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# Nucleation Events and Metastable Zone Width of Mefenamic Acid Polymorph in Ethyl Acetate

[1, 3]S.K. Abdul Mudalip, [2]M.R. Abu Bakar, [2]P. Jamal, [1]Z. Alam and [3]F. Adam
[1]Department of Biotechnology Engineering, Kulliyyah of Engineering,
International Islamic University Malaysia, 50728 Kuala Lumpur, Malaysia
[2]Department of Pharmaceutical Technology, Kulliyyah of Pharmacy,
International Islamic University Malaysia, Bandar Indera Mahkota,
25200 Kuantan, Pahang, Malaysia
[3]Department of Chemical Engineering, Faculty of Chemical and Natural Resources Engineering,
University Malaysia Pahang, Lebuhraya Tun Razak, 26300 Gambang, Pahang, Malaysia

**Abstract:** Understanding of the nucleation events and metastable zone width are essential in the crystallization process. This study investigates the use of cheap process analytical technology tools namely conductivity in comparison with the turbidity system for in-line detection of polymorph nucleation event in the solution crystallization. The effects of different cooling rates and initial concentrations on Metastable Zone Width (MSZW), nucleation kinetics and polymorphism of mefenamic acid in ethyl acetate solution were analyzed. The MSZW data and nucleation kinetics parameter were estimated based on the recorded nucleation temperatures. The recorded nucleation temperatures based on in-line conductivity data are in agreement with the in-line turbidity system. The MSZW was found to increase with the increase of cooling rates and decrease with the increase of saturation concentration. The nucleation order and nucleation rate constant $k_n$ calculated from MSZW data using Nyvlt classical theory varied with the initial solution concentration. The highest solution concentration which was 3.6/100 g ethyl acetate, shows highest (0.1460) and lowest n (4.1374) values. This indicates fast nucleation at higher solution concentration. The crystallization using different cooling rates does not show significant effect on the final polymorphs chemistry where mefenamic acid Form I was produced.

**Key words:** Batch crystallization, metastable zone width, turbidity, conductivity, pharmaceutical

## INTRODUCTION

Primary nucleation is a paramount important in the crystallization process as it determine the final properties and characteristic of the crystals produced such as crystal size distributions, polymorphs and morphology. Such properties can be critically important for the further processing stage such as filtration, drying and dosage design. Primary nucleation commences once a sufficient level of supersaturation is generated in the solution (Mullin, 2001). Metastable Zone Width (MSZW), on the other hand is a region that falls within the saturation curve and a point of where the nucleation begins (Yu *et al*., 2013). The MSZW data is useful as an operating boundary for optimization of crystal properties during the crystallization process (Nagy *et al*., 2008a, b; Saleemi *et al*., 2012). Primary nucleation and MSZW are influenced by several factors such as a cooling rate (Barrett and Glennon, 2002; Ni and Liao, 2008), mixing (Grady *et al*., 2007), solution concentration (Ni and Liao, 2008), type of solvents or additives used (Han *et al*., 2014), impurities (Peng *et al*., 2012) and stirring material (Liang *et al*., 2004). Therefore, the evaluation on how these factors influence the nucleation and MSZW at the targeted operating condition of desired Active Pharmaceutical Ingredient (API) are essential prior to crystallisation operation (Zhang *et al*., 2015).

The determination of nucleation events and MSZW for a cooling crystallization process can be done through experimental or by using model-based approach (Mullin, 2001; Sear, 2014). The model-based approach requires a suitable models and several assumptions to reflect the actual crystallization process (Kim and Mersman, 2001; Sear, 2014). Meanwhile, the experimental approach can be done either through polythermal or isothermal method. The isothermal method involves heating and cooling of a

**Corresponding Author:** S.K. Abdul Mudalip, Department of Biotechnology Engineering, Kulliyyah of Engineering, International Islamic University Malaysia, 50728 Kuala Lumpur, Malaysia

known solution concentration to a certain temperature, then held isothermally until the nucleation observed (Anuar *et al*., 2009). The polythermal technique selected in this work involves cooling of various known concentrations of the saturated solution at a constant cooling rate until nucleation events occur (Mullin, 2001). The turbidity sensor is reported as a cheap Process Analytical Technology (PAT) tools that show promising results for in-line detection of nucleation events (Han *et al*., 2014; Maosoongnern *et al*., 2012; Shiau and Lu, 2014).

