SOLID PHASE TRANSFORMATION OF CARBAMAZEPINE-SUCCINIC CO-CRYSTAL

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Thesis submitted in partial fulfilment of the requirements
for the award of the degree of
Bachelor of Chemical Engineering

Faculty of Chemical & Natural Resources Engineering
UNIVERSITI MALAYSIA PAHANG

JULY 2014

ABSTRACT

This paper presents the solid phase transformation of carbamazepine-succinic co-crystal. Solvent evaporation, slurry crystallization and cooling crystallization are the three techniques which represent the solution based method were used. In this study ethanol was used as solvent. CBZ-SUC co-crystals formations are studied by varying the mol ratio of CBZ and SUC. The CBZ-SUC co-crystals formation was characterized by using X-ray powder diffraction (XRPD), and optical microscopy. From the XRPD pattern profile, it shows that the co-crystals were formed for all the ratio of CBZ and SUC by the slurry crystallization and cooling crystallization. The results shows that the pattern profiles representing the co-crystal as no peak are develop with the raw material peak. The morphology of the co-crystals formation is needle-like co-crystals for cooling crystallization and solvent evaporation. The morphology of slurry crystallization is difficult to characterize due to agglomeration effects. Results from this research may be useful in pharmaceutical industry as the co-crystals are successfully formed.

ABSTRAK

Kertas kerja ini menunjukkan penjelmaan fasa pepejal carbamazepine - succinic bersama kristal. Penyejatan pelarut, buburan penghabluran dan penyejukan penghabluran adalah tiga teknik yang digunakan. Dalam kajian ini etanol telah digunakan sebagai pelarut. Pembentukan CBZ - SUC bersama kristal dikaji dengan mengubah nisbah mol bagi CBZ dan SUC . Pembentukan CBZ - SUC bersama kristal dicirikan dengan menggunakan X -ray serbuk pembelauan (XRPD), dan mikroskop optik. Dari profil corak XRPD, ia menunjukkan bahawa kristal telah membentuk untuk semua nisbah CBZ dan SUC oleh penghabluran buburan dan penyejukan penghabluran. Keputusan menunjukkan bahawa profil corak mewakili kristal kerana tidak ada puncak yang wujud antara puncak bahan mentah. Morfologi pembentukan kristal adalah seperti jarum bersama kristal untuk penghabluran dan penyejatan pelarut penyejukan. Morfologi buburan penghabluran adalah sukar untuk dicirikan kerana kesan penumpuan. Hasil daripada kajian ini mungkin berguna dalam industri farmaseutikal kerana kristal berjaya dibentuk.

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LIST OF ABBREVIATIONS

APIs	Active pharmaceutical ingredients
CBZ	Carbamazepine
SUC	Succinic
DSC	Differential scanning calorimetry
XRPD	X-ray powder diffraction
FTIR	Fourier transforms infrared spectroscopy
SEM	Scanning electron microscopy
SSNMR	Solid state nuclear magnetic resonance spectroscopy

LIST OF SYMBOLS

°C	degree Celsius
J/g	Joule per gram
W/g	Watt per gram
ml	millilitre

1 INTRODUCTION

1.1 Background

In the pharmaceutical industry, many life-saving drug compounds have to be disposed during the commercial production due to their low solubility. The successful development of new drugs has become the main challenges for the solubility improvement of poorly water soluble drug compounds (Qiao et al., 2012). Therefore, the improvement of the physicochemical properties of active pharmaceutical ingredients (APIs) has become an interest in the pharmaceutical industry. Many company in this industry has give the efforts and resources on the discovery of new crystalline forms of their APIs.

Pharmaceutical co crystallization is technologies that provide a way for improving physicochemical and biopharmaceutical properties of APIs. This improvement of the properties of APIs is achieved through the development of a new class of crystalline solids, called pharmaceutical co crystals (Padrela et la., 2010). The pharmaceutical co crystal is done by the mixture of API and coformer like pharmaceutically acceptable molecule inside a crystal lattice. Therefore, co crystals increase the diversity of API form (Vitthalrao et al., 2013).

Co crystals is the materials that are formed between a molecular or ionic API and a co crystal former that is a solid at room temperature, containing two or more discrete molecular entities in the crystal lattice (Almarsson et al., 2004). Co crystals are a multicomponent system in which two or more components crystallize into the same crystal lattice with distinctive physicochemical properties from the individual parent compounds. The formation of co-crystal occurs through hydrogen bond interactions between the drug and coformers. Acids and amides are widely used in research as coformers for CBZ co crystals due to their available hydrogen bonding sites (Weyna et al., 2009).

