SOLID PHASE TRANSFORMATION OF CARBAMAZEPINE-SACCHARIN (CBZ-SAC) CO-CRYSTAL

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The thesis submitted in fulfillment of the requirements for the award of the degree of Bachelor of Chemical Engineering

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UNIVERSITI MALAYSIA PAHANG

FEBRUARY 2013

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ABSTRACT

A research was conducted on the solid phase transformation and stability of carbamazepine-saccharin co-crystal. Pharmaceutical co-crystal is one of the potential methods for improving the bioavailibity of drugs with low aqueous solubility. Thus, the purpose of this research is to determine the stable region of carbamazepine-saccharin (CBZ-SAC) co-crystal formation by using solution based method. In this method, three technique are used which are cooling crystallization, solvent evaporation and slurry, to prepare the chemical and use ethanol as a solvent. Different mol ratio of CBZ and SAC are being tested, in order to study CBZ-SAC cocrystal formation. Physical characterizations of the co-crystal are being characterized by differential scanning calorimetry and research microscope. Overall as the concentration of saccharin increase the melting point increase and will lead to poor solubility but mostly the melting point of co-crystal resulting in lower melting point. From this research can be concluded that CBZ-SAC co-crystal can form two forms which are plate-like and needle like. Varying the mol of carbamazepine and used different solvents could be used for further studies to see the difference trending.

FASA TRANSFORMASI PEPEJAL 'CARBAMAZEPINE-SACCHARIN (CBZ-SAC) CO-CRYSTAL'

ABSTRAK

Satu penyelidikan telah dijalankan ke atas perubahan fasa pepejal dan kestabilan 'carbamazepine-saccharin co-crystal'. Farmasitikal 'co-crystal' adalah salah satu kaedah yang berpotensi untuk meningkatkan 'bioavailibity' dadah yang mempunyai kelarutan rendah akueus. Oleh itu, tujuan kajian ini adalah untuk menentukan julat stabil pembentukan 'carnamazepine-saccharin co-crystal' dengan menggunakan kaedah berasaskn larutan. Tiga teknik akan digunakan dalam kaedah ini iaitu penghabluran penyejukan, penyejatan pelarut dan 'sluury', untuk menyediakan bahan kimia dan menggunakan etanol sebagai pelarut. Nisbah mol CBZ dan SAC yang berlainan akan diuji dalam usaha untuk mengkaji pembentukan CBZ-SAC 'co-crystal'. Pencirian fizikal 'co-crystal' akan dianalisis menggunakan DSC and mikroskop penyelidikan. Apabila kepekatan saccharin meningkat, takat lebur akan meningkat juga dan membawa kepada kelarutan rendah tetapi kebanyakannya takat lebur 'co-crystal' adalah rendah. Daripada kajian ini, dapat disimpulkan bahawa CBZ-SAC co-crystal boleh membentuk dua bentuk iaitu 'plate-like' dan 'needle-like'. Mengubah mol carbamazepine dan pelarut yang berbeza-beza boleh digunakan untuk kajian lanjut untuk melihat perbezaan trendnya.

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LIST OF ABBREVIATIONS

APIs	-	Active pharmaceutical ingredients
CBZ	-	Carbamazepine
SAC	-	Saccharin
BCS		Biopharmaceutical classification system
DSC	-	Differential scanning calorimetry
FTIR	-	Fourier transform infrared spectroscopy
PXRD	-	Powder X-ray diffraction
SEM	-	Scanning electron microscopy
TGA	-	Thermogravimetric analysis

LIST OF SYMBOLS

°C	-	degree Celsius
atm	-	atmospheric pressure
L	-	Litre
m	-	Metre
mg	-	miligram
mL	-	mililiter
rpm	-	revolutions per minute (r/min)
mM		milimol
g		grams
μm		micrometer
J		Joules
ΔH_{fus}		Heat of fusion