The occurrence of nucleation events is somehow related to the sudden decrease in solution concentration during formation of solid particles in the solution. Based on this principle, other PAT tools such as conductivity system that can measure the concentration of the solution will be an excellent alternative for measurement of the nucleation events. Conductivity values reflect the chemical characteristics of solvents or solution that can support current flow or in other words the mobility or concentration of ions in the electrolyte. The conductivity is frequently used for concentration measurement of sparingly soluble or strong electrolytes in water, organic solvents and ionic liquid. A vast application of the conductivity system in the crystallization of API in an organic solvent with low conductivity value (nS/cm) is yet to be reported in contrast to the turbidity system.

In this present research, an example is presented for the first time to research the feasibility of the in-line conductivity system to provide data on the onset of nucleation events and MSZW in addition to turbidity system. Batch cooling crystallization of mefenamic acid (2-(2, 3-dimethylphenyl)aminobenzoic acid) in ethyl acetate solution was selected as a case study. Mefenamic acid is a nonsteroidal Active Pharmaceutical Ingredient (API) that commonly used for management of pain due to menstrual disorders (Panchagnula *et al*., 2004). This API shows the character of a weak acid due to the presence of the carboxylic group-COOH as shown in Fig. 1

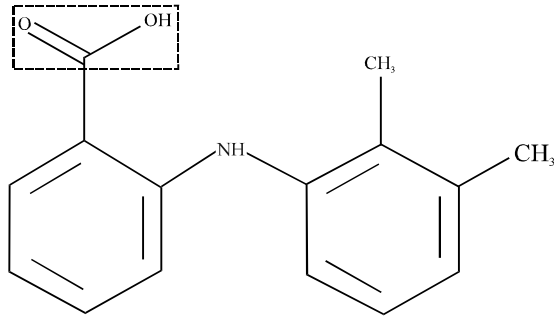


Fig. 1: Chemical structure of mefenamic acid. The carboxylic group is highlighted in a rectangular box

(Iwasaki *et al*., 2007). The application of conductivity sensor during the crystallization process is expected to complement the turbidity sensor at lower cost and at the same time allow in-line determination of solution concentration. Moreover, the effect of different saturation concentrations and cooling rates on MSZW and nucleation parameters were investigated. The solid-state properties of the crystallized particles were examined by using various analytical instruments.

## MATERIALS AND METHODS

### Experimental section

**Material:** Mefenamic acid powder (98 wt. % purity, Baoji Tianxin Pharmaceutical Co., Ltd., China) and ethyl acetate (99.5 wt. % purity, Fischer Scientific) were used.

**Equipment:** The experiments were performed in a 500 mL jacketed crystallizer equipped with a 3-bladed propeller of diameter 5 cm and Daihan digital overhead stirrer HS-30D shown schematically in Fig. 2. The crystallizer was sealed and operated with a condenser at 10°C. The control of the temperature in the vessel was done using PTFE coated PT-100 sensor connected to Julabo H25 ME heating/cooling system. The transmission turbidity and conductivity sensor manufactured by Mettler-Toledo were positioned in the crystallizer as shown in Fig. 2. The in-line recording of these values was done using turbidity transmitter (Trb 8300) and conductivity transmitter (Thornton M300) which was connected to DA_Trb8300 and M300 data logging software, respectively. The transmission turbidity sensor used in this work measured the concentration of the suspended particles or turbidity in a liquid medium based on the principle of the back scattered light technology. In contrast to the reflectance turbidity probe, the transmission turbidity sensor offers more advantages such as direct measurement of light that scattered due to the presence of

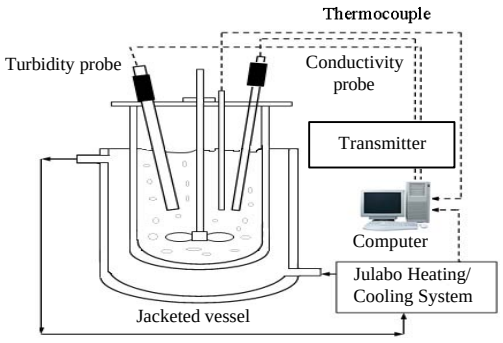


Fig. 2: A schematic representation of the experimental set-up for MSZW experiments

solid particles in the solution. The conductivity sensor, on the other hand is a two electrode sensors that are specially designed to withstand various chemical applications.

