SOLVENT SCREENING STUDY OF CARBAMAZEPINE CRYSTAL POLYMORPH

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ABSTRACT

Realizing solvents can be paramount critical and important in crystallizing specific polymorphs, complete manual, references, method and approach in predicting the polymorph formed from the specific parameter need to be developed. Solvent screening is the process of determining the relation between solvent choose and respective crystal form mainly focused on the solubility and its related properties. For this particular research, the approaches is by choosing specific properties of solvent used to find the relationship between them to relate with the crystallize structure formed. Polarity, hydrogen-donor-acceptor, and dipole moment is known to give much effect on the polymorph formation. By selecting the solvent with distinct properties considering its polarity, hydrogen-donor-acceptor, and dipole moment, the carbamazepine will be dissolve and recrystallize. Gravimetric method was used to determine the solubility of carbamazepine. DSC and optical microscopes was used to characterize the polymorph. Van `t Hoff plot was constructed from the solubility data and the stability prediction was made based on the free energy value calculated. It is found that weak interaction of solvent-solute will result in more stable polymorph but not necessarily correct because other factor such as temperature need to be consider during dissolution and crystallization process. One solvent having a tendency to produce more than one type of polymorph depend on the temperature of dissolution. Morphology of carbamazepine polymorph inconsistent for several trials and can be change easily through the process. This result will be potential additional reference for more perfect approaches in the future especially for molecular dynamic simulation.

KAJIAN PENYARINGAN PELARUT PADA POLIMORF HABLUR KARBAMAZEPIN

ABSTRAK

Menyedari kepentingan pelarut dalam penghabluran polimorf tertentu, manual lengkap, rujukan, kaedah dan pendekatan dalam meramalkan polimorf yang terbentuk daripada parameter tertentu perlu dibangunkan. Penyaringan pelarut adalah proses menetukan kaitan antara pelarut yang dipilih dan hablur yang terhasil terutamanya tertumpu kepada kelarutan dan ciri-ciri yang berkaitan. Bagi tujuan penyelidikan ini, pendekatan yang diambil adalah memilih sifat tertentu pelarut yang digunakan dan dikaitkan dengan struktur hablur yang terbentuk. Kekutuban, penerima-penderma ikatan hidrogen, dan momen dwikutub adalah diketahui sangat memberi kesan kepada pembentukan polimorf. Dengan memilih pelarut dengan sifat-sifat yang berbeza seperti kekutuban, penderma-penerima ikatan hidrogen, dan momen dwikutub, carbamazepine akan dilarutkan dan dihablurkan semuala. Kaedah gravimetrik telah digunakan untuk menentukan kelarutan carbamazepine. DSC dan mikroskop optik telah digunakan untuk menentubeza polimorf. Graf Van `Hoff telah dilukis daripada data kelarutan dan ramalan kestabilan telah dibuat berdasarkan nilai tenaga bebas yang dikira. Didapati bahawa interaksi yang lemah antra pelarut bahan larut akan menghasilkan polimorf lebih stabil namun tidak keseluruhanya diterima kerana faktor lain seperti ganguan suhu semasa pelarutan dan proses penghabluran perlu dipertimbangkan. Satu pelarut mempunyai kecenderungan untuk menghasilkan lebih daripada satu jenis polimorf bergantung kepada suhu pelarutan. Morfologi polimorf carbamazepine adalah tidak konsisten untuk beberapa cubaan penghabluran dan mudah sepanjang proses penghabluran. Dapatan kajian ini berpotensi sebagai rujukan tambahan untuk pendekatan yang lebih sempurna di masa hadapan terutamanya bagi simulasi dinamik molekul.