CHAPTER 1

INTRODUCTION

1.1 Research Background

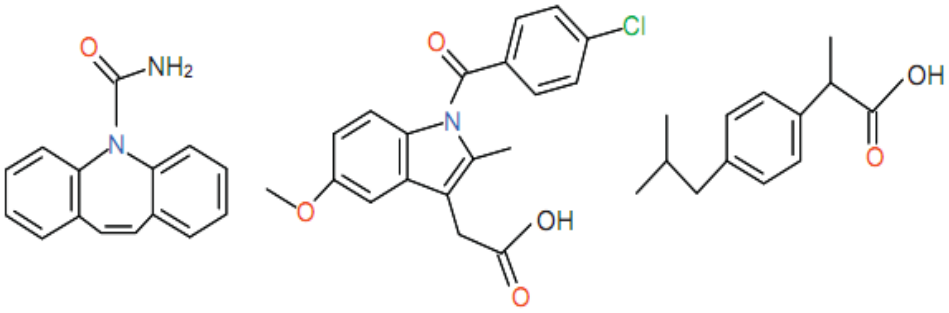
Drug molecules with limited aqueous solubility are currently the major problem for the pharmaceutical industry. These gives a lot of disadvantages such as lead to slow dissolution in biological fluids, insufficient and inconsistent systemic exposure and consequent sub-optimal efficacy in patient, particularly when delivered via the oral route of administration. Drug molecules can exist in the solid form in either crystalline or amorphous states. Because of the instability of many amorphous materials, most drugs are formulated in the crystalline state (Vippagunta et al., 2001).

Co-crystallization is a technique to modify key solid-state properties of pharmaceuticals which have useful attributes in terms of physical properties, such as solubility, hygroscopicity, stability and dissolution rate. Currently, it has been widely used in the pharmaceutical industry in order for improving the solubility of drugs since the drug often discarded during commercial production due to their low solubility.

A pharmaceutical co-crystal means a crystal with one of the crystal components as an active pharmaceutical ingredient (API) and the other called co-former. The Figure1.1 above shows some examples of APIs and co-former. Co-former is substances that are solids at ambient conditions in their pure form and in the presence of drug can form crystalline solids that exhibit non-ionic intermolecular interactions and contain both components. This can be designed by crystal engineering with the intention to improve the solid-state properties of an API without affecting its intrinsic structure (Qiao *et al*, 2011).

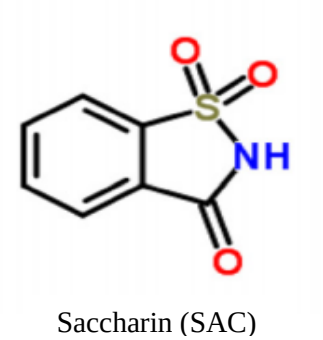
Table1.1 Chemical structure of the representative APIs and co-former

Active pharmaceutical ingredients (APIs):

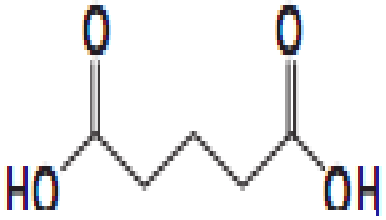


(1) carbamazepine (2) indomethacin (3) ibuprofen

Co-formers:



Saccharin (SAC)



Glutaric acid (GLU)

(Source: Wu et al., 2011)

Co-crystal can be prepared by several methods such as solvent and solid based methods. The solvent-based methods involve slurry conversion via solvent evaporation, cooling crystallization and precipitation while the solid based methods involve dry grinding and solvent-assisted grinding (Padrela, 2010). It can be characterized in a wide variety of ways. Qiao (2011) pointed out that Powder X-ray diffraction (PXRD) was the most commonly used method in order to characterize co-crystals. Besides that, Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) were other common spectroscopic methods may be used.

1.2 Problem Statement

Carbamazepine poses multiple challenges for oral drug delivery, including a narrow therapeutic window, autoinduction of metabolism and dissolution-limited bioavailability (Magali et al., 2006). Carbamazepine is characterized as having low solubility in an aqueous media, but a high permeability across the human intestinal membrane or an appropriately predictive *in vitro* model. Therefore, formulation strategies are aimed at improving the solubility, stability and dissolution rates in order to enhance the bioavailability of this highly permeable drug.

