SOLID PHASE TRANSFORMATION AND STABILITY OF CARBAMAZEPINE-SACCHARIN CO-CRYSTAL

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LIST OF ABBREVIATION

SAC	Saccharin
CBZ	Carbamazepine
C-C	Co-Crystal

ABSTRACT

Formulation of drug products is a multidisciplinary field, with pharmaceutical materials science being a fundamental branch that continuously provides important insights, theories, and technologies to formulation sciences. The recent advances in this area have brought this research possibility to produce pharmaceutical materials by crystallization design. This research is conducted to determine the character by both physical and chemical properties beside to determine the solubility of Carbamazepine and Saccharin. It is started by determine the co-crystal solubility of Carbamazepine and Saccharin by applying the different concentration and temperature of Carbamazepine and Saccharin solution by following gravimetric method. It is proceed by determine the characterization of solution by screening using FTIR, TGA and DSC to get morphology, melting point, weight loss and wavelength. The final discussion after result finding, it can be concluding that concentration and temperature are the main factor to control the solubility of Carbamazepine and Saccharin co-crystal. By using the solubility that was obtained from the gravimetric method, the characterization process of both Carbamazepine and Saccharin are also conclude by their own properties. As an additional conclusion, solid state form of active pharmaceutical ingredients (APIs), co-crystals not only offer a tool for tailoring physicochemical properties, but also create new opportunities for the research-based pharmaceutical companies to address intellectual property (IP) protection issues.

ABSTRAK

Formulasi produk dadah adalah satu bidang pelbagai disiplin, dengan sains bahan farmaseutikal menjadi satu cabang asas yang berterusan memberikan pandangan yang penting, teori dan teknologi untuk sains penggubalan. Kemajuan terkini dalam bidang ini telah membawa kemungkinan ini penyelidikan untuk menghasilkan bahan-bahan farmaseutikal oleh reka bentuk penghabluran. Penyelidikan ini dijalankan untuk menentukan watak ciri-ciri fizikal dan kimia untuk menentukan kelarutan Carbamazepine dan Sakarin. Ia bermula dengan menentukan keterlarutan bersama kristal Carbamazepine dan Sakarin dengan menggunakan berbeza kepekatan dan suhu penyelesaian Carbamazepine dan Sakarin dengan mengikuti kaedah gravimetrik. Ia diteruskan dengan menentukan pencirian penyelesaian oleh saringan menggunakan FTIR, TGA dan DSC untuk mendapatkan morfologi, takat lebur, berat badan dan panjang gelombang. Perbincangan akhir selepas keputusan ditemui, ia boleh disimpulkan bahawa kepekatan dan suhu adalah faktor utama untuk mengawal kebolehlarutan kristal bersama Carbamazepine dan Sakarin. Dengan menggunakan kebolehlarutan yang diperolehi daripada kaedah gravimetrik, proses pencirian kedua-dua Carbamazepine dan Sakarin juga boleh didapati berdasarkan kaedah tertentu mengikut alatan perincian yang digunakan. Sebagai kesimpulan tambahan, pepejal bahan aktif farmaseutikal (API), bersama-kristal bukan sahaja menawarkan alat untuk penghasilan sifat fizikokimia, tetapi juga mewujudkan peluang-peluang baru bagi syarikat-syarikat farmaseutikal berasaskan penyelidikan untuk menangani harta intelek (IP) isu-isu perlindungan .

CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND STUDY

Pharmaceutical industry is a rapidly growing industry in line with the interests of pharmacy to human health globally. Because of that, chemists and engineers in the pharmaceutical industry generally seek to deliver the best effort from them to produce better research and development in pharmaceutical especially in crystallization. One flourishing area in the field of crystal engineering is based upon the formation of crystalline molecular complexes, or co crystals (Nehm, et al. 2006).

