depending on the crystallization

parameters. Several researchers studied the crystallization of mefenamic acid using different solvents and in batch cooling crystallization conditions. Their findings showed that crystals of mefenamic acid with different polymorphs and in various sizes were produced [11-13]. Large size crystals, however, is not preferable in industry since it can creates problems during the formulation stage due to low bioavailability and followability characteristics. Techniques such as antisolvent, seeded crystallization or combined cooling and antisolvent crystallization have been studied to control the crystal size distribution of APIs such as fesoterodine fumarate and L-asparagine monohydrate [14, 15]. To the best of our knowledge, the study to produce small and uniform crystal size distribution (CSD) of mefenamic acid crystals, specifically is still less.

Ultrasonic waves has demonstrated profound effect in various fields including separation processes such as extraction, distillation and crystallization [16-20]. In contrast to other separation fields, the application or the study on ultrasonic waves in crystallization process or known as sonocrytallization is relatively new. Sonocrystallization is believed to influence the mass transfer rate of solutes from the solution (nucleation and growth) through cavitation effects. This is because the cavitation effects indirectly improve the degree of mixing that control the onset of nucleation and crystal size distributions [18]. The sonocrystallization of various fine chemicals including APIs such as mefenamic acid have been reported, recently [19, 21]. Works performed by Kumar et al. [21] and Iyer and Gorgate [19] examined the influence of ultrasonic waves on crystal size distributions of mefenamic acid produced using melt crystallization and solution crystallization, respectively. The works, however, utilized different ultrasonic frequencies and solution concentrations.

In this work, the effect of sonocrystallization parameters (ultrasonic power and sonication time) at frequency of 65 kHz on crystal properties namely polymorphic form, shape and CSD of mefenamic acid with ethanol as solvent during crystallization process were investigated. Indirect irradiation of ultrasonic waves was introduced to the crystallization vessel using an ultrasonic bath. A classical approach, namely using One-Factor-At-A-Time (OFAT) was used to determine the best range of the selected process parameters during the batch crystallization process. Through this technique, one level of the factor to be investigated was changed over the desired range and at the same time keeping the level of other factors constant. The mefenamic acid crystals obtained were further analyzed using Fourier transform infrared spectroscopy (FTIR), Malvern Mastersizers, and an optical microscopy. Powder X-ray diffractometer (PXRD) analysis was used to confirm the polymorphic form of the crystals produced.

2. Materials and method

2.1. Materials

Mefenamic acid powder (98 wt% purity) and analytical grade ethanol (99.9 wt% purity) were purchased from Baoji Tianxin Pharmaceutical Co. Ltd., China and Sigma-Aldrich Sdn. Bhd., Malaysia, respectively. The materials were used without further purification.

2.2. Experimental Method

Saturated solution of mefenamic acid in ethanol at 25°C was prepared by dissolving 9.4 g of mefenamic acid in a conical flask containing 100 ml of ethanol [22]. The solution was heated to 55°C above the saturation temperature and continuously stirred at 300 rpm on Cimarec hot plate stirrer until complete dissolution. Then, the solution was immersed in an ultrasonic bath supplied by Crest Ultrasonic (M) Sdn Bhd and allowed to cool to room temperature. The temperature and ultrasonic power of the bath were set at 25°C and 153.3 W, respectively. The sonication time was set for 30 min. The crystallization process was stopped 30 min after the nucleation commences. The obtained crystals were filtered and dried in the oven at 50°C until a constant weight was achieved. The dried crystals were stored in glass vials until further analysis. The same procedures were repeated using experimental conditions tabulated in Table 1.

Table 1. Summary of process parameters for OFAT experiments.

