TRANSFORMATION OF CARBAMAZEPINE DIHYRATE TO ANHYDROUS CARBAMAZEPINE

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ABSTRACT

An investigation of carbamazepine dihydrate transformation to anhydrous carbamazepine was presented. In this works, carbamazepine dihydrate and solvents (ethanol, methanol, propanol, acetonitrile, ethyl acetate and methyl acetate) were used. The crystallization process was conducted using different solvents by applying solid state method using differential scanning calorimetry analysis and solution based method. For solution based method, three conditions of the experiment were implemented i.e. dissolution with heating and cooling without stirring, dissolution with heating and cooling with stirring, dissolution with heating and stirring followed by cooling without stirring. Solid state characterization of the crystals were analysed using Differential Scanning Calorimetry (DSC) and Powder X-Ray Diffraction (PXRD). Analysis data obtained from DSC revealed that the crystals produced from the transformation of carbamazepine dihydrate to anhydrous carbamazepine using solid state and solution based method were not successful. From DSC analysis, the melting point of carbamazepine dihydrate with six solvents for both methods were in the range of 70-160^{o}C. The finding from DSC analysis showed that the melting point of crystals did not fall within the melting point value of the anhydrous form. Referring to the PXRD analysis, the pattern profile of carbamazepine in six solvents with three different conditions does not similar to the literature for the indicative peaks of anhydrous form. It was suggested that the crystals obtained from the dissolution of carbamazepine dihydrate with six solvents using three different conditions were unsuccessful to transform carbamazepine dihydrate to anhydrous carbamazepine. Further study using different techniques and conditions were suggested in order to study the transformation of carbamazepine dihydrate to anhydrous carbamazepine.

ABSTRAK

Satu penyiasatan transformasi carbamazepine dihidrat kepada carbamazepine anhidrat telah dijalankan. Dalam penyiasatan ini, carbamazepine dihidrat dan pelarut (etanol, metanol, propanol, asetonitril, etil asetat dan metil asetat) telah digunakan. Proses penghabluran akan dijalankan menggunakan enam pelarut yang berbeza dengan mengaplikasi kaedah keadaan pepejal menggunakan analisis pengimbas pembezaan kalorimeter dan kaedah berasaskan larutan. Untuk kaedah berasaskan larutan, tiga keadaan telah dilaksanakan iaitu pelarutan dengan pemanasan dan penyejukan tanpa kacau, pelarutan dengan pemanasan dan penyejukan dengan kacau, pelarutan dengan pemanasan dan kacau diikuti dengan penyejukan tanpa kacau. Ciri-ciri keadaan pepejal kristal telah dianalisis menggunakan Pengimbasan Perbezaan Kalorimeter (DSC) dan Perbezaan X-Ray (PXRD). Analisis DSC menunjukkan bahawa kristal yang telah diperolehi daripada transformasi carbamazepine dihidrat kepada carbamazepine anhidrat menggunakan kaedah keadaan pepejal dan kaedah berasaskan larutan tidak berjaya. Daripada analisis DSC, takat lebur carbamazepine dihidrat menggunakan enam pelarut untuk kedua-dua kaedah berada di dalam suhu antara 70-160^{o}C. Hasil daripada analisis DSC menunjukkan takat lebur kristal yang diperolehi tidak termasuk dalam takat lebur bentuk anhidrat. Merujuk kepada analisis PXRD, profil corak untuk carbamazepine dihidrat dan enam pelarut dengan tiga keadaan yang berbeza adalah tidak sama dengan bentuk puncak andihidrat. Ia membuktikan bahawa kristal yang diperolehi daripada pelarutan carbamazepine dihydrate dengan enam pelarut menggunakan tiga keadaan yang berbeza tidak berjaya untuk mengubah carbamazepine dihidrat untuk carbamazepine andihidrat. Kajian lanjut dengan menggunakan teknik dan keadaan yang berbeza diperlukan untuk mencapai transformasi carbamazepine dihidrat kepada carbamazepine anhidrat.

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API	Active pharmaceutical ingredient
BCS	Biopharmaceutical classification system
C	Carbon
CBZ	Carbamazepine
DSC	Differential scanning calorimetry
DVS	Dynamic vapour sorption
FTIR	Fourier transform infrared
H	Hydrogen
MW	Molecular weight
O	Oxygen
SLS	Sodium lauryl sulfate
STC	Sodium taurocholate
PXRD	Powder X-ray differential

Greek

^{o}C	Celcius
^{o}C/min	Heating rate
W/g	Heat flow
%	Percent
min	Minutes
mL	Millimeter
psi	Pounds per square inch
rpm	Rotation per minutes

1 INTRODUCTION

1.1 Overview

This chapter will discuss about the background of the research including the materials used in the research, motivation and problem statement, objectives and scope of studies.

