Indian Journal of Science and Technology, *Vol 10(7), DOI: 10.17485/ijst/2017/v10i7/111216, February 2017*
ISSN (Print) : 0974-6846
ISSN (Online) : 0974-5645

Preliminary Study on Operating Parameters toward the Metastable Zone-Width of Carbamazepine Co-Crystal

Engku Nadia Engku Mat Nasir[1], Fatinah Ab Rahman[1], Syarifah Abd Rahim[1]*, Raihana Zahirah Edros[2] and Nornizar Anuar[3]

[1]Faculty of Chemical and Natural Resources Engineering, Universiti Malaysia Pahang, 26300 Gambang, Pahang, Malaysia; enadia_emnasir@yahoo.com, fatinahabrahman@gmail.com, syarifah@ump.edu.my
[2]Faculty of Engineering Technology, Universiti Malaysia Pahang, 26300 Gambang, Pahang, Malaysia; rzahirah@ump.edu.my
[3]Faculty of Chemical Engineering, Universiti Teknologi MARA, Jalan Ilmu 1/1, 40450 Shah Alam, Selangor, Malaysia; nornizar@salam.uitm.edu.my

Abstract

Objectives: Metastable zone width (MSZW) is a crucial parameter in designing co-crystallization process in order to achieve required crystal habits. The effects of operating parameters toward metastable zone width of carbamazepine-saccharin (CBZ-SAC) co-crystal were studied in this research. **Methods/Statistical Analysis:** Crystallization study was conducted using cooling crystallization method which involves polythermal method. A 250 ml scale size-reactor was used to study the effects of operating parameters on metastable zone width of CBZ-SAC co-crystal which tested with various mol ratio of SAC/CBZ, concentration of CBZ, cooling and heating rates and stirring speeds. Differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and optical microscopy were applied to characterize the CBZ-SAC co-crystals. **Findings:** The results show that MSZW decreases as the mol ratios of SAC/CBZ increases, whilst also decreases with CBZ concentrations, cooling rates and stirring speeds. **Application/Improvements:** Cooling crystallization process is extensively used in the manufacture of pharmaceutical drugs.

Keywords: Co-Crystal, Metastable Zone Width, Nucleation Kinetics, Polythermal Method

1. Introduction

Co-crystallization is considered as an alternative to optimize drug properties as it alters molecular interactions and composition of drug materials. An understanding in co-crystallization process is needed in order to have desirable crystal habits for materials. One of the studies important in designing co-crystallization process is kinetics study. In this work, carbamazepine (CBZ) and saccharin (SAC) were chosen as model compounds. Metastable zone width (MSZW) can be described as the contrast between the saturation temperature and temperature of which the first crystal is discovered at constant cooling rate[1] and is one of the main impressions in industrial crystallization. The method which commonly used to experimentally determine MSZW is polythermal method[2]. Polythermal method is a moment of lowering the temperature below freezing point at which "initial nucleation events" or "primary crystals" are detected in continuously cooled mixture at consistent rate[3]. The temperature of solution is decreased by constant cooling rate from temperature above saturation temperature to a point of temperature at which first crystals are detected[4]. MSZW is heavily influenced by the following parameters including temperature, concentration, cooling rate, impurities and mechanical effects[5].

*Author for correspondence

Nucleation kinetics can be calculated using the Nyvlt's approach[3] from which the data of nucleation order, m and nucleation kinetic constant, k can be obtained. The purpose of this paper is to investigate the effect of concentration of CBZ, mol ratio values of SAC/CBZ, cooling rate and stirring speed on the MSZW of CBZ-SAC co-crystal using polythermal method.

2. Materials and Methods

2.1 Materials

Carbamazepine (CBZ) and Saccharin (SAC) were obtained from ECA Corporation USA and Sigma Aldrich, respectively. Absolute ethanol (EtOH 99.4 %) was used as solvent in producing co-crystals.

2.2 Preparation of CBZ-SAC Co-Crystal

A 250 ml reactor supplied with a stirrer with stirring speeds of 250 and 300 rpm manufactured by Syrris Company was used in this research. The feed materials with the mol ratios of SAC/CBZ (1.0 and 2.0) and CBZ concentrations (19.14 and 17.96 mg/ml) in 200 ml ethanolic solution were prepared. Three heating and cooling rates (0.06, 0.08 and 0.10°C/min) were selected to be used throughout the experiments.

