

**CARBAMAZEPINE-IBUPROFEN CO-CRYSTAL
SCREENING USING NON-STOICHIOMETRIC
METHOD**

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CARBAMAZEPINE-IBUPROFEN CO-CRYSTAL SCREENING USING NON-STOICHIOMETRIC METHOD

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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
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JANUARY 2014

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SUPERVISOR'S DECLARATION

We hereby declare that we have checked this thesis and in our opinion, this thesis is adequate in terms of scope and quality for the award of the degree of Bachelor of Chemical Engineering.

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STUDENT'S DECLARATION

I hereby declare that the work in this thesis is my own except for quotations and summaries which have been duly acknowledged. The thesis has not been accepted for any degree and is not concurrently submitted for award of other degree.

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Dedication

*To my beloved Parents,
My family members that always love me,
My friends, my fellow colleague
My supervisor,
And all faculty members,
For all your care, endless support and believe in me.*

*Sincerely,
Nurul Aini Rosli, 2014*

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ABSTRACT

Co-crystals is a facilitating technology that is used in new or existing drug delivery systems by majority of pharmaceutical companies in formulation of drug development. However the challenging aspects in development of drug molecules are correlated with their slow dissolution in biological fluids and thus insufficient and inconsistent systemic exposure, and consequent sub-optimal clinical effectiveness. The traditional approaches to deal with the issues of poor aqueous solubility often fail to create a viable solid form which is insufficient to provide enough enhancement of bioavailability. And so, there is enormous potential to explore co-crystal design of marketed APIs among each other to enhance the solubility and bioavailability of the product. This paper presents the co-crystal screening approach through the study of carbamazepine (CBZ) and ibuprofen (IBU). The screening was conducted using non-stoichiometric methods (solid addition of CBZ to saturated solution of IBU). In the experiment, CBZ-IBU co-crystal was prepared in various solvents and left to equilibrate in three conditions; stagnant, manually agitated and shaken in three days to produce the co-crystal. Physical characterization of the solid co-crystal is being characterized by using optical microscopy for its morphology as well by using differential scanning calorimetry (DSC) to determine the thermal properties. The only co-crystal of CBZ-IBU success to form using the non-stoichiometric approach is in formic acid solvent whereas for the others, they behaving more likely to be CBZ in different forms. Overall, DSC analysis shows that either CBZ or IBU occurred due to the peak which corresponded to their melting point. From this study, it can be concluded that co-crystal formation between CBZ-IBU using non-stoichiometric method only successful in formic acid.

ABSTRAK

Ko-kristal adalah teknologi mudah yang digunakan dalam sistem penyampaian ubat baru atau sedia ada oleh majoriti syarikat-syarikat farmaseutikal dalam formulasi ubat-ubatan. Walau bagaimanapun, aspek mencabar dalam formulasi ubat-ubatan berkait rapat dengan kadar disolusi yang perlahan dalam cecair biologi yang secara tidak langsung menyebabkan pendedahan yang tidak cukup dan konsisten seterusnya memberi kesan kepada keberkesanan sub-optimum klinikal. Pendekatan tradisional yang digunakan untuk menangani isu-isu berkenaan dengan kelemahan larutan akueus seringkali gagal untuk mereka bentuk pepejal yang bertepatan untuk meningkatkan bioavailabiliti. Oleh itu, terdapat potensi yang besar untuk meneroka reka bentuk bersama ko-kristal antara API dan API yang dipasarkan untuk meningkatkan tahap kelarutan dan bioavailabiliti produk. Kertas kerja ini mengkaji ujikaji saringan pembentukan ko-kristal antara carbamazepine (CBZ) dan ibuprofen (IBU). Pemeriksaan pembentukan co-kristal telah dijalankan menggunakan kaedah tidak stoikiometri (penambahan pepejal CBZ kepada larutan tepu IBU). Dalam eksperimen ini, ko-kristal CBZ - IBU telah disediakan dalam pelbagai pelarut dan dibiarkan dalam tiga keadaan; bertakung, dikacau secara manual dan digoncang dalam tiga hari untuk menghasilkan ko-kristal. Analisis terhadap sifat fizikal pepejal co-kristal menggunakan mikroskop optik untuk memeriksa morfologi ko-kristal dan sifat-sifat thermal dianalisis menggunakan pengimbasan kolimetri (DSC). Satu-satunya ko-kristal CBZ – IBU yang berjaya terbentuk menggunakan teknik bukan stoikiometri adalah dalam larutan asid formik manakala bagi yang lain, mereka lebih cenderung untuk menjadi CBZ dalam bentuk yang berbeza. Secara keseluruhannya, analisis DSC menunjukkan bahawa sama ada CBZ atau IBU berdasarkan titik leburnya. Dari kajian ini, kesimpulan yang boleh dibuat ialah pembentukan ko-kristal antara CBZ - IBU hanya berjaya dalam asid formik.

