Indian Journal of Science and Technology, Vol 10(6), DOI: 10.17485/ijst/2017/v10i6/111137, February 2017
ISSN (Print) : 0974-6846
ISSN (Online) : 0974-5645

Effect of Seed Loading and Temperature of Seeding on Carbamazepine-Saccharin Co-Crystal

K. A. Mohammad[1], S. Abd Rahim[2]* and M. R. Abu Bakar[3]

[1]Faculty of Engineering Technology, Universiti Malaysia Pahang, Gambang, Pahang - 26300, Malaysia; kazizul@ump.edu.my
[2]Faculty of Chemical and Natural Resources Engineering, Universiti Malaysia Pahang - 26300, Malaysia; syarifah@ump.edu.my
[3]Kulliyyah of Pharmacy, International Islamic University Malaysia, Bandar Indera Mahkota, Kuantan, Pahang - 25200, Malaysia; rushdi@iium.edu.my

Abstract

Objectives: In pharmaceutical industries, the properties of desired final crystal can be modified by seeding process. Seeding activities depend on seed loading, seed size, seed quality and the temperature of supersaturated solution at the time of seed addition. The effect of amount of seed and temperature of seeding on crystallisation and size distribution of carbamazepine-saccharin (CBZ-SAC) co-crystals have been investigated. **Methods/Statistical Analysis:** 0.5, 1.0 and 1.5 wt% seeds of constant size were added to the metastable zone width region during cooling crystallisation at seeding temperatures of 38.45, 40.35, 42.25, 44.15 and 46.05 °C. **Findings:** During the crystallisation process of CBZ-SAC co-crystal, nucleation occurred faster when seeding is close to the super solubility curve which is at the highest supersaturation. Crystal size distribution (CSD) results showed more fine particles formed at 38.45°C seed temperature. On the other hand, nucleation occurred slower when seeding is close to the solubility curve, which is at low supersaturation and therefore resulted in less number of fine particles formed. **Application:** Nucleation of CBZ-SAC co-crystals can be controlled easily by seeding, in which the addition of seed expedites the crystallisation process by providing the surface area for crystals to grow. The size and characteristic of the desired crystal can be adjusted via seeding application.

Keywords: Carbamazepine-Saccharin, CSD, Co-Crystal Seeding, Seed Loading, Seeding Temperature

1. Introduction

A co-crystal is known as a pharmaceutical co-crystal when the active pharmaceutical ingredients (API) component is combined with other components (i.e. co-formers) in one crystal structure[1]. Several studies have focused on discovering the primary advantages of co-crystals towards enhancing their stability either physically or chemically, improving the moisture uptake and mechanical behaviour. Another major concern among researchers are to improve the rate of dissolution, the solubility, and to enhance the bioavailability of APIs[2]. There are various methods in producing co-crystals such as co-dissolving and evaporating solvent, slurry performing, co-milling, or co-melting[3].

Seeding has been studied over the latest few decades because it can alter the properties of desired final crystal. In seeding process, the supersaturated solution was enhanced by addition of crystalline (seed) to allow the growth of the seed crystals prior to the occurrence of nucleation[4]. As co-crystallisation is concerned, an introduction of seeding are mean to provide a co-crystal phase in solution during crystal growth and to prevent inconsistent primary nucleation of another solid phase during crystallisation[5]. By considering the different parameters in seeding process such as size of seed, amount of seed, seeding temperature and cooling profile, seeding is therefore believed can expedite the nucleation process, optimise the crystallisation behaviour and ensure the final particle size[6].

*Author for correspondence

2. Methodology

2.1 Materials and Equipment

Saccharin (SAC) and Carbamazepine (CBZ) were purchased from Sigma Aldrich and ECA Corporation USA, respectively. The solvent used in co-crystals production was an absolute ethanol (EtOH 99.4 %).The crystalliser was purchased from Syrris Ltd equipped with 250 mL Syrris Globe® glass-jacketed reactor. The reactor was equipped with Globe Reactor Master for data logging and PC software for full control of reaction parameters. Temperature in the jacketed vessel was adjusted via JULABO CF41 circulator, which have an operating temperature between -40°C to +200°C.

2.2 Metastable zone width (MSZW) Determination

Experiments to determine the MSZW of CBZ-SAC co-crystals have been done in previous paper[7]. The experiment was repeated to validate the outcomes. The temperature of initial suspension (SAC/CBZ mole ratio of 2 and CBZ concentration of 17.96 mg/mL in 200 mL ethanol) was increased to 60°C for 40 minutes to ensure that carbamazepine and saccharin compounds were entirely dissolved in the ethanol solution. Afterward, the mixture followed a cooling profile of 0.6°C/min until the nucleation formed, which can be detected by turbidity probe. The solution was kept constant at crystallisation temperature for 40 minutes and then heated at a rate of 0.6°C/min until the value of turbidity begun to decrease. This value of temperature served as a dissolution temperature. The experiments were repeated with different cooling and heating rates (0.2, 0.4 and 0.8°C/min). All experiments were repeated five times to get the consistency of the results. The difference between dissolution and the crystallisation temperature at equilibrium was a MSZW.