2.3 Determination of Crystallization Temperature and Dissolution Temperature

The initial mixture of 2.0 SAC/CBZ mol ratio and 19.14 mg/ml of CBZ was heated to 60°C with 300 rpm of stirring speed in approximately 1 hour. The mixture was then cooled at a rate of 0.06°C/min. The crystallization temperature of the co-crystal formation was observed visually using eyes and noted. Similar methods were redone with other cooling rates; 0.08 and 0.10°C/min and after that with the various ratio of SAC/CBZ, CBZ concentration and stirring speed. To determine the dissolution temperature, the solution containing the feed materials of predetermined SAC/CBZ mol ratio was dissolved at 60°C for 1 hour. After that the solution was cooled at cooling rate of 0.1°C/min. The solution was then kept constant for 1 hour. The mixture then was heated at a rate of 0.06°C/min to observe the first dissolution temperature. Similar steps were repeated for different heating rates (0.08 and 0.10°C/min) and various mol ratio SAC/CBZ, CBZ concentration and stirring speed.

2.4 Solid-State Characterization

The melting point of the produced co-crystal was determined using differential scanning calorimetry (DSC). A mortar and pestle was used to grind the crystals for smaller sample size and more uniform thermal contact with the standard crucible pan. Sample with weight between 2 to 3 mg was compressed in aluminium pan and analysed in the DSC from 30 to 300°C. The heating rate of 10°C/min was used and nitrogen gas with a flow rate of 50 ml/min was applied to purge vapour product from the heating process. The produced co-crystal was identified using x-ray powder diffraction (XRPD) using RIGAKU (Miniflex II) diffractometer with Cu Kα radiation. The system was run at 30 kV and 15 mA with the 2θ (angle) from 3° to 40°. The step size was 0.01° and the step time was 1 second/step. The shape of the crystals was observed using a Carl Zeiss Model optical microscopy with 5x magnification.

3. Results and Discussion

3.1 Metastable Zone Width (MSZW)

The MSZW was measured by plotting the value of crystallization temperature and dissolution temperature in linear form. The difference between dissolution and crystallization temperature is taken as MSZW[1]. The values of MSZW with the effect of various process parameters of concentration, mol ratio, cooling rate and stirring speed were summarized shown in Table 1.

Table 1. MSZW values of CBZ-SAC

Stirring Speed (rpm)	Concentration (mg/ml)			
	19.14		17.96	
	Mol Ratio (SAC/CBZ)			
	2.0	1.0	2.0	1.0
300	17.49	19.81	14.99	17.46
250	12.74	13.37	9.02	12.86

3.1.1 Effect of CBZ Concentration and Mol Ratio on MSZW

In this work, the effect of CBZ concentration on MSZW was investigated using two CBZ concentrations of 17.96 mg/ml and 19.14 mg/ml. The findings indicate that the MSZW is large for the high CBZ concentration as shown in Table 1. This finding is consistent to the previous work[6].

Higher solution concentration lead to produce more molecules and results in higher probability of molecular collision[7]. Thus, supersaturation increased as the count of nuclei formed increased which is related with nucleation rate becomes high[8]. The nuclei become stable when it reach higher supersaturation and grow faster[7]. This reveals that the nucleation is easy to occur when concentration increase and result in large MSZW.

To determine the influence of mol ratio on MSZW, two mol ratio of SAC/CBZ (1.0 and 2. 0) were used in this study. Table 1 reveals that with the increase of mol ratio, the MSZW decreases for both stirring speeds and CBZ concentrations. An increase in co-former concentration can significantly increase the co-crystallization rate thus the co-crystal can form faster[9] and as a result the MSZW decrease. This could be a determining factor for decreasing MSZW values as the increase of co-crystallization rate enhance the nucleation and crystallization occurs sooner.

3.1.2 Effect of Cooling Rate and Stirring Speed on MSZW

The effect of cooling rate on MSZW was examined by three cooling rates (0.06°C/min, 0.08°C/min and 0.1°Cmin) with various concentrations and mol ratios. From the finding it was found that the MSZW increases as the cooling rate increases. This finding agrees with the work of[10]. Higher cooling rates applied to the system are known able to produce higher solution supersaturation and results in the occurrence of more rapid nucleation rate[11]. Thus, a large amount of small nuclei start to grow with fast growth rate to form crystal[12] and MSZW become increase. The increase of MSZW also possibly due to limit of time requires for the development of a nucleus to a detectable size. When the MSZW measurement process reaches a fast cooling rate as much, the limit time for the development of a nucleus to a detectable size can be disregard and give a large MSZW[13]. This trend is believed due to the larger MSZW values as a result from increasing nucleation rate.