**Measurement of metastable zone width:** Aturated solutions of mefenamic acid in ethyl acetate at temperatures from 40-60°C were prepared in the crystallizer using solubility data reported in previous work (Abdul *et al*., 2013). The stirring speed was set at 200 rpm to ensure sufficient mixing inside the vessel. The solution was heated up and kept at a temperature of 10°C higher than the saturation temperature for about 30 min to ensure complete dissolution of the solute material. The turbidity readings were calibrated to be those of a clear solution and then cooled to the final cooling temperature between 10-30°C using different cooling rates. The cooling rates were set at 5, 2.5, 1.0, 0.5 and 0.2°C/min. During this process, the turbidity values, conductivity and temperatures were recorded every 1 sec in a computer. Samples of solid crystals collected after nucleation commenced were filtered and dried in an oven at 50°C.

**Characterization methods:** The Infrared (IR) spectra of crystals produced were recorded using Perkin Elmer's ATR-FTIR Spectrometer (Frontier) with a wavenumber range of 500-4000 $cm^{-1}$. The analysis was performed with an average of 16 scans. The crystals images were captured using Leica microscope DM750 with a total magnification of 200×4×/0.10 and processed using Leica Application Suite Software Version 3.6.

## RESULTS AND DISCUSSION

**Conductivity and turbidity for detection of polymorph nucleation:** Figure 3 and 4 show a profile of temperature, conductivity and turbidity as a function of time during the cooling crystallization process of mefenamic acid in ethyl acetate. The transmission turbidity sensor used in this work is based on the principle that solution transmittance is inversely proportional to the amount of crystals presence in the solution. Therefore, the point, when the turbidity values start to increase, can be used to indicate the occurrence of nucleation events in the solution. When crystallization continues, the decrease of solution concentration may occur since the solute becomes less soluble and start to precipitate as crystals (Borissova *et al*., 2008; Mullin, 2001). As seen in Fig. 3 and 4, a decrease of conductivity value are observed during the crystallization process. This trend directly

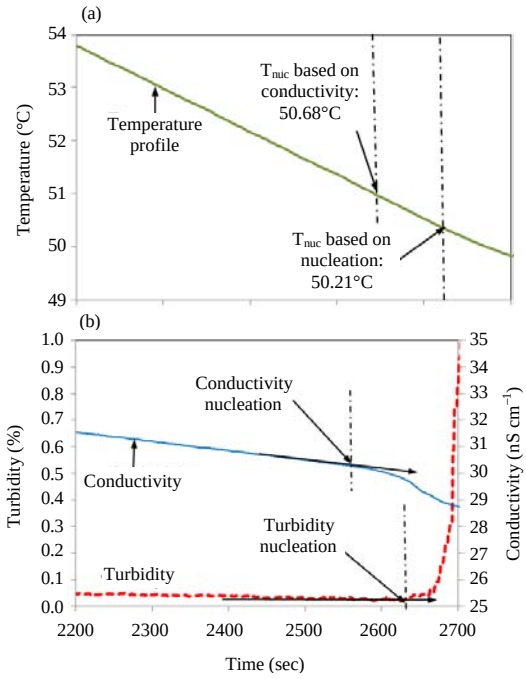


Fig. 3: a) Nucleation temperature and b) time based on in-line conductivity and turbidity reading for cooling crystallization with saturation concentration of 3.60 g of mefenamic acid/100 g ethyl acetate (saturation solution at 60°C) and cooling rate of 0.5°C/min

reflects the decrease of solution concentration with cooling prior to the formation of small nuclei and solute cluster due to self-assembly of mefenamic acid in the solution. After a while, a sudden decrease of the conductivity values was observed. This point can be used to indicate the onset of nucleation events.

The temperatures at which the turbidity values showed a sudden increase and the conductivity showed a sudden decrease are labelled as nucleation temperature $T_{nuc}$. As shown in Fig. 3, the values of $T_{nuc}$ measured by conductivity and turbidity probes are almost the same which are 50.68 and 50.21°C, respectively. In Fig. 4, where the lowest saturation concentration was used, the values of nucleation temperatures, $T_{nuc}$ measured by conductivity and turbidity probes are at 21.21 and 22.24°C, respectively.