2.3 Seed Preparation

The method for preparing seeds was described in Section 2.2. In addition, 20 minutes after the forming of nucleation, the crystal was drained and filtered. The solid was dried for 60 minutes at 30°C.The produced seed crystal was then collected and sieved using 106-125 µm of ASTM standard sieve.

2.4 Seeding Experiments

In this experiment, CBZ-SAC co-crystal solution was prepared, corresponding to a CBZ concentration of 17.96 mg/mL and mole ratio (SAC/CBZ) of 2.0, using a 250 mL jacketed crystallisation vessel equipped with thermocouple, stirrer and turbidity probe. Firstly, the solution was heated to 50°C and the temperature was maintained for 40 minutes to obtain a clear solution. Following, the clear solution was cooled rapidly until the crystal was formed and was heated again to 50°C. Then the temperature was held for 40 minutes to ascertain the complete disintegration of solids which can be shown by a reduction in turbidity value. After that, the temperature of the solution was brought down at a rate of 0.6°C/min until it hit the targeted seeding temperature. When the temperature of the solution reached 46.05°C (95% of MSZW range), 1.5 wt% seed was added whilst the solution continued to follow the temperature profile with a rate of 0.6°C/min. Once the nucleation started, which can be indicated by the changes of turbidity value, the temperature was maintained for 20 minutes before the solution was drained and seed crystal was filtered and collected. The experiment was repeated with different temperature of seeding (85, 75, 65 and 55% of MSZW range) and different amount of seed loading (1.0 and 0.5 wt%).

2.5 Crystal Size Distribution (CSD) of CBZ-SAC Co-Crystal

The crystal size distribution was obtained using laser scattering particle size analyser (Mastersizer 2000®, Malvern Instruments Ltd., Malvern, UK) equipped with Scirocco 2000 for dry particle at an air pressure of 3 bar. The particle size distribution was evaluated by cumulative distribution data. The median diameter was taken for evaluating the particle size of the seeded and unseeded CBZ-SAC co-crystals.

3. Results and Discussion

3.1 MSZW of CBZ-SAC Co-Crystals

Experiments in Section 2.2, with an initial suspension of 2.0 SAC/CBZ ratio and 17.96 mg/mL CBZ in 200 mL ethanol resulted in crystallisation temperature of 27.84°C and a dissolution temperature of 47.55°C. MSZW is defined as

different between dissolution and crystallisation temperature. This result was further used for seeding experiment, where the point of seeding is based on this MSZW. The calculated seeding point is presented in Table 1.

Table 1. Calculated seeding temperature based on MSZW range of 47.55 to 27.84°C

Seeding temperature (% of MSZW)	Calculated seeding temperature [°C]
95	46.05
85	44.15
75	42.25
65	40.35
55	38.45

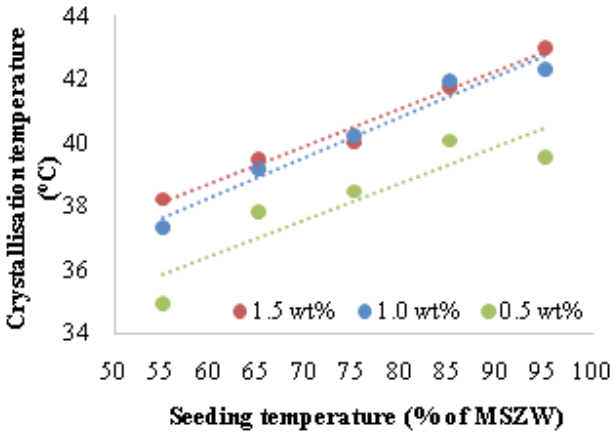

Figure 1. Effect of Seed Loading and Seeding Temperature on Nucleation.

3.2 Effect of Seed Loading on Crystallisation of CBZ-SAC Co-Crystal

Figure 1 demonstrates that, the crystallisation temperature increased with seed loading. When the seed was added at 55% of MSZW, which equivalent to 38.45°C, the crystallisation temperature for 0.5, 1.0 and 1.5 wt% of seed was 34.95, 37.33 and 38.22°C respectively. The seed provides surface area for nucleation to occur; therefore higher seed loading resulted in higher surface area[8,9], which expedites the nucleation process. Therefore, the nucleation occurs faster for seed loading of 1.5 wt%. Similar trends were also can be seen for seeding temperature of 65, 75, 85, and 95% of MSZW range shown in Figure 2. The present finding also support which studied the crystallisation of hen-egg white lysozyme and concluded that a lower seed loading resulted in slow growth of crystals due to the less particle surface area, therefore resulted in higher supersaturation (low crystallisation temperature)[10].