The effect of MSZW on stirring speeds was studied using two stirring speeds of 250 rpm and 300 rpm. In this work, the MSZW calculated is found to be higher for the higher stirring speed as compared to low stirring speed, as shown in Table 1. This result is in accordance with the literature[14]. Higher stirring speed increased the molecules collision and as a result the nucleation rate increased with high supersaturation[15]. As the supersaturation increase, the MSZW increase with increasing stirring speeds[14]. Thus, it is expected that the stirring speed is one of the important parameters for MSZW as the mechanical action applied to the solution make the solute fragments easily adhere to each other and build nuclei.

3.1.3 Nucleation Order, m and Nucleation Kinetic Constant, k of CBZ-SAC

The nucleation kinetic was estimated using the Nyvlt theory. The calculated values of m and k are revealed in Table 2. The finding shows that the nucleation order, m increases as the mol ratio of SAC/CBZ increases with decreasing MSZW. This result is similar to the finding obtained by a previous researcher[6]. The increase in mol ratio enhances the nucleation rate and results in faster formation of co-crystals in the solution[9]. This shows that the increase of nucleation order leads to the occurrence of nucleation and as a result the MSZW become small. However, the increases of stirring speeds do not give significant difference to the nucleation order[16]. On the other hand, the value of nucleation kinetic constant, k is found to increase with increasing concentration[7] for low mol ratio of SAC/CBZ and also increase the MSZW. The results are expected as in higher concentration the super saturation become higher and higher nucleation rate produced which lead to high MSZW.

Table 2. Nucleation order, m and nucleation kinetic constant, k data of CBZ-SAC

Mol Ratio (SAC/CBZ)	Concentration (mg/ml)							
	19.14				17.96			
	Stirring Speed (rpm)				Stirring Speed (rpm)			
	300		250		300		250	
	m	k	m	k	m	k	m	k
2.0	4.03	$6.04x10^{-07}$	4.34	$2.11x10^{-04}$	2.65	$4.49x10^{-05}$	4.42	$9.15 x10^{-04}$
1.0	1.97	$3.69x10^{-04}$	2.99	$3.08x10^{-05}$	2.40	$1.84 x10^{-04}$	3.87	$4.13 x10^{-06}$

3.2 Characterization of CBZ-SAC Co-Crystal

A DSC was applied to discover the melting point of co-crystal formed. The peak profile for the CBZ-SAC co-crystal indicates the melting point of the produced co-crystal and has the same value with reported literature which is 177°C correlates with co-crystals form I[17]. An XRPD was used to identify the peak profile to confirm the CBZ-SAC co-crystal. The first peak has the value of 2θ = 7.07 which in agreement with the reported literature that corresponds to the form I co-crystals[17-19]. Morphological characterization was used to observe the product crystals obtained from cooling crystallization using optical microscopy with 5x magnifications. The morphology shown in Table 3 reveals that the CBZ-SAC co-crystals have the morphology of plate-like crystal for all tested cooling rates and stirring speeds and in agreement to the results obtained by previous studies[19-21]. The results also show that the size of co-crystals produced using higher stirrer speed is smaller. High mixing speeds has decreased the crystal size[22]. This is possibly due to the higher rate of collision between co-crystal with co-crystal, stirrer and reactor wall. With increasing of cooling rates, the size of co-crystal becomes smaller[11]. This is believed due to the increasing MSZW with the increasing cooling rate enhanced the nucleation and as a result the size of co-crystal becomes smaller.

4. Conclusion

In this work, it is found that the CBZ concentration, mol ratio, cooling rate and stirring speed can strongly influence the MSZW. The findings revealed that an increase of CBZ concentrations, cooling rates and stirring speeds resulted in an increase of MSZW value due to higher supersaturation and nucleation rate. However, SAC/CBZ mol ratios increase as MSZW decrease. It is also found that an increase of stirring speeds and cooling rates produced smaller crystal size.

Table 3. CBZ-SAC co-crystals morphology of 17.96 mg/ml CBZ concentration with 5x magnification

Cooling Rate (°C/min)	Stirring Speed (rpm)	
	250	300
0.06		
0.08		
0.1		

5. Acknowledgement

The authors would like to thank Universiti Malaysia Pahang (UMP) for grant assist (RDU160338, RDU140339), equipment and facilities used.