The bioavailability of oral drug substances is a function of their solubility and dissolution in gastric/intestinal fluids as well as the drugs ability to permeate cellular membranes if efficacy requires distribution away from the gastric/intestinal fluids. Together solubility and permeability are the basis for the biopharmaceutical

classification system (BCS) that segments drugs into four classifications based on these two properties. Solubility improvements are particularly desirable for BCS class II compounds that have low solubility and high permeability.

According to Derdour et al., (2011), pharmaceutical co-crystal emerges as a potential method for enhancing the bioavailability of drugs with low aqueous solubility. Many authors agreed with this idea. Co-crystal are able to alter the physicochemical properties of active drug substances through combining drugs and additional components (i.e. co-formers) in the same crystal structure thereby altering solid-state properties and solution behavior without modifying chemical structure.

1.3 Research Objective

The objective of this experiment is to determine the stable region of carbamazepine-saccharin (CBZ-SAC) co-crystal formation using solution based method.

1.4 Scope of Research

The following are the scopes of this research to support the above mentioned objectives:

i) To study formation of carbamazepine-saccharin co-crystal using solution method via varying the mol ratio of carbamazephine and saccharin concentration.

ii) To identify the physical properties of carbamazepine-saccharin co-crystal.

1.5 Rationale and Significance

This study will provide a range of SAC/CBZ mol ratio for the formation of stabilize carbamazepine-saccharin co-crystal by using solution method. It will lead to a better understanding of the co-crystal formation. Co-crystal is constructed from intermolecular interactions such as van der Waals contact forces, Π-stacking interactions, and hydrogen bond (Qiao *et al*, 2011). Co-crystal are gaining much interest because the resulting new crystal forms of APIs many times have different pharmaceutical, physical, and chemical properties compared to the original API.

1.6 Thesis Outline

This thesis is divided into five chapters, starting with Chapter 1. In this chapter will introduce the overview about co-crystal, including the problem statement, objective and the scope of the study also are included in this chapter.

Next, Chapter 2 is about literature review on co-crystal as a solid form, and pharmaceutical co-crystal including the molecular interaction, the formation method and co-crystal characterization technique. In this section, all the relevant journal, technical paper and books taken from those researches will be studied and discussed.

Then, Chapter 3 will be covered the parts of experimental set up and will be explained more details on methodology and operating procedures. The co-crystal formation method and characterization techniques used for this system are described in detail. In addition, in this chapter also explained the material used in this experiment.

Chapter 4 will be covered on the results and discussion of the research during the operation process. All the experimental result and data will be discussed in details which are including screening methods and characterization of co-crystal with different mol ratio.

Chapter 5 will be discussed on the conclusion can be made for the study and some recommendations can be taken. Figure 1.1 shows the road map of thesis.

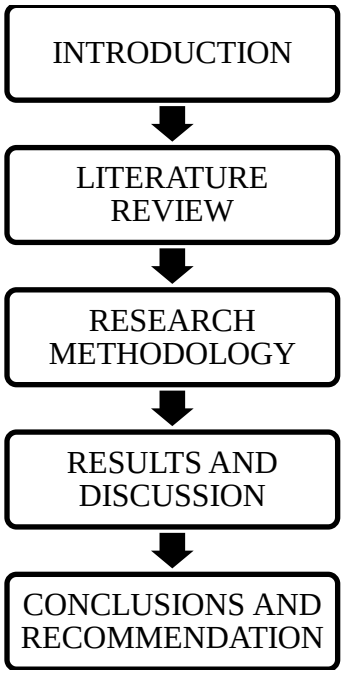


Figure 1.1 The road map of thesis

CHAPTER 2

LITERATURE REVIEW

2.1 Co-Crystal as a Solid Form

The solid forms of active pharmaceutical ingredients are important aspects of drug development in the pharmaceutical industry. Active pharmaceutical ingredients (API) can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystal and amorphous solids as shown in Figure 2.1. Yadav et al. (2009) pointed out that each form display unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug. This was seen in the recent study (Qiao et al., 2011) that co-crystal is one of the methods of great interest for the pharmaceutical industry since it offer potential improvements in solubility, dissolution rate, and enhance other essential properties of the APIs.