1.1.1 Carbamazepine (CBZ)

Carbamazepine (CBZ) which has an IUPAC name of 5H-dibenz[b,f]azepine-5-carboxamide and a molecular formula of $C_{15}H_{12}H_2O$ (MW 236.67). The molecular structure of CBZ as shown in Figure 1.1.

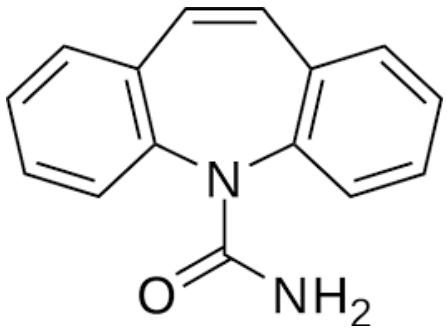

Figure 1.1: Molecular structure of CBZ

CBZ is an anticonvulsant that have been selected as the model drug having five different form which are four anhydrous forms and one dihydrate form as reported by Rustichelli and co-worker in 2000 (Rustichelli et al., 2000). Murphy et al. in 2002 stated that CBZ polymorphs were different in crystal structures and exhibits different melting points, chemical reactivity, solubility and compatibility (Murphy et al., 2002). Ceolin et al. in 1997 stated that polymorph II was a triclinic crystal with a prismatic morphology (Ceolin et al., 1997). Polymorph III and IV was different from the other polymorphs and they were fully describe in the literature. The International Centre for Diffraction Data has been reported that the polymorph III has a monoclinic crystal structure and this form is the most stable polymorph at a room temperature (Matsuda et al., 1994). Polymorph IV was presented as a needle-shape morphology and it will crystallize at high temperature (Lowes et al., 1987). Behme and Brooke in 1991 reported that the melting points for the all four polymorph was in the range 175-190˚C (Behme and Brooke, 1991).

CBZ is classified as Class 2 according to the Biopharmaceutical Classification System (BCS) (Farias and Carneiro, 2014) which mean CBZ has low solubility in water and high permeability in human tissues. Since the absorption of CBZ is limited by its solubility, the dissolution characteristic improvement can increased the rate of absorption of CBZ and enhanced its oral bioavailability (Hu et al., 2003). The different packing of the four polymorphs form was shown in the Figure 1.2.

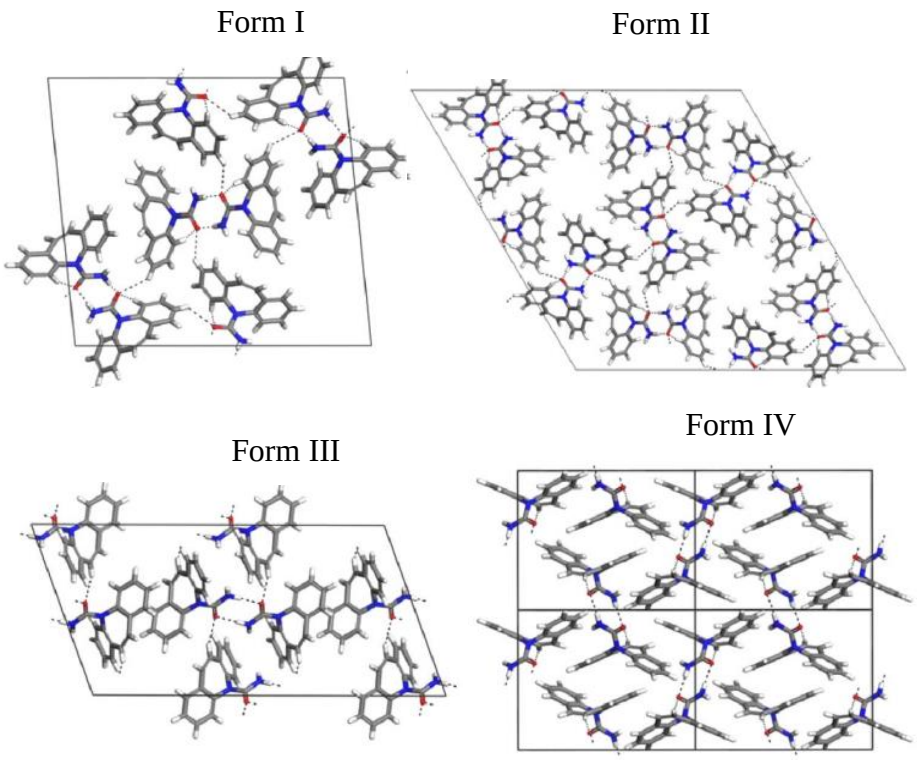

Figure 1.2: Packing diagram of CBZ polymorphs form I, II, III and IV (Rodrìguez-Spong et al., 2004)

CBZ is a main model drug to study polymorphism and phase transition. CBZ also selected because of its low solubility to investigate process method to their ability to improve the solubility. CBZ was poorly compressible and its compatibility depends on the polymorphic form (Flicker, 2011).