Pharmaceutical co-crystals contain an active pharmaceutical ingredient (API) and at least one other co-former, which is normally a solid under ambient conditions. Co crystals may be defined as materials which contain two or more discrete molecular entities in the crystal lattice. Crystal engineering, when applied to co crystal systems, generally involves the design and study of new materials in order to widen the knowledge base of successful engineering strategies, and the application of that knowledge to provide co crystals with specific properties for a multitude of applications (Braga, 2003).

Crystal engineering is actively applied within a variety of scientific disciplines as diverse as materials science, nanotechnology and the pharmaceutical industry. Crystal form can be crucial to the performance of a dosage form (Nehm, et al. 2006). This is especially true for compounds that have intrinsic barriers to drug delivery, such as low aqueous solubility, slow dissolution in gastrointestinal media, low permeability and first-pass metabolism. The nature of the physical form and formulation tends to exhibit the greatest effect on bioavailability parameters of water insoluble compounds that need to be given orally in high doses (Nehm, et al. 2006).

An alternative approach available for the enhancement of drug solubility, dissolution and bioavailability is through the application of crystal engineering of co-crystals. The physicochemical properties of the active pharmaceutical ingredients and the bulk material properties can be modified, whilst maintaining the intrinsic activity of the drug molecule. This research covers solid dispersions and polymorphs, mechanism of formation of co-crystals, methods of preparation of co-crystals and application of co-crystals to modify physicochemical characteristics of active pharmaceutical ingredients along with the experiments. (A Yadav et al., 2009).

1.2 RESEARCH OBJECTIVE

Based on the aforementioned research background and problem statement, the objectives of this study are:

1. To measure the solubility of Carbamazepine(CBZ),Saccharin(SAC) and Carbamazepine-Saccharin(CBZ-SAC) co-crystal.

2. Study the phase transformation of the CBZ-SAC co-crystal.

1.3 RESEARCH SCOPE

The scope of the research consists of:

1) Measurement of CBZ and SAC by using gravimetric and High-Performance Liquid Chromatography method.
2) Manipulation of the SAC ratio to CBZ in order to measure the co-crystal transformation based on the solubility data obtained.

1.4 PROBLEM STATEMENT

Carbamazepine solubility is very low in the water to react. To come out from this problem, co-crystal formation is studied in order to improve the Carbamazepine solubility. Before the co-crystal formation experiment is precede, the solubility of carbamazepine and the chosen co-crystal former, Saccharin solubility is measured as a guideline calculation and selection for further study.

REPORT LAY-OUT

This report contains 5 main chapters to distribute the whole report accordingly. In the first chapter, the introduction which gave the briefing about this project is discussed. The second chapter contains literature review based on crystallization and co-crystal. The third chapter explained the methodology of the experiment. In the fourth chapter, it contain results and discussions and in final chapter with conclusions and recommendations.

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CHAPTER TWO: LITERATURE REVIEW

2.1 FUNDAMENTALS OF CRYSTALLIZATION AND CO- CRYSTAL

2.1.1 CRYSTALLIZATION

Crystallization is another solid-liquid separation process,in which mass transfer of a solute from the liquid solution to a pure solid crystalline phase occurs. An important example is in the production of sucrose from sugar beet,where the sucrose is crystallized out from an aqueous solution (Geankoplis, 2003).

Crystallization is a process where solid particles are formed from homogenous phase. This process can occur in freezing of water to form ice, in the formation of snow particles from a vapor, in the formation of solid particles from a liquid melt,or in the formation of solid crystals from liquid solutions. In crystallization the solution is concentrated and usually cooled until the solute concentration become greater than its solubility at that temperature. The solute comes out of the solution, forming crystals of approximately pure solute (Geankoplis., 2003).