The co crystals can be prepared by various methods. It consists of solid-based methods or solution-based methods. Solution based method consists of solvent evaporation,

cooling crystallization and slurry crystallization. Besides, solid based method involves of solid state grinding and hot melt extrusion.

The co-crystal produced can be characterized by using powder X-ray diffraction (PXRD), single crystal X-ray diffraction (SXRD), Fourier transform infrared spectroscopy (FTIR), Raman spectroscopy, differential scanning calorimetry (DSC), solid state nuclear magnetic resonance spectroscopy (SSNMR), scanning electron microscopy (SEM), and terahertz spectroscopy.

1.2 Motivation and statement of problem

Drug molecules with limited aqueous solubility are the common issue in the research and development portfolios of discovery focused pharmaceutical companies (Blagden et al., 2007). Pharmaceutical development will be challenging as the issue of poor solubility of drug molecule may possibly cause to slow dissolution in biological fluids, insufficient and inconsistent systemic exposure and consequent lack efficacy in patients, particularly when delivered through the oral route of administration (Blagden et al., 2007). In the pharmaceutical industry, it is the poor biopharmaceutical properties rather than toxicity or lack of efficacy that are the main reasons why less than 1% of active pharmaceutical compounds sometime produce into the marketplace (Aakeroy et al., 2009). Among these biopharmaceutical properties, solubility remains a key issue (Blagden et al., 2007), with drugs often damaged during commercial production due to their low solubility.

Currently, one of the main challenges for the pharmaceutical industry is to improve the solubility of drug. The improvement of solubility and dissolution profiles of these drug molecules without changing the molecular structure is a special challenge for the successful development of pharmaceutical products (Thakuria et al., 2013). Since a long time ago, there is the interest in the design of pharmaceutical co crystals, which becomes as a potential method for improving the bioavailability of drugs with low aqueous solubility (Aakeroy et al., 2009). The improvements in the pharmaceutical sciences have provided several ways for solving the issues of low aqueous solubility (Blagden et al., 2007). Although some techniques are effective in order to improve the oral bioavailability, the successes of the ways are dependent at times on the specific

physicochemical nature of the molecules being studied. Therefore, a pharmaceutical co crystal can be designed with the aims to improve the solid-state properties of an API without influence its natural structure (Qiao et al., 2011). A solution based method is carried out in order to determine the possibility of the formation of co-crystals from two components.

1.3 Objective

The following is the objective of this research:

- To determine the stable region of carbamazepine-succinic (CBZ-SUC) co-crystals formation using solution based method.

1.4 Scope of this research

The following are the scope of this research:

i) Preparation of co-crystal by using solution based method which involve of solvent evaporation, slurry crystallization and cooling crystallization by using ethanol as a solvent.

ii) Varied to a different mol ratio of CBZ and SUC in order to study the CBZ-SUC co-crystal formation.

iii) Characterizations and analysis of the physical characterization of the co-crystal by using X-ray powder diffraction (XRPD), differential scanning calorimeter (DSC) and optical microscopy.

1.5 Organisation of this thesis

The structure of the reminder of the thesis is outlined as follow:

Chapter 2 provides a literature review about the co-crystals based on the methods of co-crystals formation. This chapter also provides the characterization of co-crystals techniques. All the relevant journal, technical paper and books are taken from those researchers will be studied and discussed in this chapter.

Chapter 3 gives a review of the methods used in this study which consists of experimental methods and characterization methods. More details and operating procedures are explained in this chapter. It also covered the material used in this study.

Chapter 4 covers on the results and discussion of the research from the experimental methods and characterization methods. All the experimental result and data is discussed in details which involves screening methods and characterization of co-crystal with different mol ratio.

Chapter 5 draws together a summary of the thesis and outlines the future work with some of the recommendations that can be taken in conducting the research.

2 LITERATURE REVIEW

2.1 Overview

This paper presents on co-crystals, methods of co-crystals formation and characterization of co-crystals techniques.

2.2 Introduction

This study is about the co-crystals based on the methods of co-crystals formation which involves of solvent evaporation, slurry crystallization, cooling crystallization, solid state grinding and hot melt extrusion. The characterization of co-crystals techniques consists of differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and x-ray powder diffraction (XRPD).

