A Study on Nucleation Kinetics of Carbamazepine-Fumaric Acid Form A Cocrystal

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Abstract—**Nucleation kinetics study has a great value for better plan and process of industrial crystallizer. However, the analysis of nucleation kinetics for carbamazepine (CBZ)-fumaric acid (FUM) has not yet been studied. The nucleation kinetics of a solution system can be estimated from the measured metastable zone width (MSZW). Thus, the objective of this paper is to study the nucleation kinetics of CBZ-FUM form A cocrystal by utilizing polythermal crystallization in a batch reactor equipped with refrigerated bath. First, the CBZ-FUM form A cocrystals were prepared by utilizing a stoichiometric ratio of 1:1. The nucleation kinetics of CBZ-FUM, were estimated by using Nývlt's approach. By employing the polythermal technique, the crystallization temperature at the dissolution temperature for every cooling rate and concentration were recorded and the analysis shows that the MSZW had increased as the cooling rate and the concentration increased. The estimated MSZW were plotted as a log function of MSZW versus cooling rate which were used to estimate the nucleation parameters. This study found that the nucleation rate increase as the cooling rate and the solute concentration increase. In addition the characterization of the cocrystal using FTIR and optical microscope shows that there are new bonds formed in the cocrystals, however, by comparing the results with CBZ-FUM form B cocrystals, it is found that some concentration form CBZ-FUM form A cocrystal instead of CBZ-FUM form A cocrystal and all cocrystal has plate-like morphology and the shape of cocrystal elongated as the cooling rate decrease.**

Keywords*— *Carbamazepine, Cocrystal, Fumaric Acid, Nucleation Kinetics, Polythermal Method

I. INTRODUCTION

Epilepsy, otherwise known as "seizure disorder" is a spectrum condition where sporadic electrical storms occur in the brain and can be recognized when there is a risk for seizure to reoccur. Since 1965, CBZ has been used as an antiepileptic drug (AED) which has the highest efficiency against partial seizures with or without second generalization [1]. Even though CBZ is highly and widely prescribed as AED, CBZ has a limited solubility where its solubility in water is around 170 mg/mL at 25°C [2]. Due to this poor solubility, the initial dosage of CBZ per patient which is 200 mg per day will gradually increases to 800-1200 mg per day to ensure maximum absorption. Besides having low solubility, CBZ also has a poor bioavailability due to its biological half-life which is between 18 to 65 hours [3].

Therefore, alternative method to increase the solubility and bioavailability of CBZ need to be studied and one of the approaches to improve the physicochemical characteristics of CBZ is through cocrystallization process. Cocrystal is said can increase not only the solubility of drugs, but enhance the dissolution rates as well as improving the bioavailability of poor soluble drugs especially during the oral route of administrations [4]. Cocrystal is a crystalline material that exists in solid state, composed of two or more molecules in the same crystal lattice. Cocrystal of CBZ can be done by adding suitable coformer, which in this study; FUM is used as the coformer.

There are several methods of cocrystallization that can be used which include slow evaporation, isothermal and polythermal method, hot melt extrusion, solid state grinding, slow cooling and sonocrystallization [5]. For the purpose of this study, polythermal method was used to grow the CBZ-FUM cocrystals where this method utilizes the concept of metastability to study crystallization processes [6]. In polythermal technique, a constant rate was used to cool down a saturated solution in order to introduce the nucleation of the cocrystal. The difference in temperature between the nucleation temperature and the saturation temperature is taken as the MSZW [7] , which signifies as the region between the supersolubility and the solubility curve where crystal growth is considered ideal in this particular region [8]. Therefore, the main purpose of this paper is to study the nucleation kinetics of CBZ-FUM form A cocrystal. Besides that, the morphology of CBZ-FUM form A cocrystal is investigated as well.

