CRYSTAL SIZE DISTRIBUTION CHARACTERISATION OF CARBAMAZEPINE-SACCHARIN CO-CRYSTAL IN BATCH COOLING CRYSTALLISATION

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We hereby declare that We have checked this thesis, and in our opinion, this thesis is adequate in terms of scope and quality for the award of the degree of Master of Science.

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I hereby declare that the work in this thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at Universiti Malaysia Pahang or any other institutions.

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ABSTRAK

Carbamazepine (CBZ) mempunyai masalah kadar penyerapannya yang perlahan ketika diberikan melalui oral di mana dos ubat yang lebih tinggi diperlukan agar berkesan untuk merawat pesakit. Baru-baru ini, kristal carbamazepine-sakarin (CBZ-SAC) telah dilaporkan dapat meningkatkan kelarutan melalui kaedah penghabluran larutan. Kelarutan kristal bersama CBZ-SAC kebanyakannya dipengaruhi oleh faktor-faktor seperti luas permukaan, transformasi fasa, taburan saiz kristal, dan dinamika bendalir. Untuk mendapatkan sifat kristal yang diinginkan, parameter operasi harus dikendalikan dalam lebar zon metastabil (MSZW) sepanjang proses penghabluran. Terdapat laporan terhad mengenai kristal bersama CSD CBZ-SAC. Oleh itu, taburan saiz kristal carbamazepine-sakarin dalam penghabluran penyejukan kumpulan telah dikaji dalam kajian ini. Kaedah polythermal penyejukan penghabluran dilakukan untuk mengkaji MSZW dan CSD CBZ-SAC dalam penyejukan penghabluran dengan menguji dengan nisbah mol SAC ke CBZ yang berbeza, kadar penyejukan yang berbeza dan kelajuan putaran yang berbeza pada pelbagai kepekatan CBZ. Kristal bersama CBZ-SAC dicirikan menggunakan penganalisis ukuran zarah, pengimbas kalorimeter (DSC), difraksi serbuk sinar-X (XRPD), pengimbas sinar merah (FTIR) dan mikroskop optik. Hasil kajian mendapati bahawa kepekatan meningkatkan suhu penghabluran, Tcryst dan suhu larut, Tdiss juga meningkat. MSZW lebih tinggi untuk kepekatan CBZ dan kelajuan putaran yang lebih tinggi. Urutan nukleasi, m meningkat apabila nisbah mol SAC / CBZ meningkat dengan penurunan MSZW. Nilai pemalar kinetik nukleasi, k didapati meningkat dengan peningkatan kepekatan untuk nisbah mol rendah. Sementara itu, untuk penyejukan perlahan kajian CSD terhadap kristal CBZ-SAC, ukuran kristal CSD yang luas dan purata saiz kristal yang lebih besar didapati pada kepekatan CBZ yang lebih tinggi dengan kelajuan putaran yang rendah. CSD yang sempit dan ukuran purata kristal yang lebih kecil diperhatikan pada kelajuan putaran yang lebih tinggi untuk semua nisbah mol dan kadar penyejukan. Kajian CSD kristal CBZ-SAC untuk penyejukan pantas juga menunjukkan CSD luas dengan ukuran purata kristal besar dan CSD sempit dengan ukuran purata kristal kecil pada kepekatan CBZ yang lebih tinggi untuk nisbah mol berbeza dan kadar penyejukan. Analisis pencirian DSC, XRPD dan FTIR menunjukkan bahawa pepejal yang dihasilkan adalah bentuk I kristal CBZ-SAC. Mikroskop optik menunjukkan bahawa bentuk I Kristal CBZ-SAC mempunyai morfologi kristal seperti plat. Dapatan daripada kajian ini boleh digunakan dalam pemprosesan kristal, pengendalian dan penyimpanan terutama dalam industri farmaseutikal.

ABSTRACT

Carbamazepine (CBZ) has a problem of slow rate of absorption when administered orally in which a larger dose of the drug is needed in order to be effective in treating patients. Recently, the carbamazepine-saccharin (CBZ-SAC) co-crystal has been reported to improve the solubility through solution crystallisation method. The solubility of CBZ-SAC co-crystal is mostly influenced by factors such as surface area, phase transformation, crystal size distribution (CSD), and fluid dynamics. In order to obtained the desired crystal properties, the operating parameters should be controlled in the metastable zone width (MSZW) throughout the crystallisation process. There is limited report on the CSD of CBZ-SAC co-crystal therefore, the crystal size distribution of carbamazepine-saccharin co-crystal in batch cooling crystallisation was studied. Polythermal method of cooling crystallisation was conducted to study the MSZW and CSD of CBZ-SAC co-crystal by testing with different mole ratio of SAC to CBZ, different cooling rates and different stirring speeds at various concentration of CBZ. The CBZ-SAC co-crystal were characterised by using particle size analyser, differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), Fourier transforms infrared (FTIR) and optical microscopy. The findings found that the concentration increases the crystallisation temperature, Tcryst and dissolution temperature, Tdiss also increased. The MSZW is higher for the higher CBZ concentration and stirring speed. The nucleation order, m increases as the mole ratio of SAC/CBZ increases with decreasing MSZW. The value of nucleation kinetic constant, k is found to increase with the increasing concentration for low mol ratio. Meanwhile, for slow cooling of CSD study of CBZ-SAC co-crystal, the broad CSD and larger mean crystal size is found at higher concentration of CBZ with low stirring speed. The narrow CSD and smaller mean crystal size is observed at higher stirring speed for all mole ratio and cooling rate. The CSD study of CBZ-SAC co-crystal for fast cooling also shows broad CSD with large mean crystal size and narrow CSD with small mean crystal size at higher CBZ concentration for different mole ratio and cooling rate. The characterisation analysis of DSC, XRPD and FTIR revealed that the produced solid is CBZ- SAC co-crystal Form I. Optical microscopy showed that the CBZ-SAC co-crystal Form I have the morphology of plate-like crystal. The findings obtained in the study are useful in the crystal processing, handling and storage especially in pharmaceutical industries.

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