2.3 Co-crystals

Pharmaceutical co-crystals have recently been suggested as good materials in drug discovery and development (Almarsson, 2004). A pharmaceutical co crystal is defines as a co crystal with one of the co crystal components as an Active Pharmaceutical Ingredient (API) and the other components are known as coformers. From the definition, it state that an API hydrate is not a co crystal, however a solid-state API hydrate can co crystallise with a solid coformer to form a co crystal (Chieng et al., 2009). Co-crystals are self-assembled at the molecular scale and can significantly expand the number of crystal forms of a given API over polymorphs, solvates and salts (Almarsson, 2004).Co-crystals may also play a role in modifying the physical properties of an API, including stability, solubility and dissolution(Remenar, 2003). Several co-crystals of carbamazepine have been reported (Fleischman, 2003). According to Aakeroy and Salmon (2005), the co crystal involves of two or more components of structurally homogeneous crystalline materials exists in exact stoichiometric amounts. It is important to note that a co crystal is a single phase of multiple components and not a mixture of single component crystalline phases (Seefeldt et al., 2006). Co crystals are multiple component crystals that often rely on hydrogen bonds between neutral molecules (Seefeldt et al., 2006). The co crystal components are different neutral molecular reactants which are solids at ambient temperature (Qiao et al, 2011). Co

crystals are an important class of pharmaceutical materials that can improve solubility and dissolution by forming a crystal of a drug and other favourable molecule or coformer with certain stoichiometric compositions (Thakuria et al., 2013). In order to control co crystals solubility several ways is provide by the wide range of conformer properties and interactions in the solid and solution phases. Co-crystals have different physical properties such as habit, bulk density, solubility, compressibility, friability, melting point, hygroscopy, and dissolution rate (Steed, 2013).Formation of a co-crystal is aimed to transform an amorphous or hard-to-crystallise API into a readily handled, stable crystalline solid (Steed, 2013).

2.4 Methods of Co-crystal Formation

There are a lot of methods that have been proposed for the preparation of co crystals due to the great interest in the area. The co crystal preparation methods consist of solid-based methods or solution-based methods. The solid-state method involves a stoichiometric mixture of drug and coformer and, since stoichiometric or nonstoichiometric experiments can be carried out in solution, the solution-based methods are based on the saturation condition of the co crystal systems (Alhalaweh, 2012). Solution based method includes solvent evaporation, cooling crystallization and slurry crystallization. While, solid based method involves of solid state grinding and hot melt extrusion.

2.4.1 Solvent Evaporation

Co crystallisation by evaporation of stoichiometric solutions is depends on the use of solvents or solvent mixtures where the co crystal is saturates and the components have same solubility (Qiao et al., 2011). Solvent evaporation consist super saturation of solution by evaporation, cooling and addition of solubility changing solvent or substance. Solvent evaporation involves of preparation of two or more suspensions by dissolution of stoichiometric amounts of materials in a solvent, mixing of suspensions and storage under suitable temperatures for co-crystallization (Vitthalrao et al., 2013).

2.4.2 Cooling Crystallization

Cooling crystallisation is the method of varying the temperature of the crystallisation system, which has a great interest for its potential of a large scale of co crystal production. First, large amounts of reactants and solvent are mixed in a reactor typically

a jacketed vessel, and then the system is heated to a higher temperature to make sure all solutes are totally dissolved in the solvent and is followed by a cooling down step (Qiao et al., 2011). Co crystals will precipitate when solution becomes supersaturated with respect to co crystal as the temperature drops down (McNamara et al., 2006).

2.4.3 Slurry Crystallization

Slurry crystallization is the method that involves the addition of crystallization solvent in the components like API along with its acceptable former. The selection of this method is based on the physical stability of the crystallization solution to co crystals and its solid former. The study on synthesis of co crystals through slurry crystallization was done in sixteen co crystal system with optimum result (Vishwashwar et al., 2006).Preparation of co crystals for Trimethoprim and sulfamethoxazole through slurry technique used simple distilled water as solvent and while, co crystals of aspirin is designed with 4, 4-Dipyridil as a conformer is done by using slurry crystallization method (Mundhe et al., 2013).