II. THEORY

Nývlt's approach is one of the conventional approaches to establish the nucleation kinetics by means of MSZW. Following this approach, the nucleation rate at the beginning of nucleation is expected to be consistent with the supersaturation rate for a limited time period [7]. In Nývlt's approach, the primary number nucleation rate, J can be presented by the following expression [9]

$$J = k^{'}\left(\Delta c\right)^{m} \quad (1)$$

where $k^{'}$ is the nucleation rate constant, ΔC is the supersolubility which can be computed from $\Delta c = c - c^{*}$ and m is apparent nucleation order. Since the method is classified under cooling crystallization, the rate of supersaturation generation can be expressed as a function of the cooling rate, R, as shown below,

$$\frac{d\Delta c}{dt} = R\frac{dc^{*}}{dT} \quad (2)$$

where dc^{*}/dT can be taken as the slope of the solubility curve for a given saturation temperature. During nucleation, the maximum supersaturation, Δc_{max} and MSZW can be stated by the following relationship,

$$\Delta c_{\max} = \Delta T_{\max}\frac{dc^{*}}{dT} \quad (3)$$

$$\Delta T_{\max} = T^{*} - T_{nuc} \qquad (4)$$

where ΔT_{max} can be taken as the value of corresponding MSZW.

As stated earlier, the nucleation rate is assumed to correspond with the supersaturation rate at the beginning of nucleation, thus the mass of formed nuclei can be represented as the number of nuclei formed which can be conveyed as follows,

$$\frac{dM}{dt} = k' \alpha \rho_c r^3 \Delta c^m = k\Delta c^m \tag{5}$$

where M is the mass of formed nuclei and α as well as ρ_c are the terms used to represent the volume shape factor and the density of the solute crystals, respectively. Then, equations (2), (3) and (5) are merged to obtain the following expression,

$$k\Delta c^m = k\left(\Delta T_{\max} \frac{dc^*}{dT}\right)^m = k\left[MSZW\left(\frac{dc^*}{dT}\right)\right]^m \tag{6}$$

$$k\left[MSZW\left(\frac{dc^*}{dT}\right)\right]^m = R\left(\frac{dc^*}{dT}\right)\varepsilon \tag{7}$$

where ε is a conversion factor to describe the difference in concentration due to the formation of hydrates and/or solvates. The conversion factor can be formulated as follows,

$$\varepsilon = \frac{R_h}{\left[1 - c(R_h - 1)\right]^2} \tag{8}$$

where R_h is the ratio of the molecular weights of the hydrates, whereas c is the solution concentration expressed as the mass of anhydrate per unit mass of solvents [10]. Assuming there are no known hydrates and/or solvates formed, R_h is given a value of 1, and thus the value of ε is also equal to 1. Rearranging equation (7) and convert to logarithm function for both sides, the following expression is generated.

$$\log R = m \log(MSZW) + (m-1)\log\left(\frac{dc^*}{dT}\right) + \log k \tag{9}$$

Since the above equation need to be plotted as the function of ln *MSZW* versus ln *R*, equation (9) need to be rearranged in terms of natural log and MSZW is taken as the subject which yields the following,

$$\ln(MSZW) = \frac{1}{m}\ln R - \frac{(m-1)}{m}\ln\left(\frac{dc^*}{dT}\right) - \frac{1}{m}\ln k$$

(10)

The plot of equation (10) should result in a straight line, with the slope yielding the apparent nucleation order, *m*, and the nucleation rate constant, *k*, estimated from the intercept.

I. METHODOLOGY

A. *Materials*

The CBZ was purchased from Merck whereas FUM was purchased from Sigma-Aldrich. The absolute ethanol was supplied by HmbG Chemicals with purity of 99%.

B. *Polythermal Experiment*

The preparation of CBZ-FUM form A cocrystals were done by combining CBZ and FUM which are in powder form, together with a stoichiometric ratio of 1:1. After mixing CBZ and FUM together, the compound was poured into jacketed reactor equipped with a refrigerated bath and a glass stirrer, which was then mixed with 100 mL of ethanol. To ensure the compound of CBZ and FUM were dissolved in the ethanol, the solution was heated up to 50°C and the heating as well as the stirring process need to be continued for 1 hour before cooling process to ensure the very last compound of CBZ and FUM were completely dissolved and the solution was in supersaturation phase. Next, the dissolved solution was cooled down to 20°C to introduce the formation of CBZ-FUM cocrystals. The cooling rates used for the experiments are 0.10°C/min, 0.25°C/min, 0.50°C/min and 0.75°C/min. for every cooling rate, there were five different concentrations of CBZ-FUM used which are 0.0451 mg/L, 0.0467 mg/L, 0.0482 mg/L, 0.0512 mg/L and 0.0526 mg/L.