2.1.1.1 Types of Crystal Geometry.

A crystal can be defined as a solid composed of atoms ions, or molecules which are arranged in an orderly and repetitive manner. It is a highly organized types of matter. The atom, ions, or molecules are located in three-dimensional arrays or space lattices. The interatomic distances between these imaginary plane or spaces lattices in a crystal are measured by X-ray diffraction, are the angles between these planes. The pattern or arrangement of these space lattices is repeated in all direction (Geankoplis, 2003).

There are seven classes of crystal, depending upon the arrangement of the axes to which the angles are referred:

1) Cubic system. Three equals axes at right angles to each other.
2) Tetragonal system. Three axes at right angles to each other, one axis longer than the other two.
3) Orthorhombic system. Three axes at right angles to each other, all of different length.
4) Hexagonal system. Three equal axes in one plane at 60° to each other, and fourth axis at right angle to this plane and not necessarily at the same length.
5) Monoclinic system. Three unequal axes, two at right angles in plane and a third at some angle to this plane.
6) Triclinic system. Three unequal axes at unequal angles to each other and not 30,60, or 90.
7) Trigonal system. Three equal and equally inclined axes.

The relative development of different types of faces of a crystal may differ depending on the solute crystallizing.

2.1.1.2 Equilibrium Solubility in Crystallization

Once crystallization is concluded, equilibrium is set up between the crystals of pure solute and the residual mother liquor, the balance being determined by the solubility (concentration) and the temperature. The driving force making the crystals grow is the concentration excess (supersaturation) of the solution above the equilibrium (saturation) level. The resistances to growth are the resistance to mass transfer within the solution and the energy needed at the crystal surface for incoming molecules to orient themselves to the crystal lattice (Earle, 1983).

Solubility is defined as the maximum weight of anhydrous solute that will dissolve in 100 g of solvent. In the food industry, the solvent is generally water (Earle, 1983).

During crystallization, the crystals are grown from solutions with concentrations higher than the saturation level in the solubility curves. Above the supersaturation line, crystals form spontaneously and rapidly, without external initiating action. This is called spontaneous nucleation. In the area of concentrations between the saturation and the supersaturation curves, the metastable region, the rate of initiation of crystallization is slow; aggregates of molecules form but then disperse again and they will not grow unless seed crystals are added. Seed crystals are small crystals, generally of the solute, which then grow by deposition on them of further solute from the solution. This growth continues until the solution concentration falls to the saturation line. Below the saturation curve there is no crystal growth, crystals instead dissolve (Earle, 1983).

The solubility of a substance is dependent on the forces holding the crystal together (the lattice energy) and the solvent acting on these forces. For now, we will consider only water as the solvent. As the solid dissolves, water molecules surround the ions in the solution by a process called hydration. During hydration, energy is released. The extent to which the energy of hydration is greater than the lattice energy determines the solubility (Earle, 1983).

The equilibrium involved in the solubility of a substance is:

$$M_aX_b\,(s) \leftrightarrows a\,M^{n+}\,(aq) + b\,X^{n-}\,(aq) \quad (\text{a general equation}) \qquad (2.1)$$

where M is the cation of change n+ and X is the anion of charge n-. The subscripts of the salt become the coefficients for the ions. The equilibrium mass action expression would be:

$$K_{sp} = [M^{n+}]^a\,[X^{n-}]^b \qquad (2.2)$$

Notice that only the aqueous ions are part of the mass action expression. Solids are never included. Also notice that the coefficient for each ion becomes the exponent in the mass action expression.

There are four common types of solubility equilibria problems: solubility in pure water (will a precipitate form or finding the molar solubility), solubility in the presence of a common ion and selective precipitation.

2.1.1.3 Equipment for Crystallization.

Crystallizer may be classified according to whether they are batch or continuos in operation. Batch operation is done for certain special application. Continuous operation of crystallizers is generally preferred (Geankoplis, 2003).