As seen in Fig. 4a, a small notch in the internal temperature curve is probably due to the small increment of solution temperature during nucleation. The notch, however is not observed for higher solution concentration (Fig. 3a). This is because, although crystallization process is classified as an exothermic process, the release of the heat during the formation of

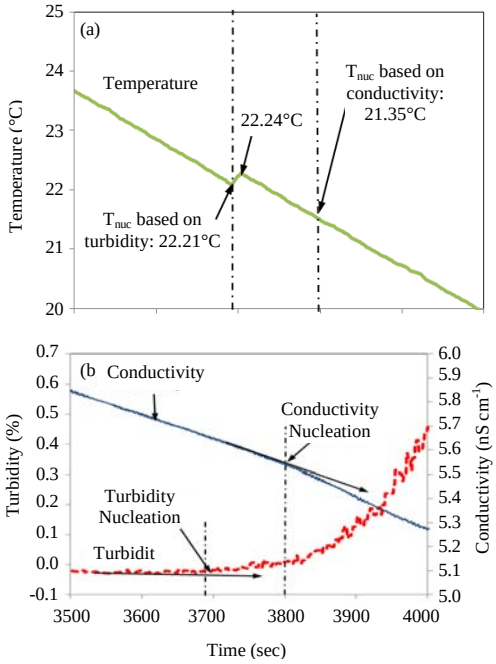


Fig. 4: a) Nucleation temperature and b) time based on conductivity and turbidity reading for cooling crystallization with saturation concentration of 1.81 g of mefenamic acid/100 g ethyl acetate (saturation solution at 40°C ) and cooling rate of 0.5°C/min

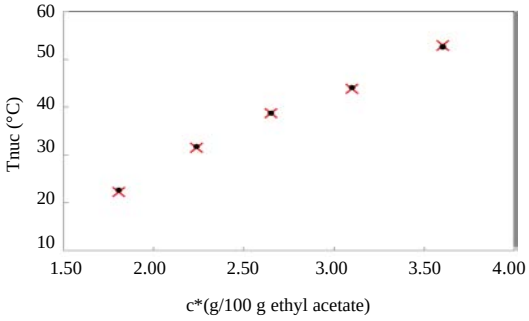


Fig. 5: Plot of nucleation temperature measured using conductivity (×) and turbidity sensor (•) versus saturation concentration for cooling rate of 0.5°C/min

solute cluster in the solution may or may not contribute to the increase in the solution temperature (Yafi and Zein, 2015). The plot of nucleation temperature $T_{nuc}$ measured using conductivity and turbidity sensor for different concentration studied is shown in Fig. 5. The average deviation for each point is small which <3% or 0.3°C. It is observed that for all the concentrations investigated, the conductivity probe detects the point of nucleation temperature $T_{nuc}$ earlier than the turbidity probe except for saturation concentration of 1.81 g of mefenamic

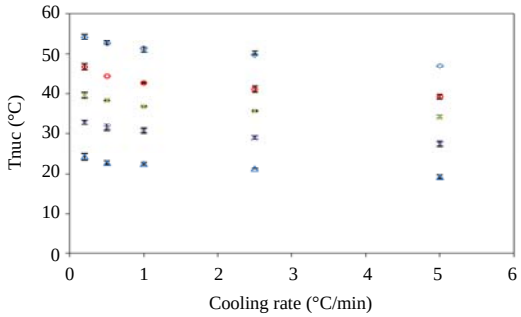


Fig. 6: Nucleation temperature, at different cooling rates for mefenamic acid solutions saturated at 40°C (Δ) 45°C (x), 50°C (*), 55°C (o), and 60°C (◊) in 500 mL

acid/100 g ethyl acetate. This finding is expected since crystallization using lower solution concentration is often correlated with low nucleation rate (Han *et al*., 2014). The low nucleation rate in low solution concentration might cause slow changes in the solution concentration prior to solute cluster formation. Thus, delayed the detection of the onset of nucleation event by conductivity sensor.

**The effect of process parameters on MSZW:** MSZW is a unique characteristic of the pharmaceutical compounds. The MSZW are influenced by various process parameters and can act effectively used as a barrier for the crystallization operation. For a particular process condition, the MSZW can be calculated using the following equation:

$$\Delta T_{max} = T_{sat} - T_{nuc}$$

Where:

$T_{sat}$ = The saturation temperature (°C)

$T_{nuc}$ = The nucleation temperature (°C) (Han *et al*., 2014; Zhang *et al*., 2015)

The $T_{nuc}$ was taken once the conductivity values started to show a sudden decrease. The variation of the $T_{nuc}$ as a function of cooling rate for different saturation concentration of mefenamic acid solution are shown in Fig. 6. It can be seen that the $T_{nuc}$ decreases with the increasing of cooling rate. This indicates that the nucleation events starts at lower temperature for higher cooling rate. Thus, resulting in an apparently wider MSZW at higher cooling rate for all concentrations studied shown in Fig. 7. This situation can be explained based on the rate of supersaturation that was generated in the solution during the cooling process. Although, faster cooling rate creates higher supersaturation rates within the same time scale, more relaxation time is required to achieve a quasi-steady-state distribution of molecular clusters before the appearance of the first nuclei.