2.4.4 Solid State Grinding

Solid state grinding is an alternative method for solution based co crystallization process. Particle size reduction is done in mixture which increases the covalent reactivity. This method has increase in selectivity and simplicity over solution crystallization technique. The application of solid state grinding was studied using six co crystals of sulfadimidine with anthranillic acid and salicylic acid, the co-crystal of sulfadimidine –salicylic acid while grinding with anthranillic acid (Mundhe et al., 2013). The replacement of Salicylic acid with anthranillic acid occurs because of usual pattern of hydrogen bonding of both of co crystals (Trask et al., 2005). The hydration of caffeine is reported but the study of preparation by solid grinding in a ball mill is also proved (Trask et al., 2005). The hydrogen bonding preferences was showed in number of fact for modification in solid grinding method (Kurod et al., 2002). The solid grinding produced co crystals which were not possible by solution evaporation. This method was used for formation of co crystal phase with several coloristic properties (Jones et al., 20050. The solid grinding approach is having problem of polymorphic transition during the process which causes in dangerous side effect.

2.4.5 Hot Melt Extrusion

Extrusion is one of the methods for synthesis of cocrystals which involves highly efficient mixing, improved surface contacts and solvent is not use in the co crystals preparation (Mundhe et al., 2013). The selection of this method is based on thermodynamic stability of compound. This method was studied with the use of four models for cocrystal formation (Dhumal et al., 2010). Solvent drop extrusion technique used to optimize and make the process more flexible. Solvent drop extrusion technique gives an advantage to do the process at lower temperature. Hot melt extrusion method was used in synthesis of Carbamazepine-nicotinamide cocrystals with polymer as former (Ruecroft, 2005). Continuous cocrystallization, API and coformer poured in the twin extruder and thus the barrel temperature also increases.

2.5 Characterization of Co-crystals Techniques

The co-crystal characterization is involves structural assessment and properties evaluation. There are several analytical techniques which are used for characterization of crystal structures and properties evaluation. The basic physicochemical properties of co crystal can usually be characterised by powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC).

2.5.1 Differential Scanning Calorimetry

DSC is the most widely used technique for the thermal property testing of co crystals. It is the chosen technique for obtaining comprehensive melting point data and additional thermal data, like the enthalpy of melting, can also be determined simultaneously. Besides to being a characterisation technique, DSC has recently been used as a screening tool for rapid co crystal screening (Lu et al., 2008; Mohammad et al., 2011). From Figure 2.1, it shows the DSC thermograms of pure components and the co crystals prepared by various methods. It can be observed that all the components have a single melting point with endothermic peaks. The heat of fusion and the onset temperature also could be obtained.

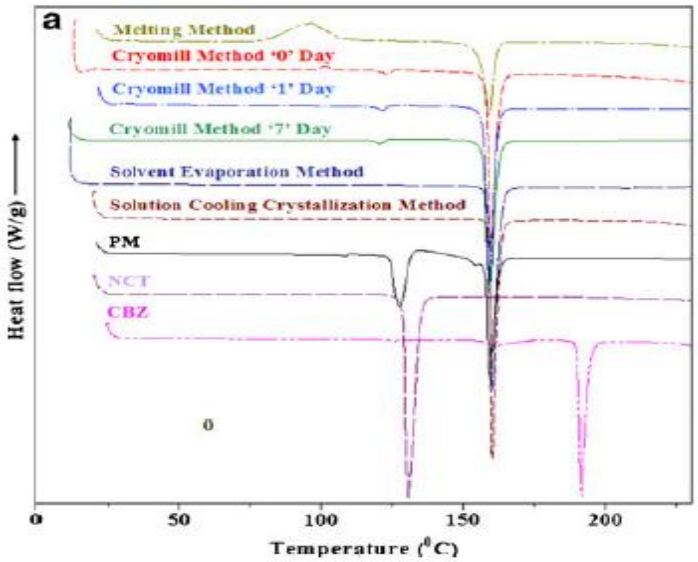

Figure 2-1: DSC thermograms of CBZ, NCT, and cocrystals (Sources: Seefeldt et al., 2006)

2.5.2 Fourier Transform Infrared Spectroscopy

Fourier Transform Infrared Spectroscopy (FTIR) is used to detect possible co crystallization. It is widely used for spectroscopic technique in determining the chemical conformation compounds. From the Figure 2.2, the co crystals prepared by the solution cooling crystallization method showed changes in the peak positions of carbonyl and amide groups, which suggested interactions between the CBZ and NCT and a new phase formation (Rahman et al., 2011).The co crystals prepared by the solvent evaporation and melting method also showed characteristic peaks of the co crystals at 1,655, 1,681, 3,386, and 3,446 cm−1, which show hydrogen bond formation between CBZ and NCT. This showed the present of unreacted CBZ which had not transformed into the co crystals.