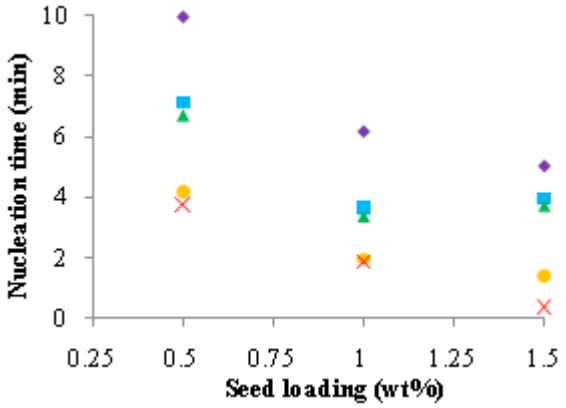

Figure 2. Effect of Seed Loading on Nucleation Rate for Different Seeding Temperatures (°C); 46.05, 44.15, 42.25, 40.35, 38.70.

3.3 Effect of Seeding Temperature on Crystallisation of CBZ-SAC Co-Crystal

As indicated in Figure 1, the crystallisation temperature increased with the seeding temperature. The presence of seed particles has significantly narrowed the metastable zone[10,11]. During seeding experiment, the solution temperature was reduced at a constant cooling rate. The earlier introduction of seed (higher seeding temperature) resulted in earlier forming of nucleation. Therefore, the seeding temperature of 1.5 wt% of seed at 95% of MSZW gave the crystallisation temperature of 43.02°C, whereas seeding at 55% of MSZW gave the crystallisation temperature of 38.22°C. In kinetics view, seeding closed to the solubility curve (46.05°C), which is at low supersaturation level causing a slow nucleation rate and therefore longer time is required for nucleation to occur[11,12] (Figure 2).

3.4 Effect of Seeding Temperature on CSD of CBZ-SAC Co-Crystal

Figure 3 exhibits that, more fine particles formed at seeding temperature of 38.45°C (55% of MSZW) compared to the seeding temperature of 44.15°C (95% of MSZW). The supersaturation is highest at metastable zone limit (0% of MSZW). Therefore, seeding at higher supersaturation leads to the faster nucleation rate which later resulting in more fine particles. On the other hand, nucleation occurred slower when seeding is close to the solubility curve which is at low supersaturation and therefore

resulted in least number of fine particles formed. The result is in lines of earlier literature that particle growth is slower if seeding close to the MSZ limit (38.45°C), which resulted in the least particle growth. Meanwhile, seeding close to the solubility curve (46.05°C) produces the highest relative growth rate and the greatest number of large particles. Similar finding by O'Sullivan et al.[12], which studied the effect of seeding temperature on agomelatine–citric acid co-crystal found that, when the system seeded early (at higher seeding temperature; i.e. 60°C), resulted in larger crystal size. This was due to crystal growth dominated over nucleation because of the concentration was still deep in the MSZ at the time of seeding[11].Another parameter that can increase the size of crystal produced are faster cooling rate and higher initial supersaturation[13].

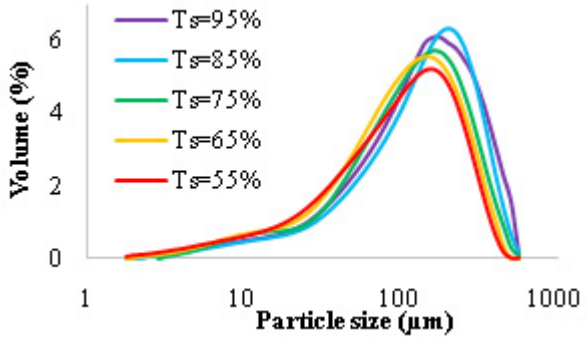

Figure 3. Effect of Seeding Temperature on CSD of CBZ-SAC Co-Crystal.