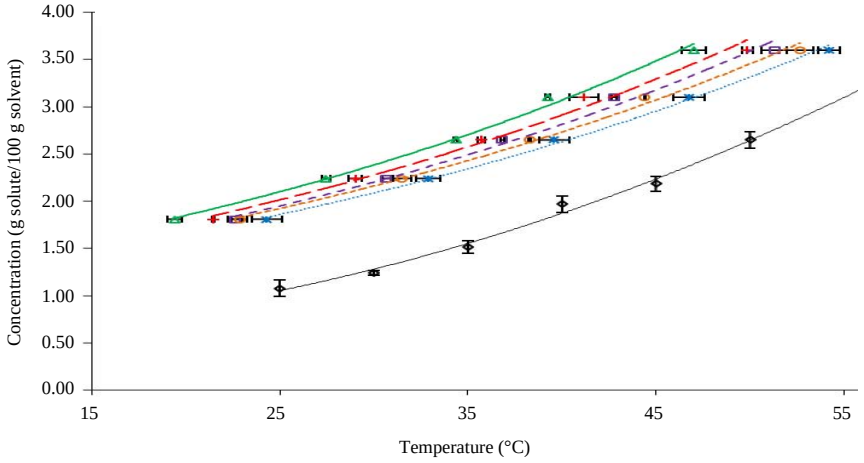


Fig. 7: Solubility (Abdul *et al*., 2013) (◊) and metastable zone width data of mefenamic acid in ethyl acetate for five different cooling rates: * = 0.2°C/min; Δ = 0.5°C/min; Δ = 1.0°C/min; + = 2.5°C/min; D = 5°C/min. The solid and dotted lines either in black, blue, brown, purple, red or green colors are the best fit to represent the solubility and metastable zone width data with $R^2$ values above 0.95

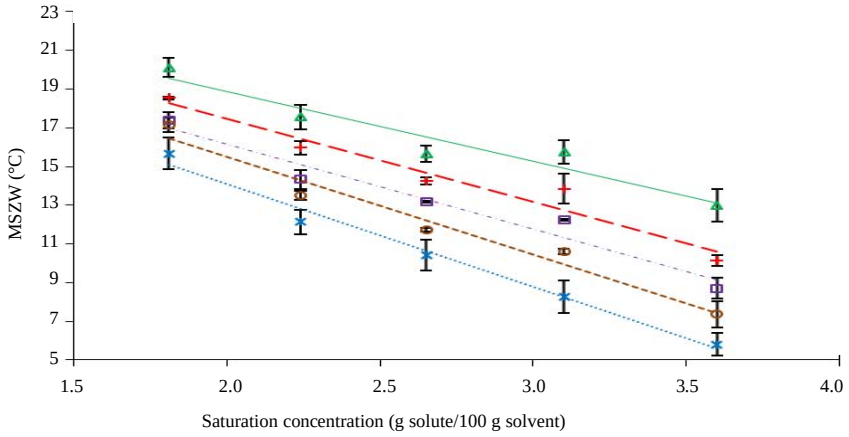


Fig. 8: The dependency of MSZW on saturation concentration measured at different cooling rates: * = 0.2°C/min; o = 0.5°C/min; Δ = 1.0°C/min; + = 2.5°C/min; D = 5°C/min. The solid or dotted lines which are either in blue, brown, purple, red or green colors are the best fit to represent the trend. The $R^2$ values are above 0.95

Hence, delays the onset of the nucleation process and widen the MSZW (Park *et al*., 2003; Svard *et al*., 2013). The relation between MSZW and solution concentration for different cooling rates are shown in Fig. 8. The measured MSZW are found to be higher at lower saturation concentration and lower at higher saturation concentration for all cooling rates. These findings show that nucleation is more difficult at a lower concentration and easier at a higher concentration. This is because; at a lower concentration less solute molecules are available for solute/solute interactions that are essential for nucleation as compared to higher solution concentration (Borissova *et al*., 2008). Moreover, higher supersaturation generated in solution with higher concentration during the cooling process makes the nucleation process easier (Park and Yeo, 2012).