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LIST OF SYMBOLS

θ	Angle of diffraction in powder X-ray differential
ΔH_{diss}	Enthalpy change of dissolution
ΔS_{diss}	Entropy change of dissolution
ΔG_{sol}	Free energy change of dissolution
R	Gas constant
T	Temperature

LIST OF ABBREVIATION

DSC	Differential Scanning Calorimetry
PXRD	Powder X-Ray Differential
TGA	Thermal Gravimetric Analysis
SEM	Scanning Electron Microscope
API	Active Pharmaceutical Ingredients
CBZ	Carbamazepine
C	Carbon atom
H	Hydrogen atom
O	Oxygen atom
H-bond	Hydrogen bond
RT	Room temperature
MTDSC	Modulate Temperature Differential Scanning Calorimetry
IR	Mid-infrared spectroscopy
NIR	Near-infrared spectroscopy
ss-NMR	Solid state Nuclear Magnetic Resonance
DVS	Dynamic Vapor Sorption
rpm	revolution per minute

CHAPTER ONE

INTRODUCTION

1.1 Background of Proposed Study

For decades, carbamazepine has served as a model compound for groups engaged in the study of crystal polymorphism, a very common phenomenon on pharmacological substance. Discovering a new polymorph is known to be time and resources consuming. A lot of trial and error need to be made if no complete or standard approaches for discovering new polymorph are establishes (Storey et al., 2004). Even there is no superior method or procedure, some distinguish feature or factor can be a guide to trial and error process. A lot of factor that can influence the formation of polymorph and one of the most important factors is solvent used. Solvent without failure

is essential remedies in pharmaceutical industry but wrong solvent will result in undesired polymorph.

1.2 Problem Statement

Determining the suitable solvent to be used in pharmaceutical industry are paramount important to avoid the formation of undesired polymorph. As one of the main factor, there is several sub-factor need to be consider related to solvent choose such as concentration, existence of water, supercritical condition, temperature, and so on (Morisette et al.,2004). It is often observed that a particular polymorph preferentially crystallizes from a specific solvent, especially when no seeds are present (Gidalevitz et al., 1997). Carbamazepine tends to presence in the four polymorphic forms because of solvent effect factor. Different polymorphs provide different desired properties for the drugs such as efficiency and bioavailability.

1.3 Research Objectives

The main objective of this research is mainly to determine the solubility of carbamazepine for the selected solvent to be correlated to the strength of molecular interaction and bonding with solute. Second objective is to determine the type of

polymorph after dissolving and recrystallization for the selected solvent. Third objective is to characterize the carbamazepine solid state properties polymorph using DSC and optical microscope.

1.4 Research Questions/Hypothesis

High solubility of solute means there is strong interaction in the molecular level between carbamazepine and selected solvent. This is predicted to happen for polar solvent. Meanwhile for low solubility, it is predicted to happen for non-polar molecule, where there is weak interaction between the solvent-solute at molecular level. The crystal products can be easily being characterized through PXRD and DSC by compare it with the past study.

1.5 Scope of Proposed Study

The scopes of this study are focusing on the relation of solvent properties with the crystallization polymorph of carbamazepine. It studies the solute-solvent interaction and the inter-atomic distances between specified atoms on solute molecules by determine their time-solubility and the presence of H-bond in the crystal structure and

solutions. Solubility test are planned in room temperature of 27^{o}C with the highest purity of solvent provide by the supplier. Gravimetric methods are used for as collecting method. The characterization is commonly used PXRD and DSC, but as for further clarification, other equipment such as TGA and SEM also can be used.

1.6 Expected Outcome

It is believe that strong interaction between solute and solvent will result in weak bonding during the crystallization thus producing metastable polymorph during crystallization. This likely to happened for polar solvent. While weak interaction between solute and solvent will perhaps produce high stability polymorph of carbamazepine crystal that are likely to happen for non-polar solvent or solvent with low polarity. Non-polar solvent will give very low solubility that not preferable in pharmaceutical industry.