6. References

1. Mullin JW. Oxford: Butterwort-Heinemann: Crystallization, 4th (edn). 2001.
2. Sangwal K. Novel approach to analyze metastable zone width determined by the polythermal method: physical interpretation of various parameters. Crystal Growth and Design. 2009; 9(2):942-50. Crossref
3. Kubota N. A unified interpretation of metastable zone widths and induction times measured for seeded solutions. Journal of Crystal Growth. 2010; 312:548-54. Crossref
4. Bogacz W, Wojcik J. The metastable zone of aqueous solutions. Chemik. 2014; 68(3):198-201.
5. Jin M, Frohberg P, Sun Y, Li P, Yu J, Ulrich J. Study on metastable zone width and crystal growth of a ternary system: case study MgCl2 . 6H2O.1, 4-dioxane. Chemical Engineering Science. 2015; 133:181-9. Crossref
6. Mohammad KA, Abd Rahim S, Abu Bakar MR. Nucleation kinetics of carbamazepine-saccharin (CBZ-SAC) Co-Crystal. International Conference on Global Sustainability and Chemical Engineering (ICGSE). 2014.
7. Anuar N, Wan Daud WR, Roberts KJ, Kamarudin SK, Tasirin SM. An examination of the solution chemistry, nucleation kinetics, crystal morphology, and polymorphic behavior of aqueous phase batch crystallized L-Isoleucine at the 250 mL scale size. Crystal Growth and Design. 2009; 9(6):2853-62. Crossref
8. Liu X, Wang Z, Duan A, Zhang G, Wang X, Sun Z, Zhu L, Yu G, Sun G, Xu D. Measurement of L-arginine trifluoroacetate crystal nucleation kinetics. Journal of Crystal Growth. 2008; 310(10):2590-92. Crossref
9. Rodriguez-Hornedo N, Nehm SJ, Seefeldt KF, Pagan-Tores Y, Falkiewicz JC. Reaction crystal-

lization of pharmaceutical molecular complexes. Molecular Pharmaceutical. 2006; 3(3):362-7. Crossref PMid:16749868

10. Mitchell NA, Frawley PJ. Nucleation kinetics of paracetamol-ethanol solutions from metastable zone widths. Journal of Crystal Growth. 2010; 312(19):2740-46. Crossref
11. Ni X, Liao A. Effects of cooling rate and solution concentration on solution crystallization of l-glutamic acid in an oscillatory baffled crystallizer. Crystal Growth and Design. 2008; 8(8):2875-81. Crossref
12. Kitamura M. In situ observation of growth process of ά-L-Glutamic acid with atomic force microscopy. Journal of Colloid and Interface Science. 2000; 224(2):311-6. Crossref PMid:10727341
13. Hussain K, Thorsen G, Malthe-Sorenssen D. Nucleation and metastability in crystallization of vanillin and ethyl vanillin. Chemical Engineering Science. 2001; 56(1):2295-304. Crossref
14. Kubota N. An interpretation of the metastable zone width concerning primary nucleation in anti-solvent crystallization. Journal of Crystal Growth. 2008; 310:4647-51. Crossref
15. Zou F, Zhuang W, Wu J, Zhou J, Yang P, Liu Q, Chen Y, Ying H. Determination of metastable zone widths and the primary nucleation and growth mechanisms for the crystallization of disodium guanosine 5'-monophosphate from a water-ethanol system. Industrial and Engineering Chemistry Research. 2015; 54:137-45. Crossref
16. Liang K, White G, Wilkinson D. Examination of the process scale dependence of l-glutamic acid batch crystallized from supersaturated aqueous solutions in relation to reactor hydrodynamics. Industrial and Engineering Chemical Research. 2004; 43:1227-34. Crossref
17. Lee MJ, Wang IC, Kim MJ, Kim P, Song KH, Chun NH, Park HG, Choi GJ. Controlling the polymorphism of carbamazepine-saccharin cocrystals formed during antisolvent cocrystallization using kinetic parameters. Korean Journal Chemical Engineering. 2015; 32(9):1910-17. Crossref
18. Porter III WW, Elie SC, Matzger AJ. Polymorphism in carbamazepine cocrystals. Crystal Growth and Design. 2008; 8:14-6. Crossref PMCid:PMC2668533
19. Abd Rahim S, Hammond RB, Sheikh AY, Robert KJ. A comparative assessment of the influence of different crystallization screening methodologies on the solid forms of carbamazepine co-crystals. CrystEngComm. 2013; 15:3862-73. Crossref
20. Kudo S, Takiyama H. Production method of carbamazepine/saccharin cocrystal particles by using two solution mixing based on the ternary phase diagram. Journal of Crystal Growth. 2014; 392:87-91. Crossref
21. Hickey MB, Peterson ML, Scoppettuolo LA, Morrisette LS, Vetter A, Guzman H, Remenar JF, Zhang Z, Tawa MD, Haley S, Zaworotko MJ, Almarsson O. Performance comparison of a co-crystal of carbamazepine with marketed product. European Journal of Pharmaceutics and Biopharmaceutics. 2007; 67:112-9. Crossref PMid:17292592
22. Liszi I, Hasznos-Nezdei M, Farkas B. Effect of mixing on primary nucleation. Hungarian Journal of Industry and Chemistry. 1997; 25(3):181-4.