**Effect of process parameters on nucleation:** The MSZW data for different cooling rates and the saturation concentration can be used to estimate the nucleation kinetics parameters (Kulkarni *et al*., 2013; Nagy *et al*., 2008a, b; Ciardha *et al*., 2011). Using the classical theory of nucleation proposed by Nyvlt combined with the MSZW, the nucleation kinetics parameters can be determined by:

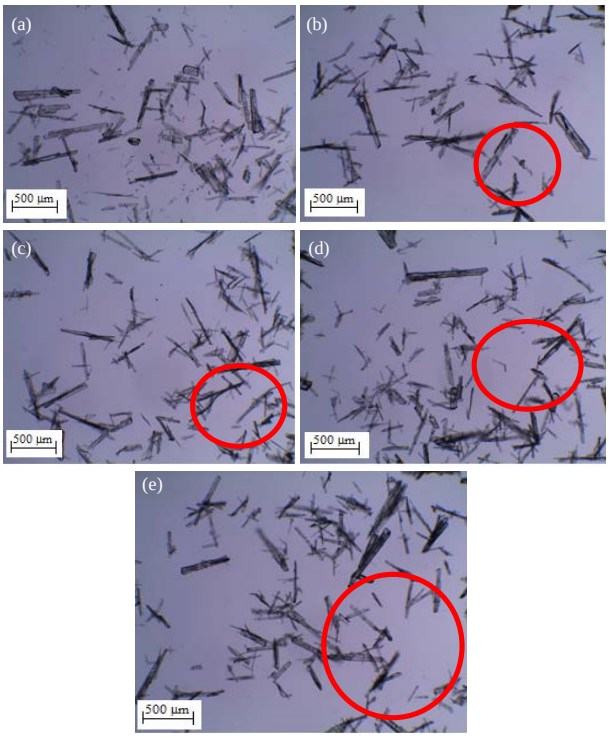


Fig. 9: Microscopy images of crystals obtained from cooling crystallization of saturated solution at 40°C with different cooling rates: a) 0.2°C/min; b) 0.5°C/min; c) 1.0°C/min; d) 2.5°C/min and e) 5°C/min

$$\log(r) = (n-1)\log\frac{dc^*}{dT} + \log K_N + n\log\Delta T_{max}$$

Where:

r = The cooling rate
$dc^*/d$ = T a temperature coefficient of solubility
$K_N$ = A nucleation rate constant
n = The nucleation order

Based on Eq. 2, the plotting of versus log ($\Delta_{tmax}$) will results in a straight line with a slope and an intercept which are equal to the value of nucleation order n The nucleation rate constant $K_N$, respectively.

As tabulated in Table 1, the saturation concentration of 3.6 g mefenamic acid/100g ethyl acetate shows the highest nucleation rate constant, $K_N$ (0.1460) and the lowest nucleation order, n (4.1347). On the other hand, the lowest saturation concentration studied which is 1.81 g mefenamic acid/100 g ethyl acetate shows the lowest nucleation rate constant $K_N$ (0.0054) and the highest nucleation order n (13.4630). The high value of nucleation rate constant $K_N$ and low value of nucleation order n indicates that nucleation is easier to occur at higher saturation concentration. This is probably due to the presence of more mefenamic acid molecules in the solution with higher concentration that have potential for solute/solute interactions through hydrogen bonding formations as compared to the solution with lower concentration (Borissova *et al*., 2008; Davey and Garside, 2002). The results on the dependency of nucleation order, n and the nucleation rate constant, $K_N$ with initial solution concentration reported in this work are in agreement with those reported in literature (Ni and Liao, 2008). The findings also aligned with the MSZW data illustrated in Fig. 9.