1.7 Significance of Proposed Study

Determining the correct solvent to be used will bring great advantages to the pharmaceutical industry. The benefit is not only for carbamazepine production, the careful selection of solvent based on analysis of it characteristic can be helpful reference for determining solvent for other pharmacological compound. Moreover, the collected data can be used for simulation in the future. Use of simulation especially in pharmaceutical industry will help the researcher in doing the research in short time and low cost because they don't have to set up the real experiment.

1.8 Conclusion

As a summary, realizing the important of understand the polymorphism, research to determine the specific properties toward the polymorph formation is indeed very relevant. Event it cannot find the superior approaches, at least it can be a valuable data for future references. By determining the molecular interaction of the solvent-solute, it is expected that it can be related to the stability of polymorph form. This study is not only focused on crystallization, but including understanding of theoretical approaches and most recent experimental method.

CHAPTER 2

LITERATURE REVIEW

2.0 Introduction

The objective of this chapter is to extract and combine some of the finding in the past study that may relate to this research paper. As theory only is not enough for the research, there comes literature review as the supported information prior to the research. This chapter also will provide some data for comparison is discussion part. It will cover several main sub-chapters including polymorphism, short explanation on carbamazepine, polymorphism in carbamazepine, and solvent.

2.1 Polymorphism

The ability of a compound to crystallize into more than one crystalline phase with different arrangement and conformation of the molecules in the lattice are called as polymorphism (Grant, 1999). In other word, it is a similar compound but with different crystal line. It is challenging enough for the manufactures and developers of such compounds since they exist in various solid-state forms, crystalline or amorphous (Morris et al., 2001). Polymorph known to give significant different in the physicochemical properties such as melting point, density, morphology, solubility and colour. It may affect the stability; physically or chemically, bioavailability and processability during production or in their final product form (Heinz et al., 2009). Worst case is undesired polymorph can be toxic (Knapman, 2000) that rise the concern to increase the regulatory requirement by Food and Drug Administration (Byrn et al., 1995).

Thermodynamically metastable forms are often desired in pharmaceutical development due to their enhanced biopharmaceutical properties, a result of higher solubility and faster dissolution rates. In different cases, metastable forms are not desired because of crystallization and transformation to a more thermodynamically stable form during processing, storage, or dissolution (Byrn et al., 1995; Shekunov and York, 2000). Recently, a multiple component crystal in which all components are solid under ambient conditions when in their pure form or called co-crystal have attracted interest in

pharmaceutical world as they offer an alternative way to overcome poor aqueous solubility without neglecting the stability (Miroshnyk et al., 2009).

Often, new polymorphs are discovered by trial-and-error by recrystallizing the compound of interest from various solvent. This is because no standard approach are developed in industry even realizing the importance of polymorphism and the need of solid-form screening for pharmaceutical related study (Getsoian et al, 2007). It is known that such factors as solubility, solvent viscosity, solvent polarity, evaporation rate, cooling rate, and initial solution concentration can affect the outcome of a crystallization but approaches to vary those factor are typically not systematic (Morissette et al., 2004; Hilfiker et al., 2006). Indeed, discovering new polymorphs is a time consuming and resource consuming process. Still, no polymorph screen can guarantee that all possible, or even pharmaceutically relevant, forms have been found regardless of the effort (Getsoian et al., 2007).

2.1.1 Polymorphism of Active Pharmaceutical Ingredients (API)

When a new API is launched on the market it is essential to have a thorough knowledge of its differing solid phases and to respect the Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (http://www.ich.org, 2012). Recent history in the pharmaceutical industry has shown that the emergence of a new phase can seriously compromise the intended process and potentially the patient's life (Dunitz and Bernstein, 1995). Chemburkar, of Abbott laboratories, who dealt with the Ritonavir case

in the nineties, drew the following conclusion: “Dealing with polymorphism is potentially precarious practice and the proper way to play this game is with patience and perseverance” (Chemburkar et al., 2000).