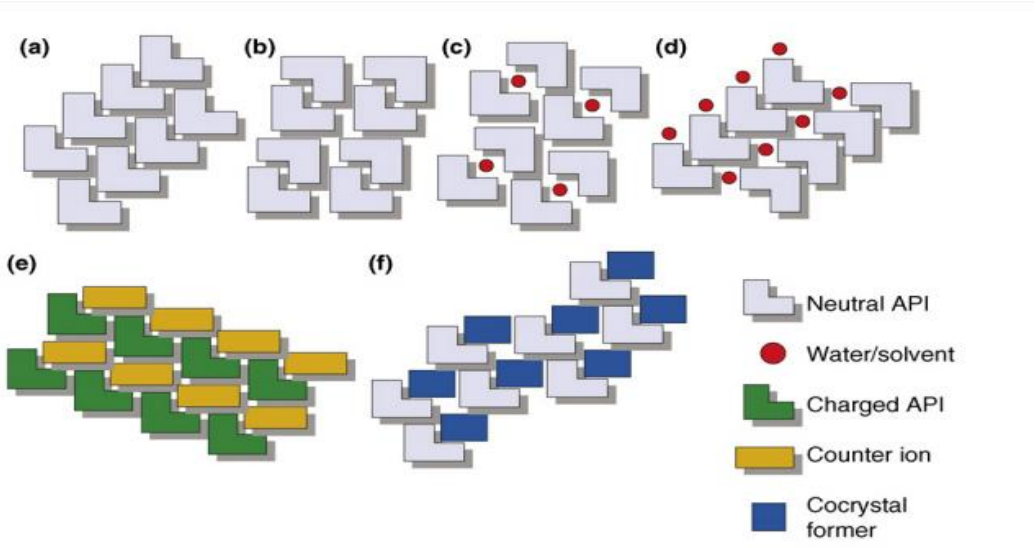


Figure 2.1 The range of single crystalline forms that is possible for an API: (a) pure API; (b) polymorph of pure API; (c) solvate of API; (d) clatharte hydrate/solvate of API; (e) salt of API; (f) pharmaceutical co-crystal. Salts and co-crystal can form hydrates, solvates and polymorphs. (Source: Shan et al., 2008)

To distinguish between co-crystal and solvates are their physical state of the isolated pure components (BS 2009). If one component is a liquid at room temperature, the crystals are designated as solvates; if both are solids at room temperature; the crystals are designated as co-crystal. To reduce the risk of solvate formation, solvent with a high solubility of the co-crystal former is chosen.

A major limitation of salts is the APIs have to seize a suitable (basic or acid) ionizable site only. Co-crystal becomes an alternative to salts when APIs had limited pharmaceutical profiles based on their nonionizable functional group. This is because APIs could potentially be co-crystallized regardless of acidic, basic or ionizable groups. Although the solubility of the salt, which is governed by the solubility products of API and the counter salt, may not be much better than that of the free form, the dissolution

rate is usually much faster due to alterations in the microenvironmental pH (Kawakami 2012).

Polymorph is a crystalline solid which have the same compound or composition but difference crystalline form. This was seen in the recent study (Spong et al., 2004) that polymorphisms of carbamazepine have four forms which are the triclinic (form I), trigonal (form II), monoclinic (forms III and IV) and form V. Figure 2.2 shows packing diagram of carbamazepine polymorphs. However, the polymorphs can convert spontaneously from less stable to more stable forms and vice versa since the solubility is low. Then, Llinas and Goodman (2008) come out with suggestion which is find out the most stable form of polymorph instantly, so that it can be used for subsequent testing.