Table 1: Calculated nucleation order n and the nucleation rate constant, $K^N$ for different saturation concentration $C^*$

| (g/100 g ethyl acetate) | n | $K_N$ |
|---|---|---|
| 1.81 | 13.4630 | 0.0054 |
| 2.24 | 8.8380 | 0.0251 |
| 2.65 | 7.9052 | 0.0323 |
| 3.10 | 5.0664 | 0.0472 |
| 3.60 | 4.1374 | 0.1460 |

**Effect of cooling rates on polymorphism:** The cooling rate is important to generate supersaturation in the cooling crystallization process. Figure 9 shows the image of crystals obtained from different cooling rates solution concentration of 1.81 g/100 g ethyl acetate and mixing intensity of 200 rpm. In general, the shape of the crystals is long and needle-like. The size of the crystals becomes

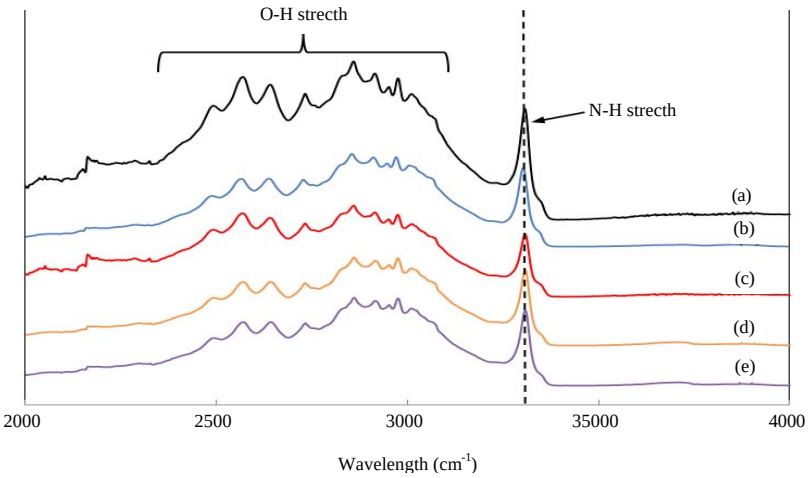


Fig. 10: Partial FTIR spectra of mefenamic acid crystallized using saturated solution at 40°C and cooling rate of: a) 0.2°C/min; b) 0.5°C/min; c) 1.0°C/min; d) 2.5°C/min and e) 5°C/min

wider when the cooling rate increased. It can be observed that the crystals produced at a cooling rate of 0.5°C/min and above seem to form flower-like crystals (Fig. 9). This phenomenon is probably due to the greater supersaturation and faster nucleation which generated at a higher cooling rate. The fast nucleation process produced a large number of small nuclei that provide surfaces for crystals to grow and become attached to each other during the crystallization process. This phenomenon may also promote the secondary nucleation (Kulkarni *et al*., 2014). For mefenamic acid crystals, although the size of the crystals has changed, the polymorphic outcome is the same as evidence with FTIR spectrum shown in Fig. 10.

Previous research by Romero *et al*. (1999) highlighted that the N-H stretching band occurs between 3300 and 3350 $cm^{-1}$ is an important spectral that can be used to distinguish between Form 1 and 2 of mefenamic acid. Specifically, the N-H stretching frequency which occurs at 3311-3313 and 3346-3350 $cm^{-1}$, show the presence of Form 1 and 2, respectively. The mefenamic acid Form 1, 2 and 3 are enantiotropic related where Form 1 is relatively more stable than Form 2 and at ambient condition. 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. As seen in Fig. 10, the FTIR spectrum of mefenamic acid crystals that crystallized using ethyl acetate at different cooling rates only show 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 1 reported by previous work (Romero *et al*., 1999).

## CONCLUSION

In this contribution, the in-line conductivity system has been successfully applied for detection of nucleation events during solution crystallization process of mefenamic acid-ethyl acetate solution with low conductivity value ($nScm^{-1}$). The sudden decrease of conductivity values can be used as a point where the onset of nucleation event occurs to complement the turbidity reading. The onset of nucleation event detected by in-line conductivity is confirmed by turbidity measurement. The estimated MSZW based on the measured nucleation temperature is wider with the increase of cooling rate and narrower as the saturation concentration increases. The increase of nucleation rate constant with the increase of saturation concentration demonstrates faster nucleation process at higher saturation concentration. The FTIR spectra of crystals produced using different cooling rates only shows the characteristics of Form I.

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## NOMENCLATURE

$K_n$ = Nucleation rate constant
n = Nucleation order
r = Cooling rate (°C/min)
$T^*$ = Saturation temperature (°C)
$T_{nuc}$ = TnuNucleation temperature (°C)
$\Delta_{Tmax}$ = Metastable zone width (°C)
$dc^*/dT$ = Temperature coefficient of solubility, g solute (100 g solvent °C)$^{-1}$

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