4. Conclusion

The present research was aimed to investigate the effect of seed loading and temperature of seeding on CBZ-SAC co-crystals. These findings suggest that in general the seed loading and the temperature of seeding strongly influences the crystallisation kinetic parameters and the produced crystals size distribution. Seed serves as a surface area for initiating the nucleation. By increasing the amount of seed, more surface area exists and therefore the nucleation is likely to occur. Nucleation forms faster in high supersaturated solution. More fine particles can be obtained if seeding in high supersaturated solution. Seeding close to the solubility curve (at 46.05°C) resulted in larger crystal size compared to the seed added close to MSZ limit. The results of this study also indicates that the effect of seeding in co-crystal is similar with that in crystal. Further studies investigating the morphology of seeded and unseeded CBZ-SAC co-crystals, effect of cooling rates and the effect of stirring speed, with different SAC to CBZ molar ratios and various concentration of CBZ, are strongly recommended. The International Conference on Fluids and Chemical Engineering (FluidsChE 2017) is the second in series with complete information on the official website[14] and organised by The Center of Excellence for Advanced Research in Fluid Flow (CARIFF)[15]. The publications on products from natural resources, polymer technology, and pharmaceutical technology have been published as a special note in volume 2[16]. The conference host being University Malaysia Pahang[17] is the parent governing body.

5. Acknowledgement

This work was supported by Universiti Malaysia Pahang, UMP with sufficient grants (RDU 140339).

6. References

1. Ghadi R, Ghuge A, Ghumre S, Waghmare N, Kadam VJ. Co-Crystals: Emerging Approach in Pharmaceutical Design. Indo American Journal of Pharmaceutical Reserach. 2014; 4(7):3881–92.
2. Duggirala NK, Perry ML, Almarsson Ö, Zaworotko MJ. Pharmaceutical Cocrystals: Along the Path to Improved Medicines. Chemical Communication. 2016; 52:640–55. https://doi.org/10.1039/C5CC08216A PMid:26565650
3. Hattori Y, Sato M. Otsuka M. Initial Dissolution Kinetics of Cocrystal of Carbamazepine with Nicotinamide. The Journal of Pharmacy and Pharmacology. 2015; 67(11):1512–8. https://doi.org/10.1111/jphp.12461 PMid:26285918
4. Ulrich J. Jones MJ. Industrial Crystallization Process Monitoring and Control.Wiley-VCH Verlag & Co. KGaA; 2012.p.127–38.
5. Gagniere E, Mangin D, Veesler S, Puel F. Pharmaceutical Salts and Co-crystals. The Royal Society of Chemistry. 2012;188–211.
6. Aamir E, Nagy ZK, Rielly CD. Optimal Seed Recipe Design for Crystal Size Distribution Control for Batch Cooling Crystallisation Processes. Chemical. Engineering Science. 2010; 65(11):3602–14. https://doi.org/10.1016/j.ces.2010.02.051
7. Mohammad KA, Abd Rahim S. Abu Bakar MR. Nucleation Kinetics of Carbamazepine-Saccharin (CBZ-SAC) Co-crystal. Proceedings of the International conference on Global sustainability and chemical Engineering, Springer; 2015.p.263.

8. Mousaw P, Saranteas K, Prytko B. Crystallization Improvements of a Diastereomeric Kinetic Resolution through Understanding of Secondary Nucleation. Organic Process Research and Development. 2008; 12(2):243–8. https://doi.org/10.1021/op700276w
9. Long B, Yang H, Ding Y. Impact of Seed Loading Ratio on the Growth Kinetics of Mono-Ammonium Phosphate under Isothermal Batch Crystallization. Korean Journal of Chemistry Engineering. 2016; 33(2):623–8. https://doi.org/10.1007/s11814-015-0173-0
10. Liu JJ, Ma CY, Hu YD, Wang XZ. Effect of Seed Loading and Cooling Rate on Crystal Size and Shape Distributions in Protein Crystallization- A Study Using Morphological Population Balance Simulation. Computers & Chemical Engineering. 2010; 34(12): 1945–52. https://doi.org /10.1016/ j.compchemeng.2010.06.020
11. Holaň J, Ridvan L, Billot P, Štěpánek F. Design of Co-Crystallization Processes with Regard to Particle Size Distribution. Chemical Engineering Science. 2015; 128:.36–43.
12. O'Sullivan B, Smith B, Baramidze G. Recent Advances for Seeding a Crystallization Process. http://www.selectscience.net/downloads/articles/7764_2013_09_16_Seeding-A4.pdf. Date accessed: 2013.
13. Zhang F, Liu T, Huo Y, Guan R, Wang XZ. Investigation of the Operating Conditions to Morphology Evolution of β-l-Glutamic Acid during Seeded Cooling Crystallization. Journal of Crystal Growth.2016 https://doi.org/10.1016/j.jcrysgro.2016.09.041
14. FluidChe 2017 Available from: http://fluidsche.ump.edu.my/index.php/en/
15. The Center of Excellence for Advanced Research in Fluid Flow (CARIFF) Available from: http://cariff.ump.edu.my/
16. Natural resources products prospects - International Conference on Fluids and Chemical Engineering FluidsChE 2017 Malaysia,). Indian Journal of science and technology. 2017; S2(1).
17. University Malaysia Pahang. Available from: www.ump.edu.my