During the experiments, the nucleation temperatures or the crystallization temperatures, T_{cryst} where the first crystal is formed were recorded. The crystals were allowed to grow within the duration of 2 hours after the temperature of the solution was dropped from 50°C to 20°C following the cooling rates used. When all the crystal had formed, they will be filtered and dried. Then, using the same rates, the crystals obtained were heated up and dissolved in new 100 mL of ethanol. The dissolution temperatures, T_{dis} where all the crystals have dissolved completely were recorded. During dissolution process, the concentrations of CBZ-FUM used are 0.0192 mg/L, 0.0199 mg/L, 0.0206 mg/L, 0.0224 mg/L and 0.0234 mg/L. The recorded T_{dis} and T_{cryst} were used to determine the corresponding MSZW.

C. *Crystal Characterization*

The functional groups present in the crystals were identified using Fourier Transform Infrared (FTIR) spectroscopy (Thermo Nicolet). This FTIR spectrometer has a range numbers of 500 cm^{-1} to 400 cm^{-1} with several scans to achieve average pattern for the detected functional groups. Before placing the samples onto the plate, the plate is cleaned using acetone to remove any impurities present. Besides that, Differential scanning calorimetry (DSC) is used to measure the melting points of samples. In this study, DSC measurements are conducted using Metler Toledo DSC 820. 6 mg of CBZ-FUM cocrystal samples are analyzed in crimped aluminium pan. DSC measurements were carried at constant flow rate of nitrogen gas with a heating rate of 10°C/min. In addition, the morphology of the crystals was characterized using Olympus BX41 model microscope.

II. RESULTS AND DISCUSSION

A. *Dissolution-Crystallization Diagram*

Set of data from T_{dis} and T_{cryst} made up the dissolution and crystallization curve for this diagram, in which the MSZW for every concentration at their corresponding cooling rate were determined. However, since the concentrations of CBZ and FUM used to determine T_{cryst} and the concentration of CBZ-FUM cocrystal used to determine T_{dis} were different, the MSZW cannot be estimated directly. Therefore, the solubility curves were extended using power trendline to extrapolate the dissolution data. The extrapolated method is essential to determine T$_{dis}$ at desired concetration because MSZW can only be computed at the same concentration as shown in Fig. 1. Using the extrapolated values of dissolution data T_{dis} for every concentration corresponds to T_{cryst} was determined in order to calculate the MSZW.

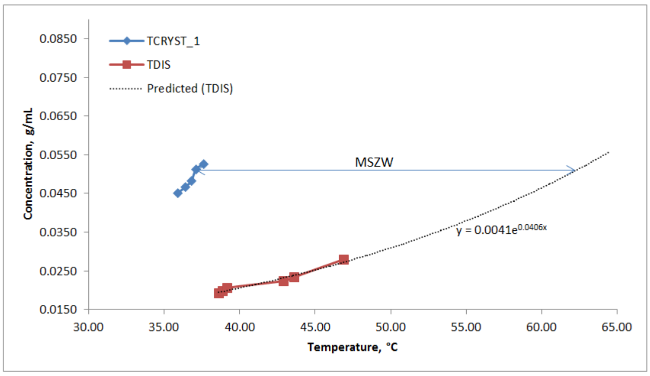

Fig 1: Extrapolated T_{dis} with corresponding MSZW for 0.10°C/min

The differences between T_{dis} and T_{cryst}, of a known concentration, were measured as metastable zone width (MSZW), which were then used in estimating the nucleation rate of CBZ-FUM Form A crystals.

B. *Metastable Zone Width*

Table 1 shows the calculated MSZW along with T_{cryst} and extrapolated T_{dis} which were calculated using equation (4). As seen in Table 1, the MSZW increased correspond to increment of cooling rate and concentration. It is usually observed that higher cooling rate results in lower T_{cryst} and wider MSZW [11]. However, in this study, it was found that the MSZW had decrease at the highest solute concentration.

