Effect of Cooling Rates on Shape and Crystal Size Distributions of Mefenamic Acid Polymorph in Ethyl Acetate

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Effect of Cooling Rates on Shape and Crystal Size Distributions of Mefenamic Acid Polymorph in Ethyl Acetate

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Abstract. This study investigate the effect of cooling rates on mefenamic acid crystallisation in ethyl acetate. The cooling rate was varied from 0.2 to 5 °C/min. The in-line conductivity system and turbidity system were employed to detect the onset of the crystallization process. The crystals produced were analysed using optical microscopy and Fourier transform infrared spectroscopy (FTIR). It was found that the crystals produced at different cooling rates were needle-like and exhibit polymorphic form type I. However, the aspect ratio and crystal size distributions were varied with the increased of cooling rate. A high crystals aspect ratio and narrower CSD (100−900 μm) was obtained at cooling rate of 0.5 °C/min. Thus, can be suggested as the most suitable cooling rate for crystallization of mefenamic acid in ethyl acetate.

1. Introduction

Crystallization is a process that typically used to obtain solid material in purified form. It was reported that about 80% of the active pharmaceutical ingredients (APIs) are produced using at least one crystallization step [1]. The main challenge in the crystallization process is to produce crystals with desired properties such as a polymorphic form, morphology and crystal size distribution [2]. Polymorphs of a API can show different physicochemical properties particularly the melting point, density, morphology, stability, bioavailability, and processability during the manufacturing process [3]. The shape of crystals and the CSD determine the quality of the final product and affect the downstream operations such as filtration and drying. For a needle-like shape crystals, the aspect ratio should be equal or greater than one to avoid any disappearance in the solution [4]. This is because crystals with high aspect ratio are susceptible to breakage during the filtration process [5]. Various process variables were reported to show the significant effect on the crystal properties during the cooling crystallization process. In order to get a desired crystal shape and CSD with good reproducibility in every batch, the operating conditions that affect these properties during the crystallization process must be controlled.

Mefenamic acid [2-(2, 3-dimethylphenyl)amino benzoic acid] is a non-steroidal anti-inflammatory and analgesic agent that widely used for management of pain during menstrual period. This API is reported as one of the active pharmaceutical ingredients (APIs) that exhibit polymorphisms and can

either exist in Form I, Form II or Form III [6-8]. The mefenamic acid Form I, Form II and Form III are enantiotropic related, where Form I is relatively more stable than Form II and Form III at ambient condition [9]. In this work, the effect of cooling rates during batch crystallization process on the crystal shape factor namely aspect ratio and CSD mefenamic acid were investigated. In-line analysers; conductivity and turbidity probes, were used during crystallization process. Comprehensive characterization of crystals produced were performed using infrared spectroscopy (FTIR) and optical microscopy.

2. Methodology

2.1. Chemicals and Materials

The mefenamic acid powder (98 wt% purity) was obtained from Baoji Tianxin Pharmaceutical Co. Ltd., China. The ethyl acetate (99.5 wt% purity) was obtained from Permula Chemical (M) Sdn. Bhd., Pahang, Malaysia. The mefenamic acid and ethyl acetate were used without further purification.

2.2. Methodology

The crystallization experiments were performed in a 500 mL crystallization vessel. A saturation concentration was prepared in the crystallization vessel by dissolving about 1.81 g of mefenamic acid in 100 g of ethyl acetate. The solution was heated at 10 ºC above the saturation temperature for 30 min. After complete dissolution of the solute is achieved, the solution was cooled to the final cooling temperature between 10 ℃ to 30 ℃ using a cooling rate of 0.5 ℃/min. The crystallization process was stopped 30 min after the nucleation commences. A conductivity and turbidity system were employed for in-line detection of polymorph nucleation event during the solution crystallization process. The onset of the nucleation events is indicated either by the sudden decrease of the conductivity values or the sudden increase in the turbidity values. The obtained crystals were filtered and dried in the oven at 50 ºC until constant dried weight was achieved. The dried crystals were stored in glass vials until further analysis. The same procedures were repeated using cooling rate of 0.2, 1.0, 2.5, and 5.0 °C/min.

2.3. Characterizations

The images of the crystals were captured using Leica microscope DM750 with a total magnification of 200x4x/0.10 and processed using Leica Application Suite Software version 3.6. For determination of the length and width of the crystals, image analysis toolbox available in MATLAB was used. Random measurement of 100 crystals were performed to determine the aspect ratio and crystal size distribution (CSD) (Liu et al., 2013). The FTIR spectra of crystals produced were acquired using a Perkin Elmer's ATR-FTIR Spectrometer (Frontier) with a wavenumber range of 500 to 4000 cm^{-1}. The analysis was performed using OMNIC software with an average of 16 scans [6].