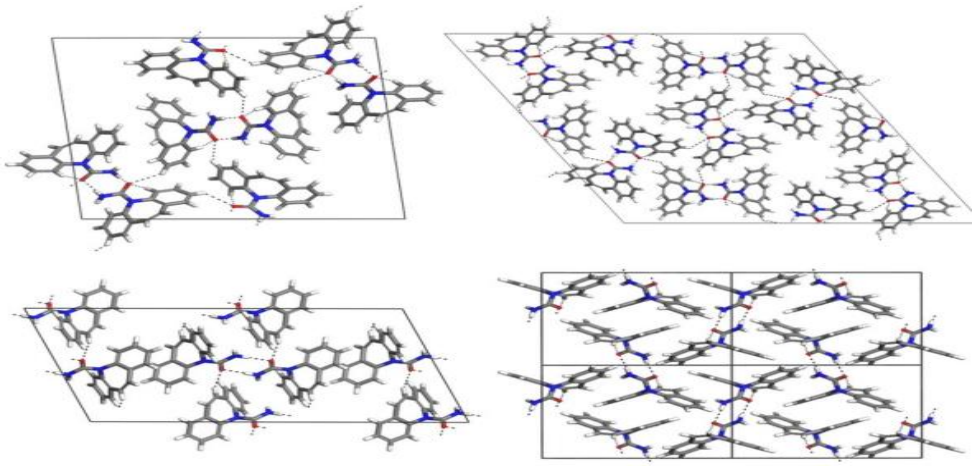


Figure 2.2 Packing diagrams of carbamazepine polymorphs. From top left clockwise: I.II, III and IV **(**Source: Price et al., (2004)

Co-crystallization technology become increasingly popular through the development of new class of crystalline solids, called pharmaceutical co-crystal. The pharmaceutical co-crystal has already proven to be useful in enhancing the solubility, dissolution rate, stability and bioavailibity of APIs (Zhang et al., 2012).

2.2 Pharmaceutical Co-Crystal

A pharmaceutical co-crystal consists of an API (host) and a pharmaceutically acceptable compound (guest, co-former). Co-crystal is designed based on the principles of crystal engineering and supramolecular chemistry, where co-crystal components are selected based on favorable molecular recognition interactions. Typically, though not exclusively, the drug component is hydrophobic and poorly soluble in water. In general the co-formers are small organic acids, though co-formers with other ionization properties have been successfully co-crystallized. Table 2.1 represents some examples of pharmaceutical co-crystal.

Table 2.1 Examples of pharmaceutical co-crystal

API	Co-formers	Reference
Carbamazepine	DMSO, benzoquinone, terephthalaldehyde, acetone, saccharin, nicotinamide, acetic acid, formic acid, butyric acid, trimesic acid, 5-nitroisophtalic acid, adamantine-1,3,5,7-tetracarboxylic acid, formamide	(Fleischman et al., 2003)
Indomethacin	Nicotinamide, saccharin	(Wu, et al. 2011)
Fluoxetine HCl	Benzoic acid, succinic acid & fumaric acid	(Shan and Zaworotko 2008)
Ibuprofen	Nicotinamide	(Qiao et al., 2011)

2.2.1 Molecular Interactions in Co-Crystal

This co-crystal is constructed from intermolecular interactions such as van der Waals contact forces, pi stacking interactions and hydrogen bond. Because of its strength and directionally, the hydrogen bond has been the most important interaction in molecular recognition (Spong et al., 2004). According to Etter et al., (1990), in the graph-set notation system that been introduced by him, four principal motif are used which are chains, dimers, rings and hydrogen bonds as descriptor of hydrogen molecular solids.