Table 1: Metastable Zone Width

0.0451 g/mL					
Cooling Rate,R (°C/min)	≈ 0.00	0.10	0.25	0.50	0.75
T_{dis} (°C)	58.31	58.10	59.06	60.05	59.44
T_{cryst} (°C)	36.87	36.70	35.90	35.10	34.50
MSZW	21.44	21.40	23.16	24.95	24.94
0.0467 g/mL					
Cooling Rate, R (°C/min)	≈ 0.00	0.10	0.25	0.50	0.75
T_{dis} (°C)	59.16	58.93	59.92	60.87	60.26
T_{cryst} (°C)	37.27	37.00	36.40	35.80	34.90
MSZW	26.89	21.93	23.52	25.07	25.36
0.0482 g/mL					
Cooling Rate, R (°C/min)	≈ 0.00	0.10	0.25	0.50	0.75
T_{dis} (°C)	59.94	59.69	60.70	61.63	60.99
T_{cryst} (°C)	37.30	37.50	36.80	36.10	35.40
MSZW	22.64	22.19	23.90	25.53	25.59
0.0512 g/mL					
Cooling Rate, R (°C/min)	≈ 0.00	0.10	0.25	0.50	0.75
T_{dis} (°C)	61.42	61.14	62.19	63.06	62.39
T_{cryst} (°C)	37.87	37.90	37.10	36.60	36.40
MSZW	23.55	23.24	25.09	26.46	26.62
0.0526 g/mL					
Cooling Rate, R (°C/min)	≈ 0.00	0.10	0.25	0.50	0.75
T_{dis} (°C)	62.08	61.78	62.85	63.70	63.02
T_{cryst} (°C)	39.09	38.30	37.60	37.30	34.50
MSZW	22.99	23.48	25.25	26.40	24.94

It is important to determine the MSZW as cooling rate approaching zero because the cooling rate used in industrial scale is very small, thus the data for T_{dis} *and* T_{cryst} were plotted against the cooling rate as shown in Fig 2.

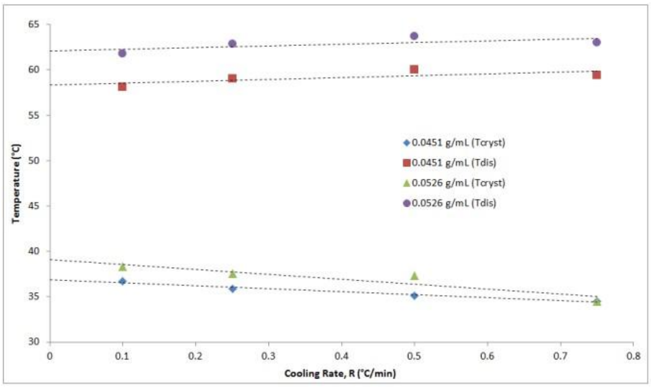

Fig 2:

C. *Nucleation Kinetics*

The nucleation kinetics of CBZ-FUM form A cocrystals were studied by using Nývlt's approach. Following the Nývlt's approach, log plot of MSZW versus cooling rate was made for every solute concentration as shown in Fig. 3. The log plots between MSZW and cooling rate are known to yield a linear relationship where the slope and the intercept of the line were utilized to estimate the nucleation parameters include *m*, *k* and *J*. Table 2 shows the calculated nucleation parameters for each concentration and cooling rate.

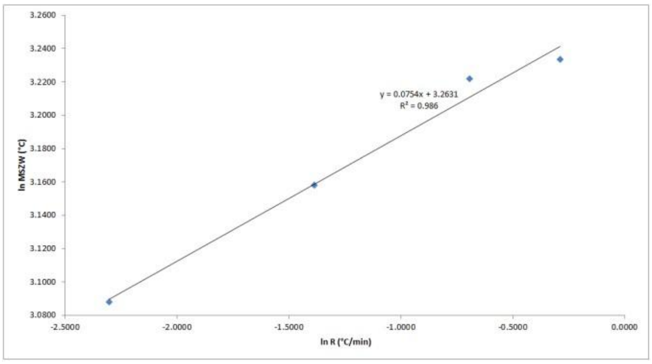

Fig 3: Procedure to determine nucleation parameters, *k* and *m* for solute concentration of 0.0451 g/mL

Using the equation for the trendline on the plots, the slope and the intercept were used to determine the value of *m* and *k* by comparing the trendline equation with equation (10). Then, the *k* values were used to determine the nucleation rate, *J* using equation (1). The trends for the values *m*, *k* and *J* were studied by plotting the calculated values of *m* against the solute concentration, whereas the values of *k* and *J* were plotted against cooling rate as shown in Fig 4, Fig 5 and Fig 6.