2.2 Carbamazepine

Carbamazepine is a chemical compound used in pharmaceutical for medicinal purpose, a first-line agent for localization-related epilepsy, and one of the most popular anticonvulsants used in children. Typically it has been used to treat seizure disorder and neuropathic pain. It may be used as a second line treatment for bipolar disorder and along with antipsychotic agents in schizophrenia. (The American Society of Health-System Pharmacists, 2012) However, carbamazepine has some adverse effects like other antiepileptic drugs. Among the adverse effects of carbamazepine are drowsiness, vertigo, headache and ataxia have been reported as adverse neurotoxic effects (Gayford & Redpath, 1969) auditory disturbance associated with carbamazepine medication, such as hyperacousis and tinnitus, has been rarely reported (Tateno et al., 1993).

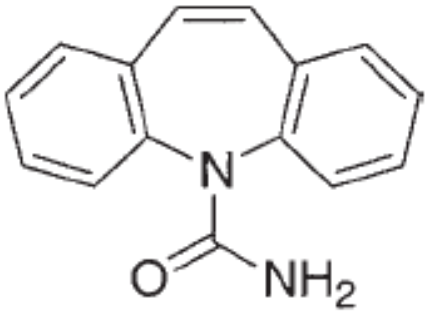

Figure 2.1 Chemical structure of carbamazepine (Grzesiak et al., 2003)

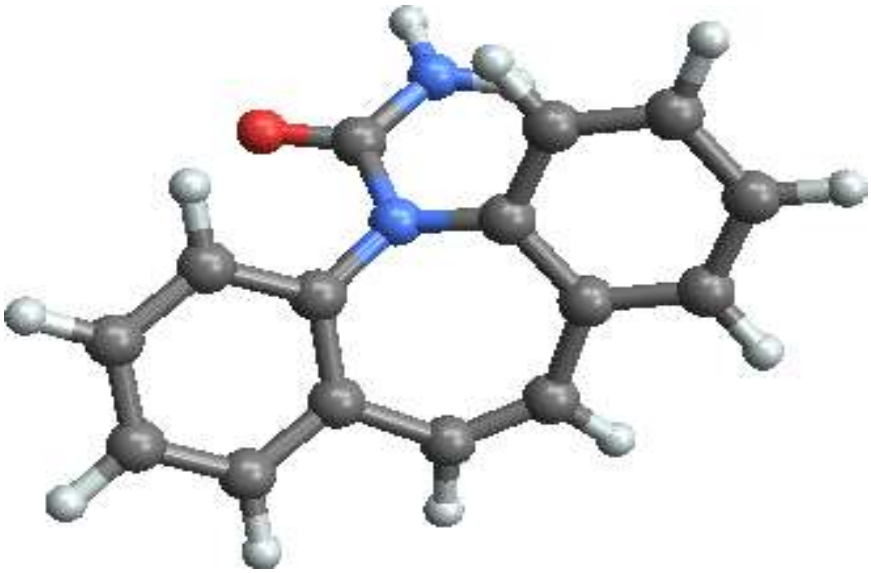

Figure 2.2 More well illustrated chemical structure of carbamazepine. Grey molecules represent carbon, white molecules represent hydrogen, blue molecule represent oxygen, and red molecule represent nitrogen. (Wolfram Web Resources, 2012)

2.3 Carbamazepine Polymorph

Carbamazepine (CBZ) is described as consisting of four polymorphs and as a dihydrate (Borka et al., 1992; Rustichelli et al., 2000). Form I or triclinic anhydrous (m.p. 190^{o}C) and Form III or P-monoclinic (m.p. 177^{o}C) is the commercial product, constitute an enantiotropic pair. Form III is the crystal form stable at ambient temperature up to 70^{o}C, while Form I is stable above 70^{o}C (Behme and Brooke, 1991). The trigonal and triclinic forms are monotropic (Edwards et al., 2001). The monoclinic polymorph is the most stable and least soluble of the anhydrous forms at room temperature while the trigonal is the least stable and most soluble form (Edwards et al., 2001). The carbamazepine properties are summarized in Table 2.1. Three CBZ polymorph Form II-1V were found to transform to Form I upon heating (Grzesiak et al.,2003) from their respective form.