In addition, Dale et al., 2004, agreed and provide guidelines for the design of hydrogen bonded solids as follow: (i)all good proton donors and acceptors are used in hydrogen bonding; (ii) if six-member ring intermolecular hydrogen bonds can form, they will usually do so in preference to forming intermolecular hydrogen bonds;

(iii) the best proton donors and acceptors remaining after intermolecular hydrogen-bond formation, form intermolecular hydrogen bonds to one another. Carboxylic acids, amides, carbohydrates, alcohols and amino acids are the examples of pharmaceutically acceptable co-crystal former that are able to co-crystallize with APIs as illustrated in Figure 2.3.

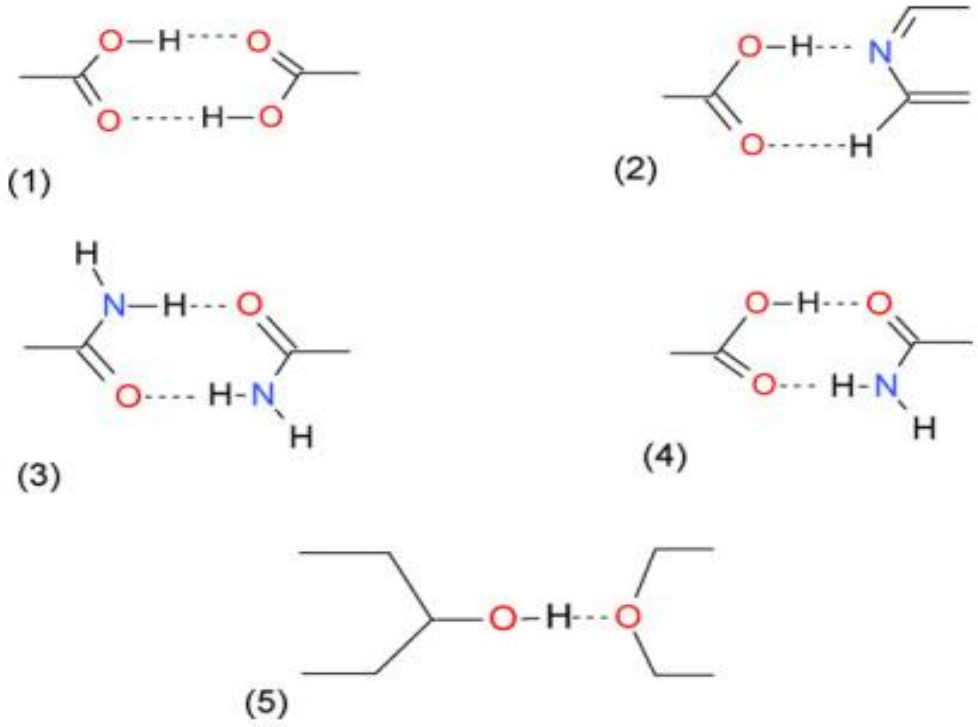


Figure 2.3 Typical hydrogen bonds utilized in crystal engineering (Source: Qiao et al., 2011)

2.3 Physiochemical Properties

The main advantage of co-crystal is the ability to generate a variety of solid forms of a drug that have physicochemical properties distinct from the solid co-crystal

components. Physiochemical properties such as crystallinity, melting point, stability, and dissolution rate are potentially modified by co-crystal formation. These properties can directly or indirectly affect the suitability of a particular API as a pharmaceutical product.

2.3.1 Melting Point

The melting point of co-crystal, in general, differs from those of the individual components due to changes in molecular interactions, composition and structure. The melting point usually in between of the APIs and co-former or lower than that of the APIs or co-formers. For example, the melting points of 10 co-crystal to the API carbamazepine (Fleischman et al., 2003) and their respective conformers showing that all these co-crystal have a melting point that fell between the melting point of the API and their correspondent co-former.

2.3.2 Stability

Stability is a very important parameter when evaluating the properties of a pharmaceutical co-crystal. Usually, the stability testing of a newly developed co-crystal includes four aspects: relative humidity stress, thermal stress, chemical stability, and solution stability. For example, co-crystallization can improve the chemical stability of an API through rearrangement of the molecules in the crystalline lattice. Carbamazepine-saccharin and carbamazepine-nicotinamide co-crystal contain azepine