Crystallization cannot occur without super-saturation. A main function of any crystallizer is to cause a supersaturated solution to form. Crystallizing equipment can be classified according to the methods used to bring about super-saturation as follows;

1) Super-saturation produced by cooling the solution with negligible evaporation-tank and batch-type crystallizer
2) Super-saturation produced by evaporation of the solvent with little or no cooling-evaporator-crystallizers and crystallizing evaporators.

3) Super-saturation by combined cooling and evaporation in an-adiabatic evaporator-vacuum crystallizer.

In another method of classification of crystallizers, the equipment is classified according to the method of suspending the product crystal. Examples are crystallizer where the suspension is agitated in a tank, is circulated by a heat exchanger, or is circulated in a scrapped surface exchanger (Geankoplis, 2003).

Tank crystallizer.

In tank crystallization, which is an old method is still used in some specialized cases, hot saturated solution is allowed to cool in open tanks. After a period of time the mother liquor is drained and the crystals removed. Nucleation and the size of crystals are difficult to control. Crystals contain considerable amounts of occluded mother liquior. Labor cost is very high. In some cases the tank is cooled by coils or a jacket and an agitation used to improved heat-transfer rate. However, crystal often builds up on these surfaces. This type of crystallizers has limited application; it is sometimes used to produce certain fine chemicals and pharmaceuticals products (Geankoplis, 2003).

Scraped surface crystallizers

One type of scraped surface crystallizers is the Swenson-Walker crystallizer, which consist of an open through 0.6 m wide with a semicircular bottom having a cooling jacket outside. A slow-speed spiral agitator rotates and suspends the growing crystals on turning. The blades pass closed to the wall and break-off any deposits of crystals on the cooled wall. The product generally has a somewhat wide-crystal-size distribution (Geankoplis, 2003).

Circulating-liquid evaporator-crystallizer

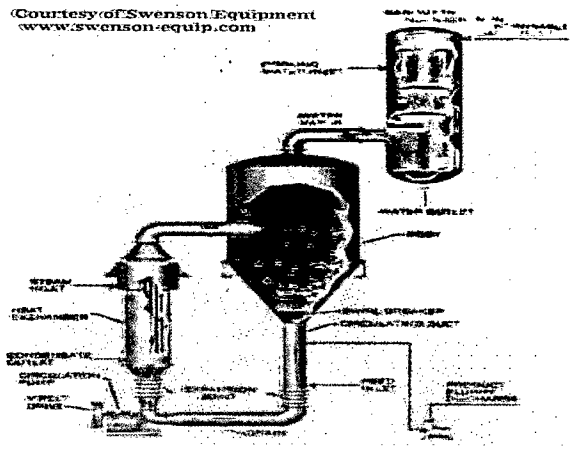

Figure 2.1 Image of Circulating-liquid evaporator-crystallizer by Swenson-equip.

From Figure 2.1, these crystallizers combine crystallization and evaporation, thus the driving forces toward supersaturation. The circulating liquid is forced through the tubeside of a steam heater. The heated liquid flows into the vapor space of the crystallization vessel. Here, flash evaporation occurs, reducing the amount of solvent in the solution (increasing solute concentration), thus driving the mother liquor towards supersaturation. The supersaturated liquor flows down through a tube, then up through a fluidized area of crystals and liquor where crystallization takes place via secondary nucleation. Larger product crystals are withdrawn while the liquor is recycled, mixed with the feed, and reheated (Geankoplis, 2003).