Parameters	Experimental Conditions	Fixed Parameters
Ultrasonic power (W)	0, 153.3, 306.7, 460.0, 613.3, 766.7	Sonication time 30 min
Sonication time (min)	5 – 30	Ultrasonic power 766.7 W

2.3. Characterization methods

The Infrared spectra of mefenamic acid crystals in a range of 500 to 4000 cm^{-1} was recorded using Thermo Fisher Scientific Nicolet iS5 Spectrometer, operated with Omnic software (version 4.1a). The average scan used was 16. The CSD of the samples were measured using a Malvern Scirocco Mastersizer 2000 with laser light scattering technology. This instrument was reported to produce accurate results for a large range of particle size, which is from 0.02 to 2000 μm [23]. The images of the crystals were captured using Leica microscope DM750 with a total magnification of 40×/0.65 NA, 0.31 mm W.D and analyzed using Leica Application Suite Software version 3.6. A Shimadzu XRD 6000 instrument equipped with vertical X-ray goniometer and Cu Kα radiation was used to determine the powder x-ray diffraction (PXRD) pattern or structure of crystals. The angle reproducibility of the instrument is ±0.001º (2θ). The crystals were softly ground using spatula before placed on the aluminium sample holder. The measurements were performed in a continuous mode with 40 kV of voltage; 30 mA of current; 5-50º (2θ) of scan range; 0.05º of step size and 3º/min of scan mode.

3. **Results and discussion**

3.1. Effect of different ultrasonic powers

The effect of ultrasonic power at frequency of 40 kHz on mefenamic acid crystals were established at 0, 153.3, 306.7, 460.0, 613.3 and 766.7 W. Figure 1 shows the FTIR transmittance spectra of mefenamic acid crystals at different ultrasonic powers. Romero et al. [24, 25] reported that the N-H stretching band occurs between 3300 and 3350 cm^{-1}, is an important spectral point that can be used to distinguish between different polymorphic form of mefenamic acid. The N-H stretching band for mefenamic acid Form I and II occurs between 3311 to 3313 and 3346 to 3350 cm^{-1}, respectively. The different of the N-H stretching at these wavelengths is due to the formation of internal hydrogen bonding between the amino group and the carboxylic group with different strength. The higher wavelength values for the N-H stretching of mefenamic acid Form II suggests a weaker hydrogen bonding interaction between amino group and the carboxylic group of mefenamic acid Form I [26]. As seen in Fig.ure1, the FTIR spectra show N-H stretching band at 3313 cm^{-1} and were consistent with those of mefenamic acid Form I reported by literature [24, 25].

The CSD profiles of mefenamic acid crystal obtained at different ultrasonic power is shown in Figure 2. It can be seen that the crystallization without the presence of ultrasonic waves (0 W) shows broad CSD. A wide CSD, however, is not preferred in industry due to difficulty during separation process [6]. Meanwhile, the measured CSD are narrower as the ultrasonic power become higher. The narrowest CSD was obtained with sonocrytsallization at ultrasonic power of 766.7 W. This findings is probably due to the cavitation phenomena that occurs during transmission of ultrasonic waves in liquid medium. During cavitation phenomena tiny bubbles were created and explodes causing formation of a strong shockwaves and microjets that caused intense mixing and crystals breakage. The crystals act as seeds for nucleation and makes the nucleation process more dominant. The explosion of cavitation bubbles also increase the collision rate and disrupt the aggregation among the crystals. The application of higher ultrasonic power may cause more formation and explosions of cavitation bubbles, thus leads to production of larger number of smaller crystals [27].