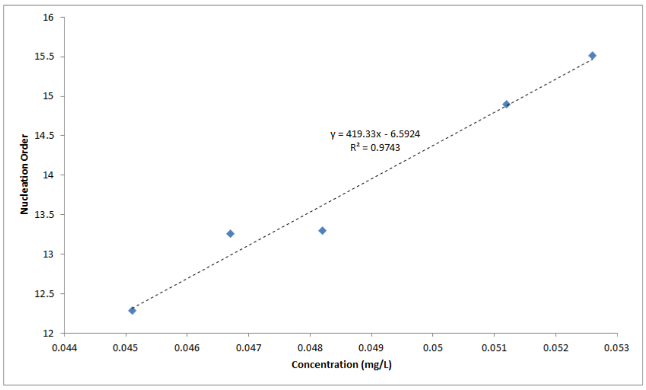

Fig 4: The trend of nucleation order against solute concentrations.

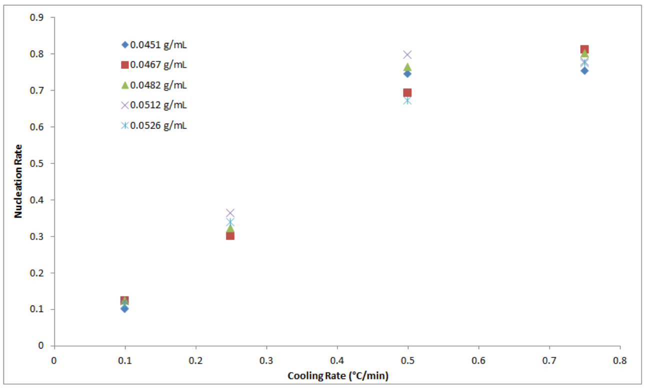

Fig 5: The trend of nucleation rate against cooling rate

From the nucleation parameters, it was found that the nucleation rate, *J* increases as the concentration and cooling rate increase. However, the nucleation parameters for the highest concentration which is 0.0526 g/mL did not follow the increment trend as the value of nucleation parameters decrease for each cooling rate.

D. Fourier Transform Infrared Spectroscopy

FTIR spectroscopy is a conventional way to identify the presence of certain functional groups in the crystal sample. Fig. 6 shows the FTIR spectrum for the lowest cooling rate which is 0.10 °C/min.