Circulating – magma vacuum crystallizer

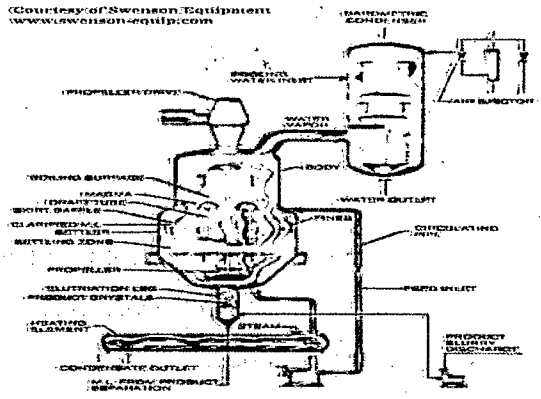

Figure 2.2 Image of Circulating-magma Vacuum Crystallizer by Swenson-equip.com

Figure 2.2 shows the example of Circulating-magma Vacuum Crystallizer. In this type of crystallizer, the crystal/solution mixture (magma) is circulated out of the vessel body. The magma is heated gently and mixed back into the vessel. A vacuum in the vapor space cause boiling at the surface of the liquid. The evaporation causes crystallization and the crystals are drawn off near the bottom of the vessel body (Geankoplis, 2003).

Evaporative crystallizers

Evaporative crystallizers are common in the sugar and salt industries. They are generally of the calandria type. Vacuum evaporators are often used for crystallization as well, though provision needs to be made for handling the crystals. Control of crystal size can be obtained by careful manipulation of the vacuum and feed. The evaporator first concentrates the sugar solution, and when seeding commences the vacuum is increased. This increase causes further evaporation of water which cools the solution and the crystals grow. Fresh saturated solution is added to the evaporator and evaporation continued until the crystals are of the correct size. In some cases, open pan steam-heated evaporators are still used, for example in making coarse salt for the fish industry. In some countries, crystallization of salt from sea water is effected by solar energy which concentrates the water slowly and this generally gives large crystals (Earle, 1983).

2.1.2 CO-CRYSTAL

2.1.2.1 Co-crystal Design

Co-crystals are multiple component systems where intermolecular interactions (including hydrogen bonds, van der Waals, and π - π interactions) and favorable geometries lead to a self-assembled supramolecular network. Co-crystals offer the advantage of generating solid forms of APIs even when they lack ionizable functional groups and in this way produce materials with a large range of properties that are not available in single API solid phases (polymorphs and amorphous forms), or in API solvates, or salt forms. Solvates are com pounds where one of the components is liquid at room temperature, such as a hydrate. In a crystalline salt, the interactions are mostly electrostatic, and the components are ionized (Childs, et al. 2008).

A pharmaceutical co-crystal contains an API and a co-former molecule(s), both of which typically exist in the neutral state and interact by hydrogen bonding or by other non-covalent bonds. (A few co-crystals have been synthesized in which the API is ionized, but the co-former is still non-ionized (Childs and Hardcastle, 2007).) The term co-crystal generally refers to components that in their pure states are solids at room temperature (Aakeroy and Salmon, 2005). Co-crystals may include two or more different components and in most cases to date, two and

three component systems are reported with the latter being mostly co-crystalline solvates, e.g. theophylline-5-fluorouracil hydrate (Zaitu, et al. 1995), carbamazepine-4-aminobenzoic acid hydrate (McMahon, Bis et al. 2005), and tetroxoprim-sulfametrole methanolate (Caira, et al. 2003).

The field of crystal engineering has focused on understanding the intermolecular interactions and connectivity that lead to the construction of super molecules or extended architectures. Because of its strength and directionality, the hydrogen bond has been the most important interaction in co-crystal formation (Wenger and Bernstein, 2008). By studying the hydrogen bond patterns in crystalline solids, valuable knowledge is gaining to identify hydrogen-bond preferences and reliable synthons that lead to co-crystal formation (Wenger and Bernstein 2008). The frequency of hydrogen bond motifs and other important interactions in crystal lattices can be studied by using the Cambridge Structural Database (CSD) by searching for specific molecules, functional groups, and synthons (Nangia and Desiraju, 1998).

2.1.2.2 Carbamazepine Co-Crystal Structure

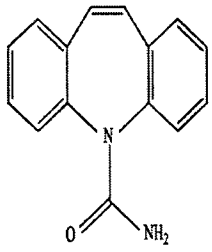

Figure 2.3 Chemical Structure of Carbamazepine