Other than four polymorphs, CBZ also exist in dihydrate form which crystallizes in the orthorhombic system (McMahon et al., 1996). CBZ dihydrate shows the best compatibility form but it is not stable under compression (Lefebvre et al., 1986).

Dihydrate of CBZ was a stable form in an aqueous solution (Sehić et al., 2010) and its relative humidity was above 52% (McMahon et al., 1996). Other than that, CBZ dihydrate is the most common solvate with two molecules of water which has high relative humidity. Figure 1.3 shows the arrangement of the CBZ dihydrate (Rodrìguez-Spong et al., 2004).

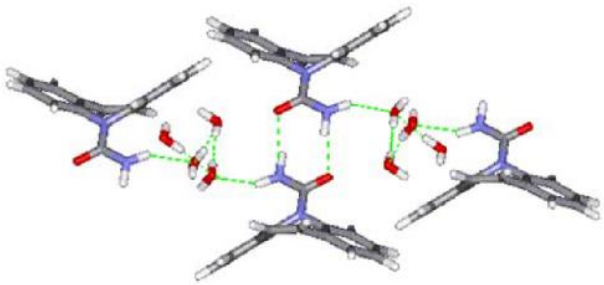

Figure 1.3: The arrangement of the CBZ dihydrate (Rodrìguez-Spong et al., 2004)

1.1.2 Pharmaceutical Hydrate

Threlfall in 1995 state that approximately there were one third of active pharmaceutical ingredients (APIs) which capable of forming in hydrate form (Threlfall, 1995). Figure 1.4 shows that CBZ dihydrate formed a tunnel structure through the crystal and the water molecule were connected to each other by hydrogen bonding.

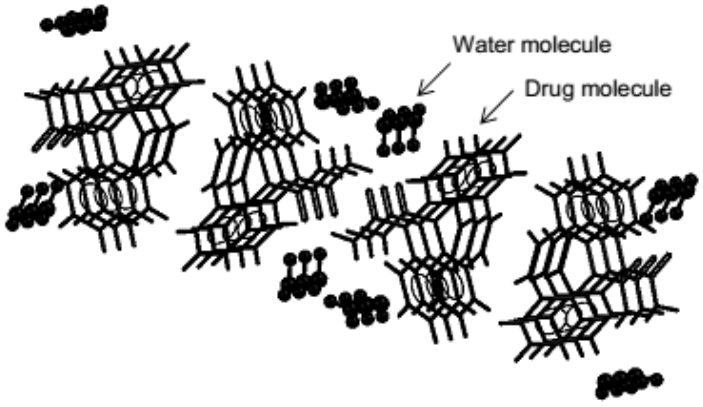

Figure 1.4: Example of the channel hydrate CBZ dihydrate (Kogermann, 2008)

The presence of water molecule can change the initial anhydrate or lower hydrate crystal structure such as the shape, symmetry, dimension and the capacity of a unit cell (Kogermann, 2008). The anhydrous forms have higher aqueous solubility and dissolution

rate compared to the hydrates which can lead to the increased bioavailability when the dissolution was the rate limiting step for the drug absorption. The hydrate forms of several APIs were reported had lower bioavailability (Halebian et al., 1971; Rodriguez-Hornedo et al., 1992) but hydrate was stable in the aqueous solution and have high humidity condition (Byrn et al., 1999). Most of the hydrate form was stable at the lowest temperature and ambient pressure (Giron, 2995).

1.2 Motivation and Problem Statement

The transformation of CBZ dihydrate to anhydrous CBZ has been investigated by many researchers. Many type of methods that have been used by the researchers to convert CBZ dihydrate to anhydrous CBZ for example dehydration, solution or solvent phase transformation or desolvation of the solvate. Many active pharmaceutical ingredients (APIs) occurred in both anhydrate and hydrate forms. During manufacturing such as wet granulation and storage under high humidity, the APIs may have been contacted with water and it may turn into hydrate formed. Otsuka et al in 1999 reported that CBZ anhydrous can formed to CBZ dihydrate during wet granulation. So, the possibility of transformation CBZ anhydrous to dihydrate CBZ was high (Otsuka et al., 1999).