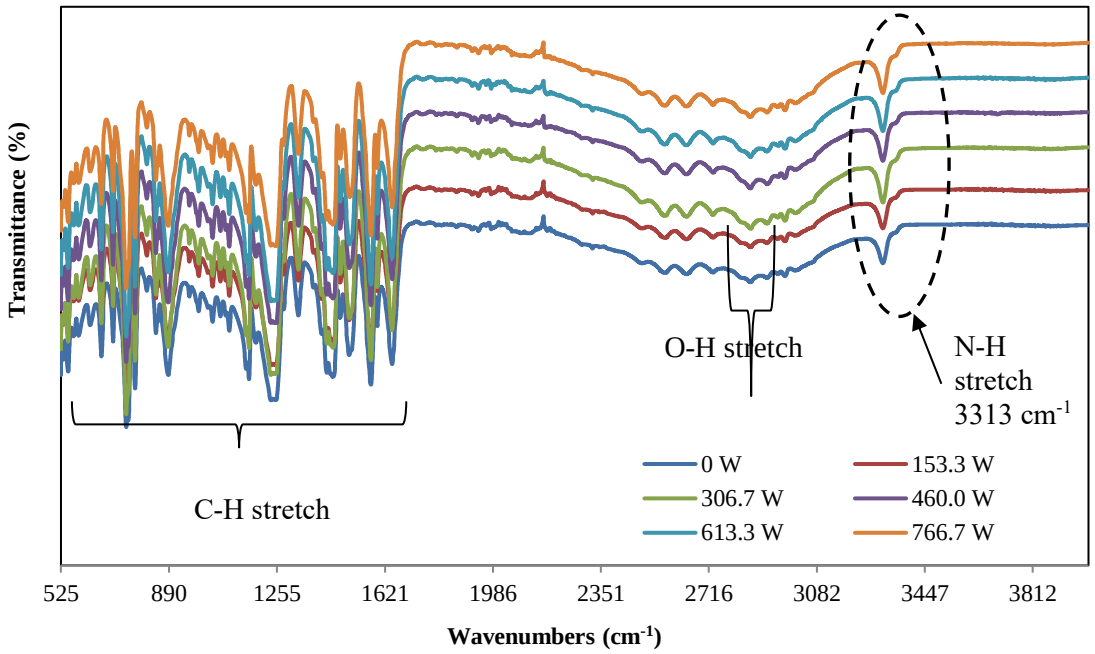

Figure 1. Infrared spectra of mefenamic acid crystals at different ultrasonic powers.

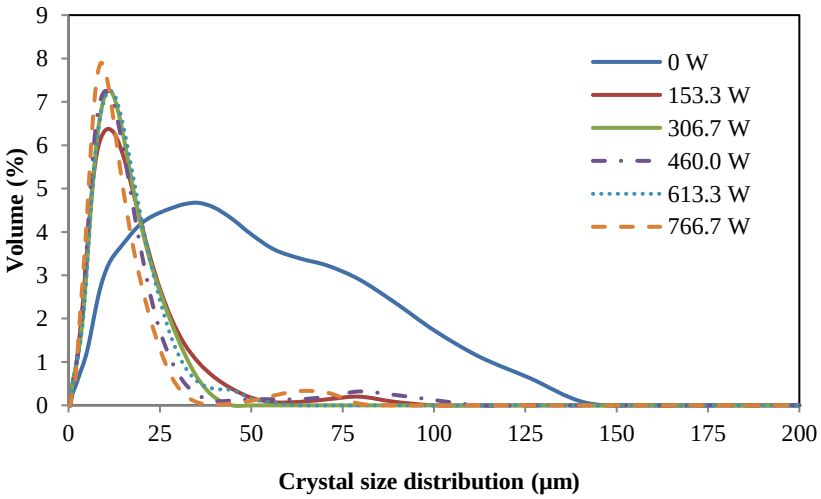

Figure 2. Crystal size distribution at different ultrasonic powers.

Figure 3 illustrates the microscopic images of mefenamic acid crystals obtained at different ultrasonic powers. It is clearly shown that the crystals produced without the presence of ultrasonic wave is long and needle-like. Lee et al. [28] reported that needle-like shape of mefenamic acid crystals is due to the formation of hydrogen between carboxylic group at crystals facet (0 0 1) with solvent molecules. The changes of crystal shape to a plate-like crystal was observed after sonocrystallization with different ultrasonic powers. The length of crystals obtained from sonocrystallization process is smaller than crystallization without ultrasonic waves. This phenomenon is probably due to the collisions of crystals that inhibit the growth at (0 0 1) facet, and thus caused a formation of smaller plate-like crystals.