2.5.3 X-Ray Powder Diffraction

X-ray Powder Diffraction (XRPD) is one of the primary techniques used to examine the physico-chemical properties of co crystals. XRPD gives a unique 'fingerprint' diffraction pattern characteristic of a particular solid form and does not need the growth of high-quality single crystals to obtain the data (Steed, 2013). From the XRPD, the new compound form and the possibility of co-crystals form for the compound can be easily seen based on the powder diffractogram. The diffractograms of the CBZ, NCT, and co

crystals are shown in Figure 2.3. The diffractogram of CBZ and its dehydrate forms showed sharp peaks at 2θ values. The diffractogram of NCT showed peaks at 2θ values. This showed the formation of a new crystalline phase.

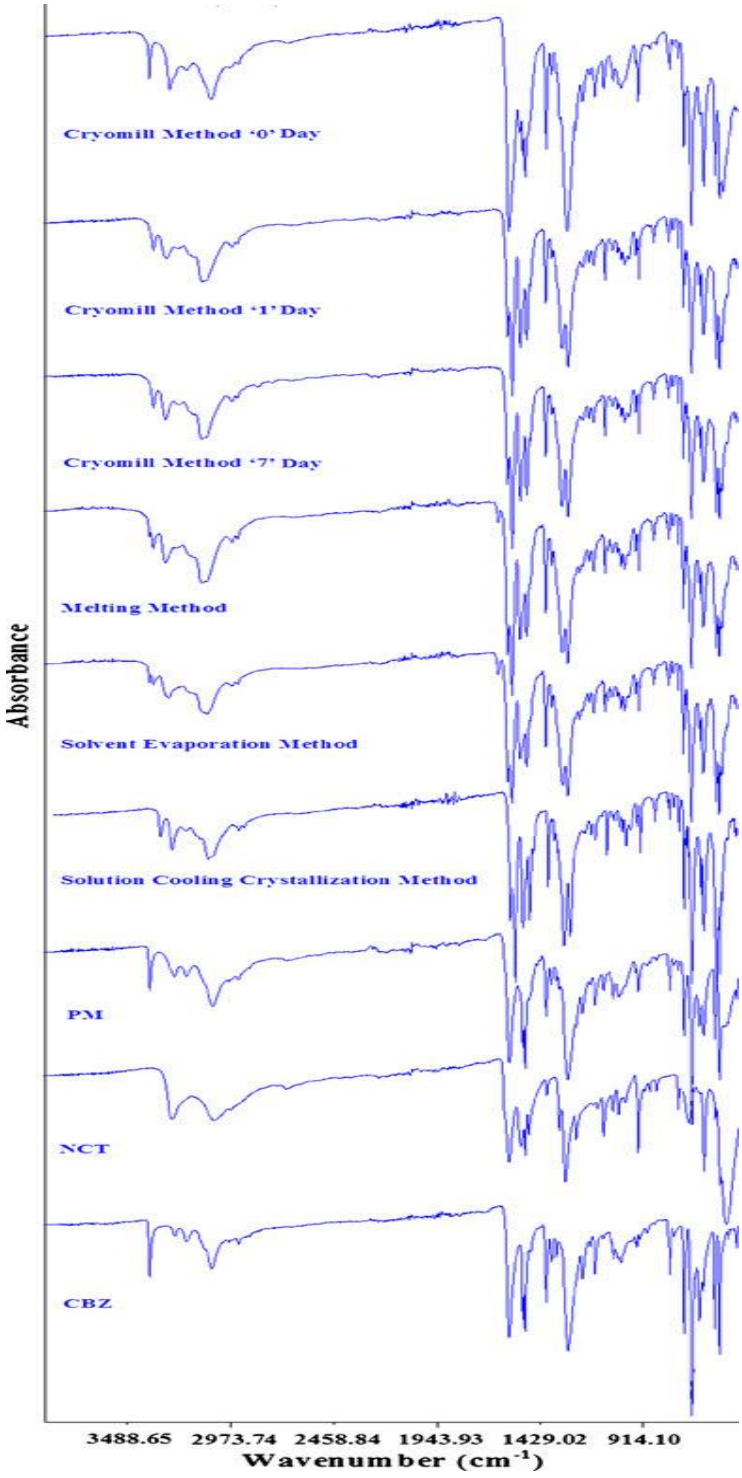

Figure 2-2: FTIR spectra of CBZ, NCT, and cocrystals (Source: Rahman et al., 2011)