3. Results & Discussion

Figure 1 (a) illustrates the partial FTIR spectrum of mefenamic acid crystals that crystallized using ethyl acetate at different cooling rates. As seen, the spectrum shows the presence of O-H and N-H bonds at wavelength of 2986 and near 3313 cm^{-1} and consistent with the IR adsorption spectra of mefenamic acid Form I reported by previous work [6]. The N-H stretching band occurs between 3300 and 3350 cm^{-1}, is an important spectral point that can be used to distinguish between Form I and Form II of mefenamic acid. Specifically, the N-H stretching frequency, which occurs at 3311 to 3313 and 3346 to 3350 cm^{-1}, show the presence of Form I and Form II, respectively. The N-H stretching at these wavelengths is observed due to the formation of internal hydrogen bonding between the amino group and the carbonyl group.

Figure 1 (b) and Figure 2 illustrate the change of crystals aspect ratio and CSD, respectively with different linear cooling rates for solution concentration of 1.81 g/ 100 g ethyl acetate and crystallization time of 30 min. It can be observed that the highest cooling rates, which is 5 ºC/min produced crystals with the lowest aspect ratio (11.90) and widest spread of CSD (0−1200 μm). Meanwhile, the higher aspect ratio (13.58) and narrower CSD (100−900 μm) are produced at a cooling

rate of 0.2 ºC/min. The differences in aspect ratio and CSD are probably due to variation of nucleation event at different cooling rates. The nucleation process is typically dominant at higher cooling rate due to fast supersaturation generation, thus produce crystals with wider CSD [4, 10]. Although the aspect ratio illustrated in Figure 1 (b) is decreasing with the increase of cooling rate, a broad CSD illustrated in Figure 2 will cause a problem during the filtration process. Hence, not suitable for the crystallization process[11, 12].

Liu and co-workers reported that the cooling rate cannot be too high, to avoid uncontrolled nucleation and changes in the crystals shape [4]. Therefore, a slow cooling rate, which is either 0.2 ºC/min or 0.5 ºC/min seems to be more suitable for the crystallization process. As seen in Figure 1 (b), Figure 2 (a) and Figure 2 (b), the aspect ratio and CSD do not vary too much with the change of cooling rate from 0.2 ºC/min to 0.5 ºC/min. A cooling rate of 0.2 ºC/min, however, is too slow, leading to a long batch time. From the industrial point of view, a long batch time is not preferable due to high operational cost [13]. Hence, 0.5 ºC/min was selected as the best cooling rate for crystallization of mefenamic acid in ethyl acetate. Igarashi and co-workers reported that the change of cooling rate also effects the final polymorphic form and shape of the glycine crystals [14]. However, for mefenamic acid system, the crystals shape remained needle-like as illustrated in Figure 2

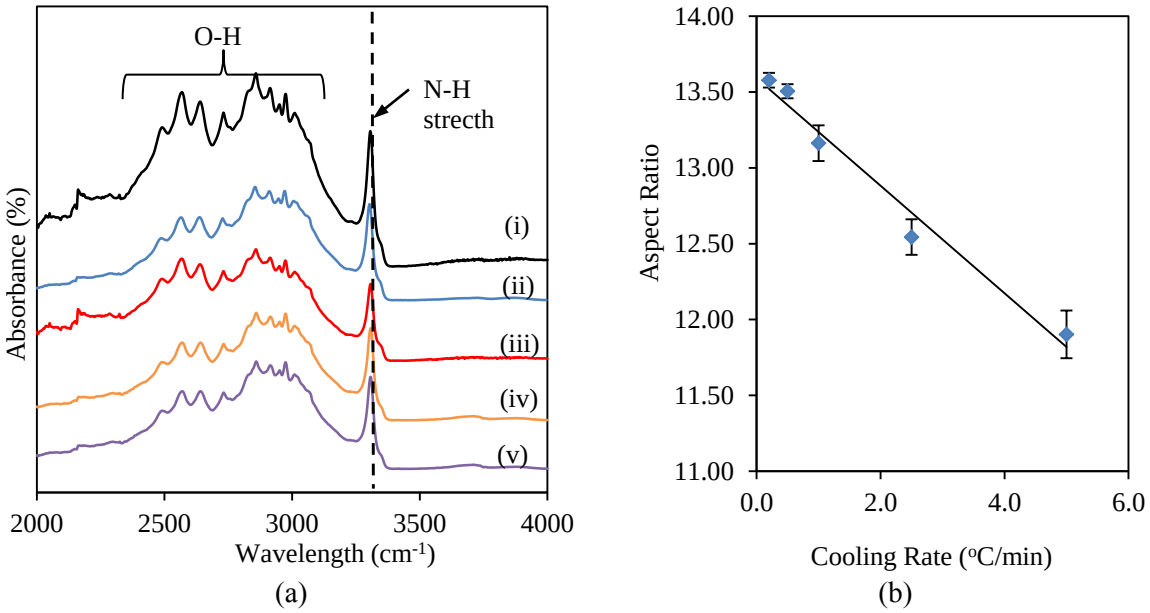

Figure 1. (a) Partial FTIR spectrum of mefenamic caid crystals obtained at cooling rate of a) 0.2 ℃/min; (b) 0.5 ℃/min; (c) 1.0 ℃/min; (d) 2.5 ℃/min; and (e) 5.0 ℃/min; and (b) Effects of cooling rate on crystals aspect ratio. The solution concentration and crystallization time were fixed at 1.81 g mefenamic acid/ 100 g ethyl acetate and 30 min, respectively.