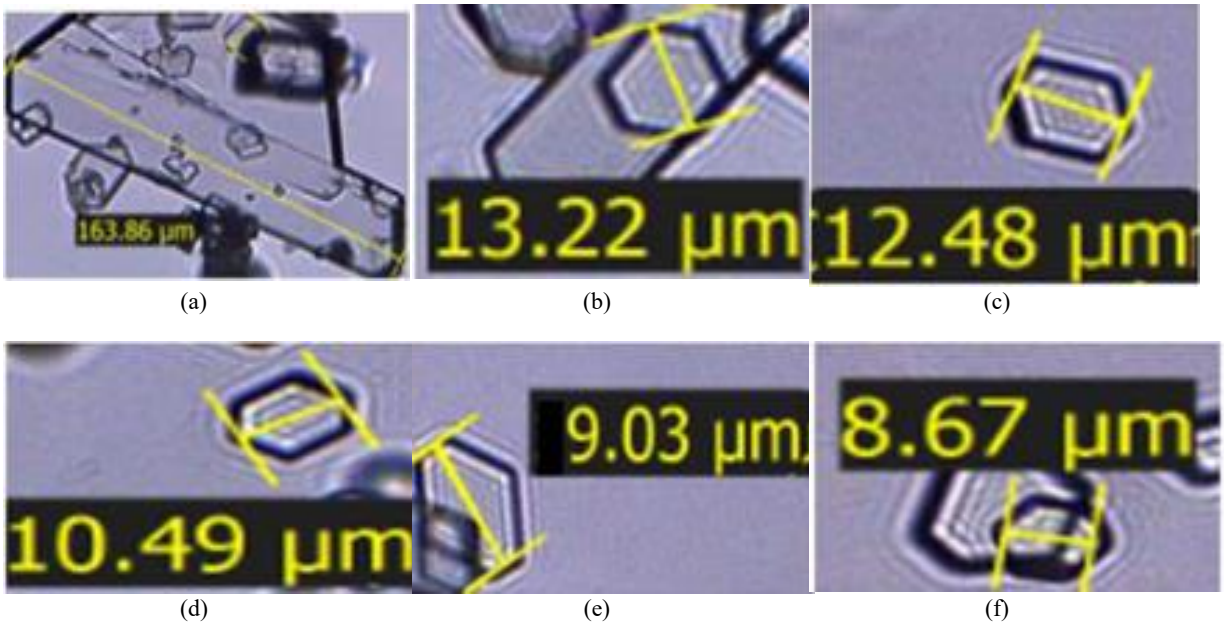

Figure 3. Microscopic image of MA crystals obtained at different ultrasonic powers: (a) 0 W; (b) 153.3 W; (c) 306.7 W; (d) 460.0 W; (e) 613.3W; and (f) 766.7W.

3.2. Effect of different sonication time

Figure 4 shows the FTIR transmittance profiles of mefenamic acid for crystallized samples obtained at different sonication time between 5 to 30 min. As can be seen in this figure, the FTIR spectra were consistent with those for mefenamic acid Form I of since the N-H stretching band occurs at 3313 cm^{-1}. The effect of sonication times on the CSD profiles of mefenamic acid crystal is shown in Figure 5. It is observed that sonication time of 30 min produced smallest and narrowest CSD as compared to 5, 10, 15 and 20 min. This is because the increase of sonication time provide more time for the crystals to collide during crystallization process, thus producing smaller and narrower crystals size distributions. The increase of sonication time, however, do not alter the shape of mefenamic acid crystals. As seen in Figure 6 plate-like shaped crystals of mefenamic acid were produced.