In addition, the influence of the environmental condition on the dehydration of CBZ dihydrate had investigated by Surana and co-workers in 2003 to know about the factors that can affect the phase transformation (Surana at al., 2003). The APIs might be exposed to the environmental condition and there was a possibility that the phase transformation of solid state will occur. The solid state changes can affect the performance of the APIs and it will cause the product quality, stability also the therapeutic effect of the product will different than the expected (Bernstein, 2002). Many APIs will be exposed to the water and formed hydrates and there is possible changes of the solid dosage form during the pharmaceutical processing such as manufacturing and storage. The possibility of solid state transformation should be investigated to avoid any changes of the solid performance.

1.3 Objective

The objective of this study is to investigate the transformation of CBZ dihydrate to CBZ anhydrous by applying solid state method using DSC and solution based method in six different solvents (ethanol, methanol, propanol, acetonitrile, ethyl acetate and methyl acetate).

1.4 Scopes

The scopes of this study are as follows:

i. Screening of CBZ dihydrate to CBZ anhydrous transformation using different solvents by applying solid state method using DSC.
ii. Screening of CBZ dihydrate to CBZ anhydrous transformation using different solvents by applying solution based method (dissolution) with three different conditions.
iii. Characterization of solid properties of the crystal using DSC and PXRD.

2 LITERATURE REVIEW

2.1 Overview

This chapter presented the related studies of phase transformation of CBZ dihydrate to the anhydrous CBZ and characterization of the crystals.

2.2 Polymorphism

Polymorphism is a solid state phenomenon and it was defined as an ability of a compound to exist in different crystalline phases that have different arrangement of the molecules in the crystal lattice (Sawant et al., 2013). In the pharmaceutical, polymorphism is one of the most important factor in production of an active pharmaceutical ingredient (API) crystals as the physicochemical properties of API crystals such as its solubility, structural stability, dissolution rate, density and melting point (Sarma et al., 2011). The physicochemical properties and pharmaceutical properties (particle habit, powder flow, hardness and compressibility) can be considered different between solid state forms (Grant, 1999). This can lead to the different bioavailability and stability that can affect the pharmaceutical performance of the solid form (Halebian and McCrone, 1969). Drug substances can be isolated in the amorphous state and more than 50 % of the drugs marketed today exhibits polymorphism (Henck et al., 1197; Karpinski, 2006).

Polymorphs can be characterized by using various solid state characterization techniques such as Powder X-Ray Diffraction (PXRD), thermal analysis, Fourier Transform Infrared (FTIR) spectroscopy and optical microscopy (Bugay, 2001). Polymorphs and hydrates were different in internal solid state structure and physical properties such as melting point, crystal habit, colour, density, thermodynamic, kinetic and flow properties (Brittain, 1999). All the differences in the physical properties have make the polymorphism special and have direct impact on the drug produce quality and performance such as stability, dissolution and bioavailability (Raw et al., 2004).

2.3 Polymorphism Pharmaceutical

Polymorphism gave an influence in pharmaceutical science especially in active pharmaceutical ingredients (API) properties such as dissolution rate, solubility, stability and biological performance including its effectiveness and toxicity (Li et al., 2009; Savjani et al., 2012). The discovery of the polymorphism in pharmaceutical industries has been growing fast leading the pharmaceutical companies carry out the systematic works to detect the polymorphism of their drugs and investigated about this application towards to the benefits of pharmaceutical industries itself (Halebian, 1989). The knowledge of the polymorphism in pharmaceutical is important to improve the dissolution rate and achieve rapid absorption of low solubility drugs in systematic circulation and bioavailability of the crystals. One of the elements that important for the drug development is polymorphism. The polymorphic forms in the drug substances have different physical and chemical properties including melting point, mechanical properties and density. All these properties can gave an effect the ability of the drug substances to be process and manufacture. In the pharmaceutical industry, polymorphs gave major challenge to differentiate and characterize individual polymorph since different polymorph exhibit different physicochemical properties such as dissolution rate that can effects the bioavailability (Thiruvengadam and Vellaisamy, 2014).

2.4 Solvent in Polymorphism

CBZ commonly known as Class II in BCS system which have high permeability and low water solubility. The chosen of solvents given big influence to the solubility and properties of the drugs. The drug crystallization step can be performed with different solvents and additives. The different crystal habits and possible solvent inclusion resulted to different solubility and dissolution behaviour (Rodrìguez-Spong et al., 2004).