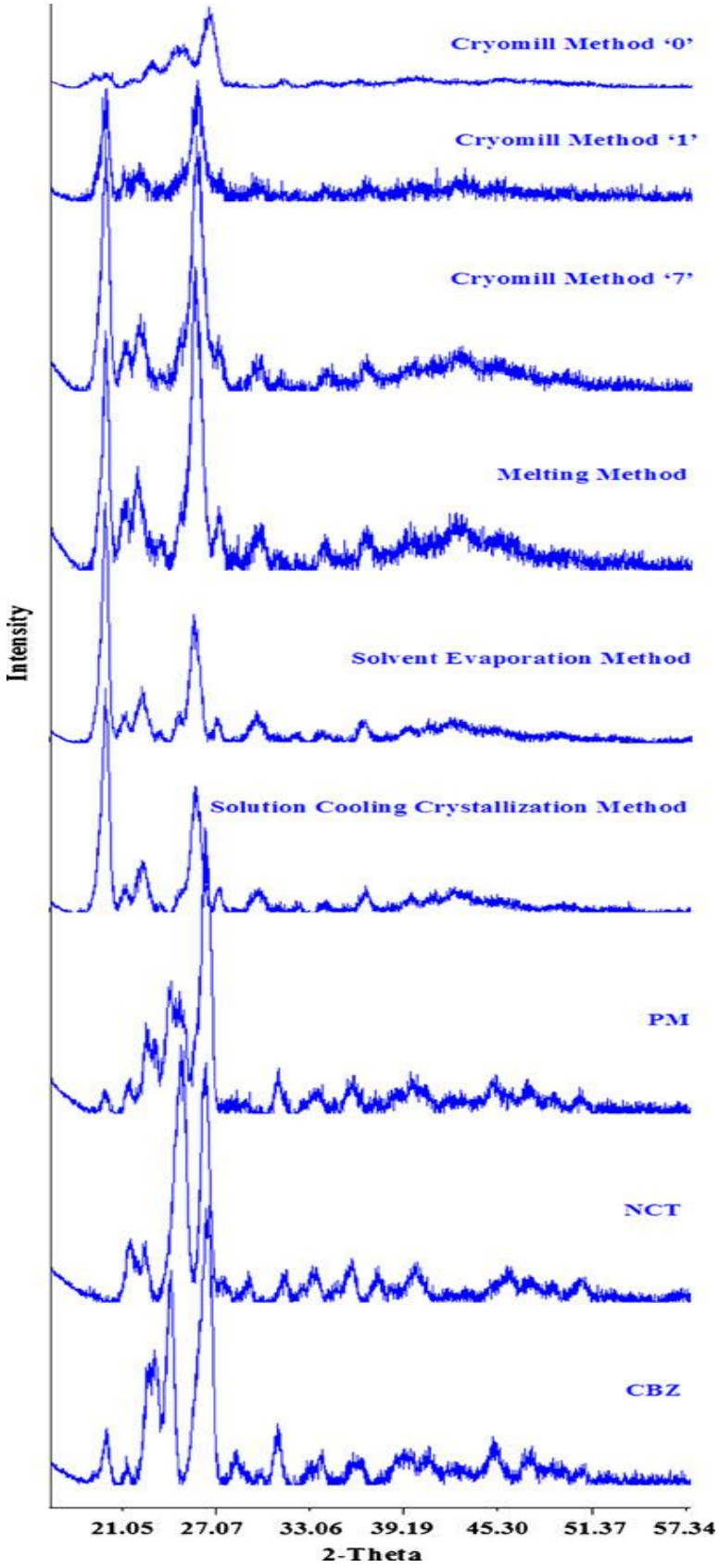

Figure 2-3: PXRD diffractograms of CBZ, NCT, and cocrystals (Source: Rahman et al., 2011)

2.6 Summary

In conclusion, the methods of co-crystals formation involves of solution based method and solid based method. Solution based method includes solvent evaporation, cooling crystallization and slurry crystallization while solid based method involves of solid state grinding and hot melt extrusion. Characterization of co-crystals techniques includes differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and x-ray powder diffraction (XRPD).