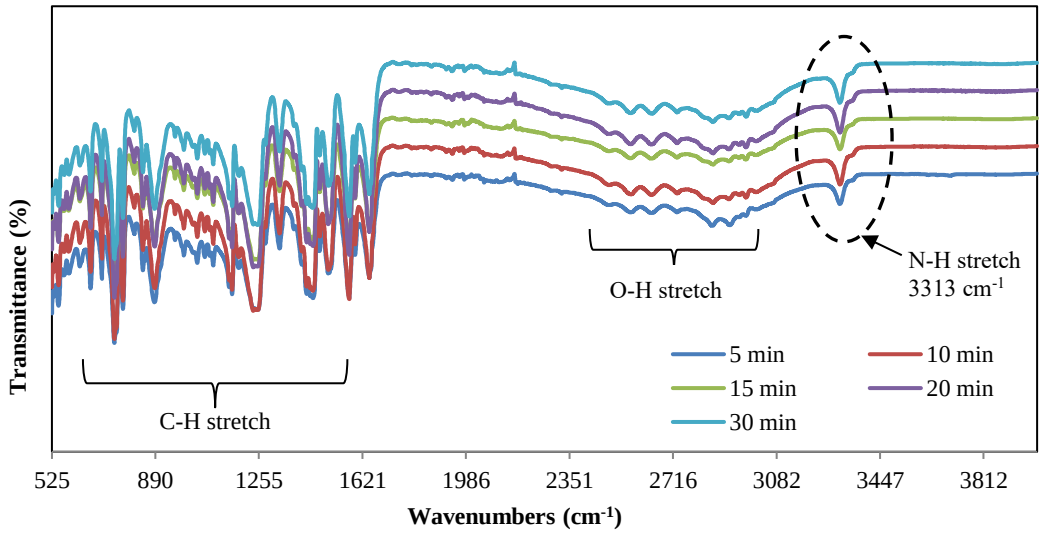

Figure 4. Infrared spectra of mefenamic acid crystals at different sonication times.

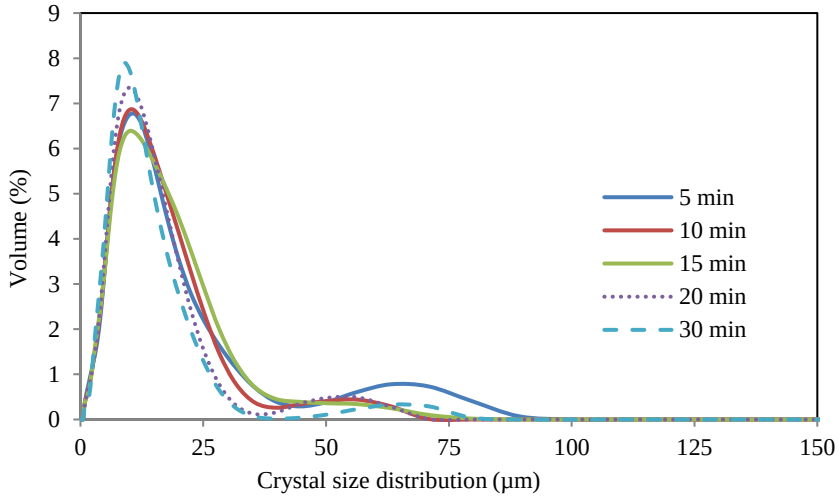

Figure 5. Crystal size distribution at different sonication times.