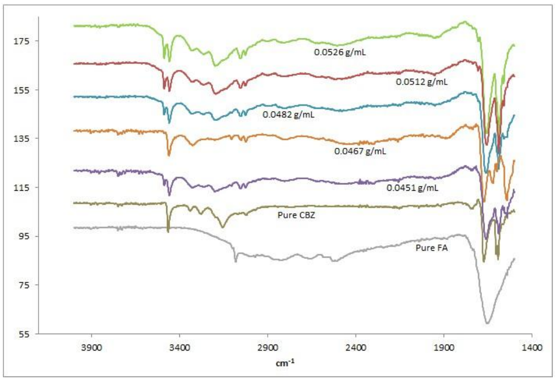

Fig. 6: FTIR spectrum for cooling rate of 0.10°C/min

Based on these figures, the peaks for IR spectrum of pure CBZ can be seen obviously at 3464.52 cm^{-1} and 3277.14 cm^{-1} which indicate the present of N-H stretch, 3154.95 cm^{-1} which indicate the present of C-H stretch, 1736.25 cm^{-1} for C=O stretching and 1674.78 to 1593.68 cm^{-1} which shows the presents of C=C bonding. On the other hand, the IR spectrum for pure FUM can be detected at peaks 3081.99 cm^{-1} and 2830.20 cm^{-1} (C-H stretching), 2513.32 cm^{-1} (O-H stretching) and 1657 cm^{-1} (C=C and C=O stretching). Referring to Fig. 6, IR spectrum for all five concentrations seem similar with the highest peak at widthbands of 3300 cm^{-1} to 3500 cm^{-1} (N-H stretch), ~3030 cm^{-1} (C-H stretch) and 1500 cm^{-1} to 1700 cm^{-1} to indicate the presents of C=C and C=O stretch [12]. Even the IR spectrum for the cocrystal seem to have additional peaks, all the peaks are in the range of widthbands as pure CBZ and FUM.

E. Morphology

The morphology of CBZ-FUM form mA cocrystals were analyzed using the Olympus BX41 optical microscope. The morphology of pure CBZ, pure FUM and cocrystals are shown in Fig. 7. CBZ-FUM form A cocrystal has plate-like shape, differ from the morphology obtained by other researcher which is needle-like shape [4]. The morphology of these cocrystals did not have any significant different with the changing of concentration and cooling rate.

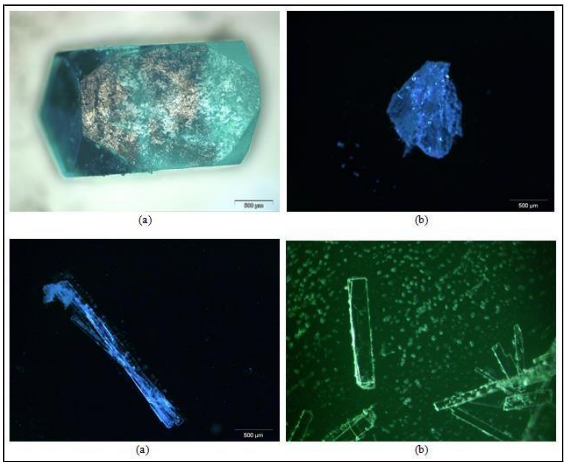

Fig. 7: Morphology of (a) Pure CBZ, (b) Pure FUM, (c) CBZ-FUM Form A cocrystal at 0.10°C/min and (d) CBZ-FUM Form A cocrystal at 0.75°C/min

III. CONCLUSION

This study was done to determine the nucleation kinetics of CBZ-FUM form A cocrystal by employing the Nývlt's theory. Stoichiometric ratio of 1:1 was used to ensure the growth of CBZ-FUM form A cocrystal. First and foremost, the experiments were done by utilizing the polythermal method with two manipulated parameters which are cooling rates and solute concentrations. The cooling rates used are 0.10 °C/min, 0.25 °C/min, 0.50 °C/min and 0.75 °C/min. For each cooling rate, 5 different solute concentration were used which are 0.0451 g/mL, 0.0467 g/mL, 0.0482 g/mL, 0.0512 g/mL and 0.0526 g/mL. During the experiments, the data of crystallization and dissolution temperature were recorded. These data were used to estimate the value of MSZW which are needed in determining the nucleation kinetics of CBZ-FUM form A cocrystals.

From the characterization of the cocrystal, the morphology of CBZ-FUM form A shows plate-like shape for every cooling rate and concentration. However, as the cooling rate start to decrease, the morphology of the cocrystal show small changes since the cocrystals start to elongate. Besides that, the FTIR analysis shows that the presents of both bonds of CBZ and FUM in the cocrystals proving that there are new bonds formed in the cocrystal samples.

From the analysis of the collected data, the values of MSZW were found to increase as the cooling rate and the concentration increase. However, the trend decreased for cooling rate of 0.75 °C/min. Therefore, it is recommended to repeat the experiment by using same cooling rate or add another cooling rate to ensure th trend of MSZW. Similar pattern was found for the nucleation parameters where the nucleation rate, J increase as the cooling rate increase from 0.10 °C/min to 0.50 °C/min, however, for the cooling rate of 0.75 °C/min, the nucleation rate starts to drop for every concentration. The study of nucleation kinetics for cocrystals should be continued further as they are important for the industrial purposes.

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