There have been studies about the use of solvents or solvents mixtures in order to control the polymorph formation along with the solubility characteristics and supersaturation of crystallization (Blangden et al., 2005; Davey et al., 2002). The type and choice of solvents will determined the polymorphic selectivity and morphology of the crystal mainly due to the solvent solute interaction at the molecular level and the solubility of the solute must be in the range 5-200 mg/mL at room temperature in order to make the solvent conducive

for crystallization process (Rohani et al., 2005). The slope of solubility curve, boiling point, viscosity and ability to form hydrogen bonding can be considered as the factors to choose the type and choice of the solvent (Vedantam and Ranade, 2013). Mimehrabi and co-workers in 2006 had developed the correlation to determine the ability of solute and solvent molecules to form intra and intermolecular hydrogen bonds (Mimehrabi et al., 2006).

2.5 Phase Transformation of CBZ dihydrate to CBZ anhydrous

Several attempts that have been made by many researchers to control the transformation of CBZ dihydrate to anhydrous CBZ but mostly dehydration method was used. The transformation of CBZ dihydrate to CBZ anhydrous was reported by Khoo and co-workers in 2013 using low pressure and atmospheric dehydration within temperature range 20.00^{o}C to 50.00^{o}C. There was a nucleation to a metastable triclinic form which known as form II during humidified dehydration below than 30.00^{o}C and CBZ form III was formed under low pressure (vacuum) dehydration (Khoo et al., 2013). The influence of the environmental condition on the dehydration of CBZ dihydrate had investigated by Surana and co-workers in 2003 about the factors that can affect the phase transformation (Surana et al., 2003). The dehydration method has been studied with the effect of ethanol vapour pressure on dehydration of CBZ dihydrate as one of the method of the transformation. Due to the lower vapour pressure used (1.20 to 4.20 torr), the dehydration was resulted in amorphous anhydrous and the rate of dehydration was increased with ethanol vapour pressure during the transformation.

In addition, Li et al. in 2000 has been demonstrated that CBZ dihydrate can be dehydrated and recrystallized into different form of polymorphs through drying using different conditions such as controlling relative humidity, elevated pressure and temperature (Li et al., 2000). The conversion of CBZ dihydrate to CBZ anhydrous form II was occurred at relative humidity above 11.00% at 44.00^{o}C and CBZ anhydrous form III was converted at elevated pressure (10^2 psi) and high temperature which (85.00^{o}C). On the other hand, Han and Suraynarayanan in 1997 studied the dehydration of CBZ dihydrate by conventional DSC and pressure DSC (Suraynarayanan, 1997). The dehydration and vaporization endotherm were separated by performed DSC at elevated pressure and the enthalpy of dehydration was determined. The high pressure (100.00-600.00 psi) of the

DSC condition was one of the factor to the formation of solid state of the anhydrous phase. The dehydration process resulted the formation of form I of the anhydrous CBZ at the ambient pressure (14.00 psi). At the elevated pressure (100.00 psi), stable anhydrous phase which is form III of CBZ was produced and it was converted to the form I anhydrous CBZ at the higher pressure. The presence of water gave significant effect on the solid state of the anhydrous phase. It appears to facilitate the nucleation growth of form III at the dehydration temperature. From this observation, drying condition can influence the solid state of dehydrated phase of an anhydrous.

Furthermore, the transformation of CBZ anhydrous to CBZ dihydrate was widely investigated by many researchers. Murphy and Rodrı in 2002 were investigated the kinetics of the solution mediated phase transformation of anhydrous monoclinic polymorph of CBZ anhydrous to dihydrate crystal form (Murphy and Rodrı, 2002). The transformation of CBZ anhydrous to CBZ dihydrate was studied from the suspension of CBZ anhydrous in solutions initially supersaturated with respect to the dihydrate phase at 25^{o}C. The supersaturation solutions with respect to the CBZ dihydrate were prepared by dissolving CBZ anhydrous in water under constant stirring at temperature range from 50-65^{o}C. The ground or unground of CBZ anhydrous was added to the solution to form a suspension from the start of the experiment. The results for the kinetics and rate controlling step had shown that the transformation was influenced by the grinding of CBZ anhydrous. The ground CBZ anhydrous was transformed to the dihydrate form at the faster rate than the unground solid. Grinding also was exposed the new crystal faces and functional group that may affect the transformation rate. It has been shown that the crystallization of CBZ dihydrate was facilitated by the surface nucleation of ground CBZ anhydrous and on the amorphous phase.