Table 2.1 Table of summarized properties of carbamazepine polymorph

	Form I	Form II	Form III	Form IV
Morphology	Needle (Grzesiak et al.,2003) -Various according method	Needle (Grzesiak et al.,2003) -Various according to method	-No previous report state clearly the correct morphology -Various according to method	-No Previous report that state clearly the correct morphology -Various according to method
Melting Point ^{o}C (Grzesiak et al.,2003)	-189 and 193 °C -No transformation occurs during heating until melt	- Transformation occurs at 135^{o}C and 170oC. -The new phase melted between 188^{o}C and 192^{o}C	-Melts and crystallizes to a new form almost simultaneously between 162^{o}C and 175 °C -The new form melts at 189 and 193°C	-Melts and partially crystallize to a new form between 178^{o}C and 187°C
Crystal structure (Grzesiak et al.,2003)	triclinic anhydrous	trigonal	P-monoclinic	c-monoclinic

Grzesiak et al. (2003) arrange the stability of the four polymorph as: Form III>Form I>Form IV>Form II. This stability order is based on the density rule where higher density will give high stability. From the structure of the carbamazepine in Figure 2.3-2.6, all four polymorph having identical anti-carboxamide dimer motif. This is significantly different to other highly polymorphic substance such as sulfapyridine, which display different conformation or strong hydrogen bonding pattern (Rodriguez-Spong et al, 2004). From Figure 2.3 and Figure 2.4, the triclinic (Form I and Form II)

pack in a similar manner. Both structure form two C-H----O intermolecular interaction at benzenic hydrogen with oxygen of urea. However, in Form III and Form IV, the intermolecular interaction of double bond involve in azepine ring to the oxygen of the urea.

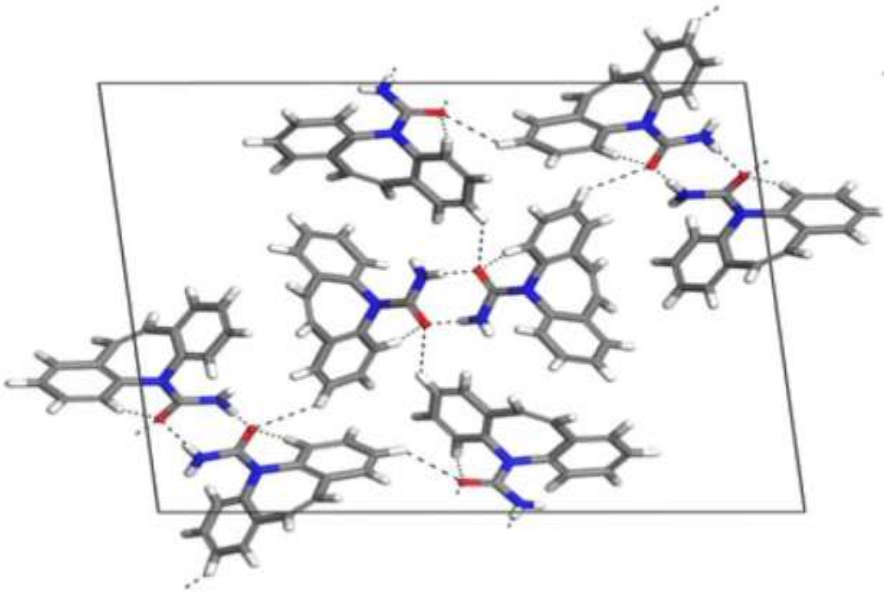

Figure 2.3 Form I carbamazepine showing its hydrogen bond. (Rodriguez-Spong et al, 2004)