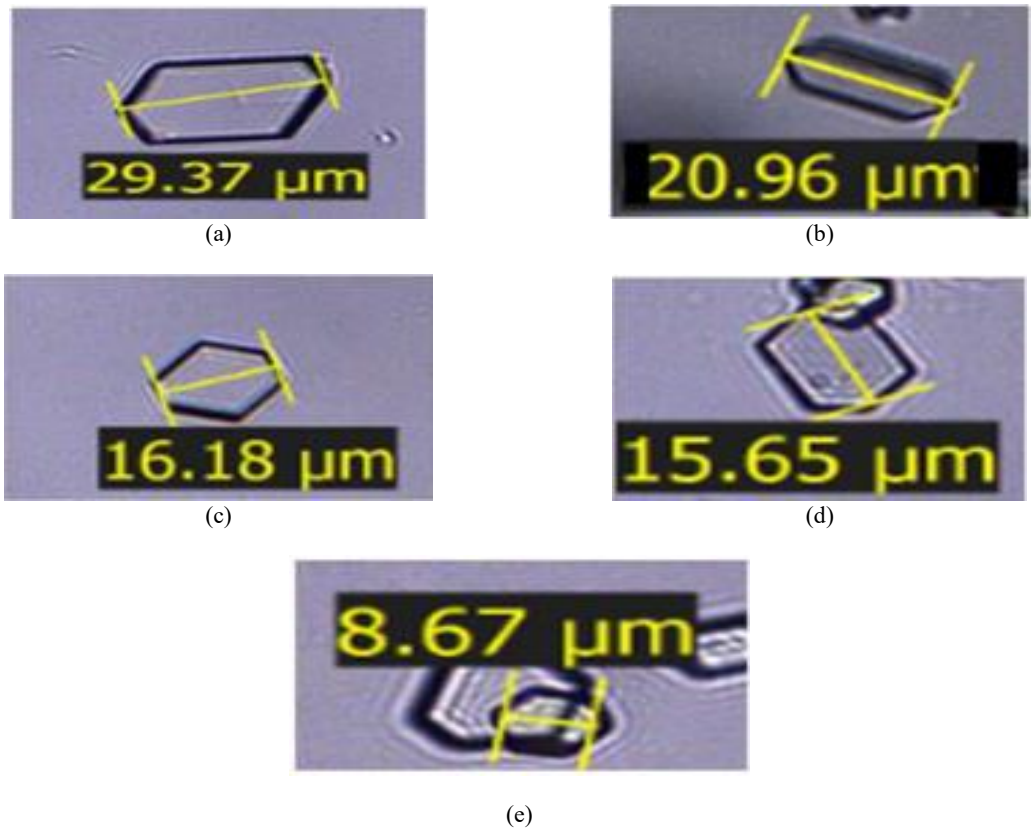

Figure 6. Microscopic image of MA crystals obtained at different sonication time (a) 5 min; (b) 10 min; (c) 15 min; (d) 20 min; and (e) 30 min.

3.3. Powder X-ray diffractometer analysis

Powder X-ray diffractometer (PXRD) was used to observe the crystal characteristics obtained at ultrasonic power of 766.7 W and 30 min of sonication time as it's given the smallest CSD. As shown in Figure 7, the high intensity of PXRD pattern was observed in mefenamic acid crystals, which demonstrates better crystallinity and purity. The purity of mefenamic acid crystal obtained was

maintained as it showed the similar PXRD pattern in comparison to the commercial sample reported in our previous work [18]. The PXRD pattern also match with the major reflection of mefenamic acid Form I at 6.3º, 21.3º, and 26.3º (2θ) as stated in the literature [25].

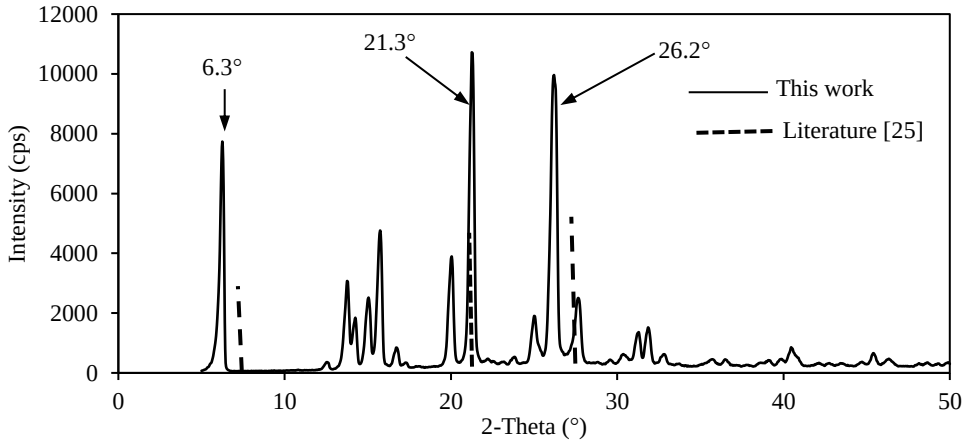

Figure 7. PXRD pattern of mefenamic acid crystals in comparison with major reflection obtained from literature [25].

4. Conclusion

The sonocrystallization of mefenamic acid in ethanol was successfully performed at different ultrasonic powers and times. The plate-like shaped crystals with narrower CSD are obtained through out process. The sonocrystallization process, however, did not alter the polymorphic form of the crystals obtained, where mefenamic acid Form I were consistently produced.

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