The surfactant facilitated crystallization of CBZ dihydrate during dissolution of anhydrous polymorph was also explored by Murphy and Rodrı in 2004 (Murpy and Rodrı, 2004). The surfactants that have been studied were sodium lauryl sulfate (SLS) and sodium taurocholate (STL). It have been proved that both surfactants promoted the crystallization of CBZ dihydrate during the dissolution of anhydrous CBZ. The crystal surface examination as shown in Figure 2.1 showed the needle of CBZ dihydrate was grew on the surface of the dissolving CBZ anhydrous with SLS.

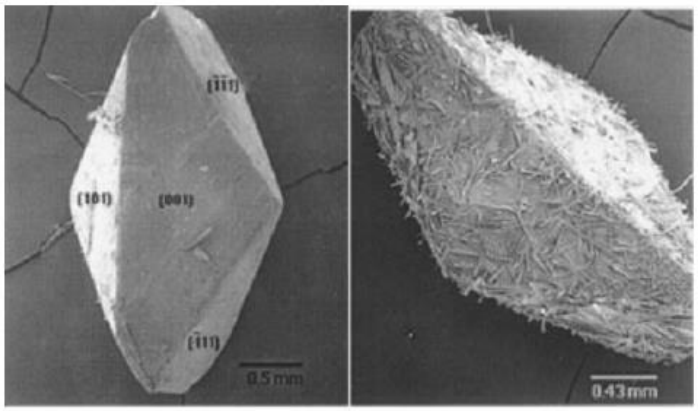

Figure 2.1: Photomicrograph of single crystals of CBZ anhydrous during transformation which: a) the crystals placed in aqueous solution without SLS; and b) crystals placed in solution with SLS (Murphy and Rodrı, 2004)

For surfactant STC, it changed the crystals morphology of CBZ dihydrate from acicular to prismatic depends on the STC concentration. The morphology from the interaction of STC and molecular CBZ dihydrate crystals faces were changed with the formation of hydrogen bonded chain of water molecules and carboxamides dimers as shown in Figure 2.2.

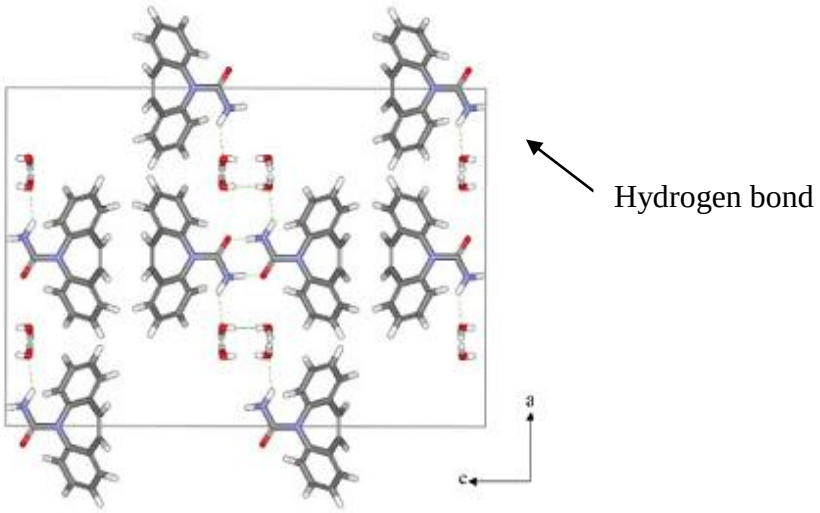

Figure 2.2: The CBZ dihydrate crystals lattice viewed down the b-axis (Murphy and Rodrı, 2004)

2.6 Characterization of Solid State Properties of Crystals

Solid state properties of the crystals can be characterized by using general equipments which are DSC and PXRD to obtained the melting point and phase identification of crystalline material.

2.6.1 Differential Scanning Calorimetry (DSC)

The differential scanning calorimetry (DSC) was a fundamental technique in thermal analysis that has been used in many industries such as pharmaceuticals, polymers, electronics and food production. The information that have been generated by using the DSC can be used to analyse the amorphous or crystalline behaviour, polymorph or other materials properties that can used to manufacture and test the product formed. DSC refers to the technique of measuring calorimetric data while scanning and specific instrument design. The biggest advantage of using DSC was the ease and speed which it can be used to see the transitions of materials. In liquid crystals, pure organics, pharmaceuticals and metals, the phase change or the polymorphs can be seen and the degree of purity materials can be studied. DSC was the common technique that has been used for thermal analysis and it can found in many analytical, process control and R&D laboratories. DSC also can detect any change of the heat flow in and out of the samples. The transitions such as melting and conversion of different crystalline phases like polymorphic forms, loss of solvent, dissolution and precipitation of the solution can be seen using DSC (Newmann, 2012).