3 MATERIALS AND METHODS

3.1 Overview

This paper presents the experimental methods and characterization methods in order to study the solid phase transformation of carbamazepine-succinic co-crystal.

3.2 Introduction

This study is conducted by experimental of solution based method which involves three techniques of solvent evaporation, slurry crystallization and cooling crystallization by using ethanol as a solvent. Then, the experimental result is characterized by using x-ray powder diffraction (XRPD) and optical microscopy. The pure component is characterized by using differential scanning calorimetry (DSC) and x-ray powder diffraction (XRPD).

3.3 Chemicals

(Carbamazepine 99%), (Succinic 99%) and (Ethanol HPLC grade 99%) were obtained from Sigma-Aldrich Chemical Co while (Acetone 99%) was obtained from Fischer company.

3.4 Experimental Methods

In this study, the experimental method is conducted using solution based method via solvent evaporation, slurry crystallization and cooling crystallization. Ethanol was used as a solvent. The experimental method is taken from (Zakiriah, 2012).

3.4.1 Preparation of Carbamazepine-Succinic Co-crystal

Different mol ratio of carbamazepine and succinic is weighed as listed in Table 3-1.

Table 3-1: Experimental conditions used in the preparation of solutions

Carbamazepine, CBZ		Succinic, SUC		Mol ratio (SUC/CBZ)
Mass (g)	Mol (mmol)	Mass (g)	Mol (mmol)	
0.167	0.71	0.042	0.355	0.5
0.167	0.71	0.084	0.710	1.00
0.167	0.71	0.105	0.886	1.25
0.167	0.71	0.126	1.065	1.5
0.167	0.71	0.147	1.243	1.75
0.167	0.71	0.168	1.42	2.00
0.167	0.71	0.189	1.589	2.25
0.167	0.71	0.210	1.775	2.5
0.167	0.71	0.231	1.953	2.75
0.167	0.71	0.252	2.130	3.00

3.4.2 Solvent Evaporation

The solvent evaporation method was used to crystallize CBZ-SUC co-crystals. A mixture of 1:0.5 mol ratios of CBZ and SUC was dissolved in 35 ml of anhydrous ethanol in 100 ml conical flask and heated to 25°C in the orbital shaker. The solution was left at room temperature (~25°C). When all solutes are totally dissolved, parafilm is used to cover the conical flask and few holes is made on the parafilm. The resulting crystals were filtered and dried over filter paper (0.2µm). The procedures were repeated for different mol ratio SUC/CBZ as shown in Table 3.1.

3.4.3 Slurry Crystallization

A stoichiometric mixture of 1:0.5 mol ratios of CBZ and SUC was slurried in 15 ml of anhydrous ethanol in a conical flask and stirred for 72 hours at room temperature in the orbital shaker. A filter paper (0.2µm) is used to filter the resulting solid and dried at room temperature. The procedures were repeated for different mol ratio SUC/CBZ as shown in Table 3.1.

3.4.4 Cooling Crystallization

A CBZ and SUC were added in 100 ml conical flask. The solids were dissolved in 15 ml of anhydrous ethanol and heated to 60°C for 1h in the orbital shaker. All the solutes were dissolved in the solvent and were followed by a cooling down step. Temperature was decreased in 5°C increments at 1h intervals to induce precipitation. The resulting solid form were filtered with a filter paper (0.2µm) and dried at room temperature. The procedures were repeated for different mol ratio SUC/CBZ as shown on Table 3.1.

3.5 Characterization Analysis

In this study, co-crystal characterization is conducted using optical microscopy and x-ray powder diffraction (XRPD). The pure component is characterized by using differential scanning calorimetry (DSC) and x-ray powder diffraction (XRPD).The characterization analysis method is taken from (Abd Rahim, 2012).

3.5.1 X-Ray Powder Diffraction (XRPD)

XRPD is used to identify the sample obtained. Lines of pattern, generally known as powder pattern are the result from this measurement. To get a fine crystal powder, the sample used for measurement was ground using a mortar and pestle. A copper X-ray tube was used to generate the X-rays, which operated at 40 kV and 40mA. The plan used was from 3° to 40° for 2θ (angle). The step size and step time were 0.01 and 1 second/step, respectively.

3.5.2 Optical Microscopy

Optical microscopy is used to see the shapes of the crystals obtained. The morphology of the co-crystals was characterized by using optical microscopy at a magnification of