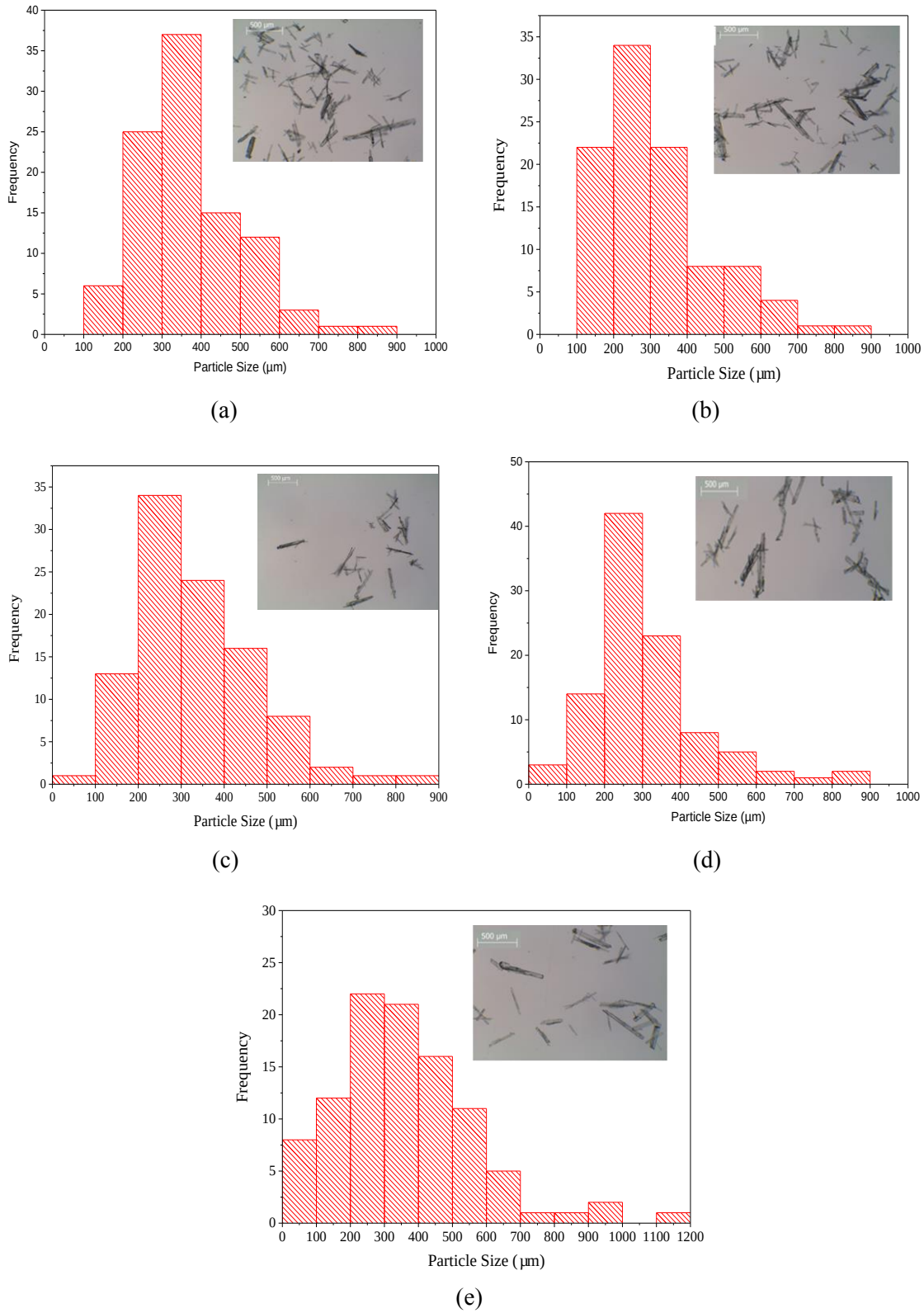

Figure 2. A CSD for different cooling rates: (a) 0.2 ℃/min; (b) 0.5 ℃/min; (c) 1.0 ℃/min; (d) 2.5 ℃/min; and (e) 5.0 ℃/min. The solution concentration and crystallization time were fixed at 1.81 g mefenamic acid/ 100 g ethyl acetate and 30 min, respectively.

4. Conclusion

The crystallization of mefenamic acid were performed in batch cooling crystallization process at different cooling rates. The cooling rates show significant effect on aspect ratio and crystal size distribution. The crystals with high aspect ratio and narrower CSD (100−900 μm) was obtained at cooling rate of 0.5 °C/min. Meanwhile, the morphology and polymorphic form of mefenamic acid are remained as needle-like and Form I, respectively. As a recommendation, this work can be extended to study the effect of other crystallization conditions such as solution concentration and time on crystals properties.

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