2.6.2 Powder X-ray Diffraction (PXRD)

Powder X-ray Diffraction which known as PXRD was a well-developed technique for the crystal structure determination (Massa, 2004). A single crystal structure can provides full structural characterization of the form at the atomic scale. PXRD is an analysis that is representative for powder material and utilizes the powder samples than are often produced than single crystals. The PXRD pattern crystal form at the thermodynamic state point serves as a fingerprint for the form under given conditions.

2.7 Summary

The transformation of CBZ dihydrate to CBZ anhydrous was investigated by many researchers. Most of the researchers has been successful to transform CBZ dihydrate to CBZ anhydrous by using different methods such as dehydration method. Besides that, the transformation of CBZ anhydrous to CBZ dihydrate also has been widely investigated as stated on literature. They found that CBZ anhydrous can be converted to CBZ dihydrate by using solution mediated phase and surfactants that can facilitated the transformation. The crystals formed from their studies had been characterized using PXRD, DSC, optical microscopy and FTIR to investigate the characteristics of the crystals.

3 METHODOLOGY

3.1 Overview

This chapter describe all the materials and methods that have been used during the study. The objective of this research is to investigate the transformation of the CBZ dihydrate to CBZ anhydrous using six different solvents by applying solid state method using DSC and solution based method (dissolution).

3.2 Introduction

The main equipment that has been used in this study is DSC and hot plate that can control its temperature and heating rate. The characterization of the crystals is important to determine the characteristics of the crystals such as crystals melting point and crystals pattern.

3.3 Chemicals

CBZ dihydrate, white crystalline powder was purchased from Jiao Wanying Trade Co. Ltd. The solvents used are propanol (C_3H_8O), methyl acetate ($C_3H_6O_2$), ethyl acetate ($C_4H_8O_2$), ethanol gradient grade (C_2H_6O), acetonitrile HPLC grade (C_2H_3N) and methanol (CH_3O). All solvents used have a purity more than 99%.

3.4 Phase Transformation of CBZ Dihydrate to CBZ Anhydrous

The phase transformation of the CBZ dihydrate to anhydrous CBZ was determined by applying solid state method using DSC and solution based method (dissolution). For solution based method, three conditions of the experiment were implemented i.e. dissolution with heating and cooling without stirring, dissolution with heating and cooling with stirring, dissolution with heating and stirring but cooling without stirring.

3.4.1 Screening of CBZ Dihydrate to CBZ Anhydrous using Different Solvents by Applying Solid State Method using DSC

CBZ dihydrate with 0.1 mL solvent (ethanol) was analysed under a nitrogen purge and heated (40.00-200.00^{o}C) at a scanning rate of 10 ^{o}C/min using DSC. The samples were placed in aluminium pans and the lids were crimped. The experiment was repeated for five different solvents (propanol, methyl acetate, ethyl acetate, acetonitrile and methanol) and two heating rate (15.00 and 20.00 ^{o}C/min).

3.4.2 Screening of CBZ Dihydrate to CBZ Anhydrous using Different Solvents by Applying Solution Based Method (Dissolution)

CBZ dihydrate to CBZ anhydrous was screened using six solvents (propanol, methyl acetate, ethyl acetate, ethanol, acetonitrile and methanol) by applying solution based method (dissolution). Three condition of this methods were implemented which are dissolution with heating and cooling without stirring, dissolution with heating and cooling with stirring, dissolution with heating and stirring but cooling without stirring. CBZ dihydrate was added to 10.00 mL of six different solvents measured into 20.00 mL vial. The hot plate stirring rate was set up at 150.00 rpm. All the samples were maintained at the selected temperature based on the boiling point of the solvent. The precipitated samples were dried in the oven. The crystals produced were characterized using Differential Screening Calorimeter (DSC) and Powder X-Ray Diffraction (PXRD). The summary of the procedure was shown in Figure 3.1.

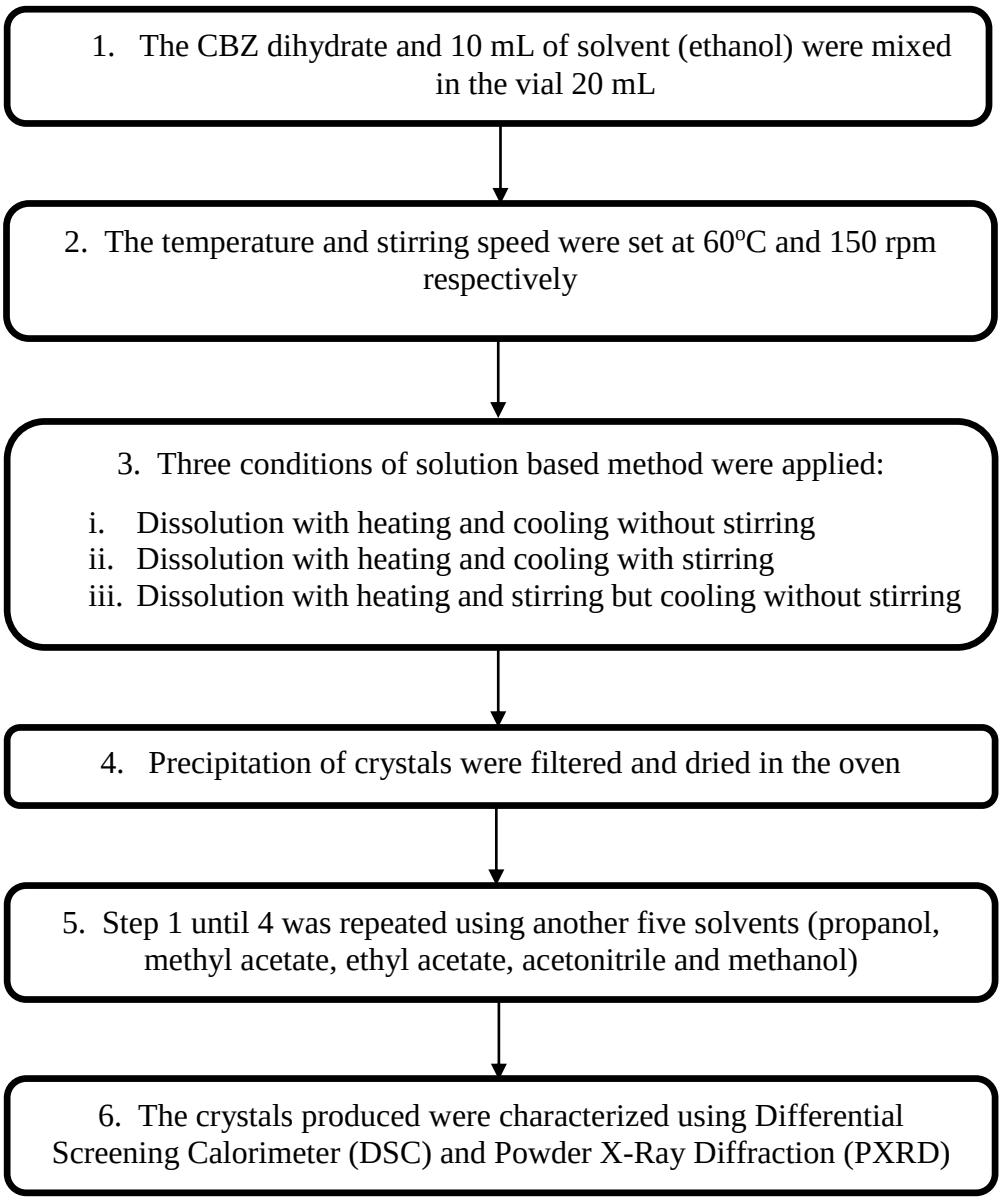

Figure 3.1: The flow chart of the screening CBZ dihydrate to CBZ anhydrous using solution based method

3.5 Crystal Analysis and Characterization

The characterization of crystals were determined by using Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction (PXRD).

3.5.1 Differential Scanning Calorimetry (DSC)

The crystals were characterized by using DSC and the analysis was analysed under a nitrogen purge and heated (40.00-200.00^{o}C) at a scanning rate of 10.00 ^{o}C/min. The samples were placed in aluminium pans and the lids were crimped. (Ab Rahman, 2014; Nasir, 2014).

3.5.2 Powder X-ray Diffraction (PXRD)

PXRD analysis was characterized using a RIGAKU, model Miniflex II diffractometer Cu Kα radiation (λ=1.54Å), a tube voltage of 40.00kV and tube current of 100.00 mA for 5.00-40.00^{o} with continuous scan rate of 0.01^{o}/s (Ab Rahman, 2014; Nasir, 2014).

3.6 Summary

In conclusion, the experimental methods were conducted by applying solid state method using DSC and solution based method. The crystals were characterized by using differential scanning calorimetry (DSC) and powder x-ray diffraction (PXRD) to study the melting point and phase identification of the crystals.