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LIST OF ABBREVIATIONS

4-ABA	4-Aminobenzoic acid
API	Active pharmaceutical ingredient
BCS	Biopharmaceutical classification system
CBZ	Carbamazepine
CBZ (D)	Carbamazepine dihydrate
CCF	Co-crystal former
CSD	Cambridge structural data
DRH	Deliquescent relative humidity
DSC	Differential scanning calorimetry
FTIR	Fourier transforms infrared
H	Hydrogen
HPLC	High-performance liquid chromatography
IBU	Ibuprofen
IP	Intellectual property
N	Nitrogen
NCT	Nicotinamide
NSAID	Non-steroidal anti-inflammatory drugs
O	Oxygen
RC	Reaction co-crystallization
RH	Relative humidity
SAC	Saccharin
SEM	Scanning electron microscopy
TGA	Thermalgravimetry analysis
TPD	Tertiary phase diagram
XRD	X-ray diffraction
XRPD	X-ray powder diffraction

1 INTRODUCTION

1.1 Motivation and statement problem

Pharmaceutical industry developed major resources in identifying novel active pharmaceutical ingredients (APIs) with suitable physiological profiles that formulated into drugs. However, the development of drug molecules is quite since it often correlated with their slow dissolution in biological fluids that will lead to insufficient as well as inconsistent systemic exposure, and consequent sub-optimal clinical effectiveness. The traditional approaches such as solid dispersions and salt formation, used to overcome these issues often fail in order to generate a viable solid form as the increase in dissolution rate; however it is insufficient to provide enough enhancement of bioavailability. In addition, all these techniques are costly and quite complex, and are only applicable for some types of drugs.

Most of APIs are developed and marketed orally as solid dosage forms that contain a defined crystalline form of an API. Hence, co-crystallization of API is now recognized as a facilitating technology that is used in new or existing drug delivery systems by majority of pharmaceutical companies in providing a route to dramatically influence material properties. And so, there is enormous potential to explore co-crystal design of marketed APIs among each other to enhance the solubility and bioavailability of the product (Zaworotko, 2006; Schultheiss et al. 2009). Yet, relatively less is known about the strategic design principles that could lead to the modification or improvements of their physical and chemical properties.

It has been reported that co-crystal can be screened using various methods. Co-crystal screening technology has the ability to discover, as well as establish new intellectual property (IP) for new drug-drug co-crystals of multiple APIs to protect the product from competition. Development of co-crystal screening may lead to commercialization of new co-crystal product along with separated single enantiomers. A patent of a drug-drug co-crystal in the case of API-API combination with enhanced drug properties than previously known forms could be of high commercial value in market. Designing drug-drug co-crystals may shorten the development time (including clinical trials) than those

of new chemical entities as co-crystals do not engage structural modification of the APIs (Shekon, 2012). Nevertheless, most of the previous co-crystal studies using stoichiometric method such as evaporation and wet grinding techniques, it is of great interest to evaluate the screening approach for co-crystal using non-stoichiometric method. Despite of researcher's interest for multi-API co-crystal study, there still no study of co-crystal between carbamazepine (CBZ) and ibuprofen (IBU) drugs. Therefore, the presents works aim to propose the experimental studies of co-crystal formation of CBZ-IBU using non-stoichiometric screening method.

1.2 Objectives

The objective of this research is:

- To access the co-crystal formation of CBZ-IBU using non-stoichiometric screening method.

1.3 Research scope

The following are the scope of this research:

- i) Prepare the saturated solution of co-crystal former (CCF) in different solvents namely acetonitrile, ethanol, ethyl acetate, propanol, and formic acid.
- ii) Co-crystal screening using non-stoichiometric method in three conditions which are stagnant, continuous shaking and manually agitated.
- iii) Co-crystal characterization using:
 - a) Differential Scanning Calorimetry
 - b) Optical microscopy

1.4 Work contribution

The value of co-crystals with pharmaceutical components lies in the ability to alter the functionality of the materials. Pharmaceutical researchers often consider alternative solid state forms to a free drug compound, such as polymorphs or salts, in order to improve pharmaceutical properties. However, some compounds without a suitable ionisable site (basic or acidic) for proton transfer, will have to eliminate salts formation as an option for drug formulation.

Thus, co-crystals which involve no proton transfer could become practical alternative in drug formulation for this type of compound. Properties relates to drug performance and that can be controlled by co-crystal formation include melting point, chemical stability, dissolution rate, bioavailability, solubility, as well as mechanical properties.

Hence, the findings of this project will lead to the potential use of drug-drug co-crystals in industrial drug formulations. The fundamental and mechanisms behind the co-crystal formation must be fully understood, hence will attracted on the industrial interest into this area of studies, providing direct benefits to the pharmaceutical field and wider long term benefits to public health.

1.5 Thesis organisation

The structure of the thesis is outline as follow:

Chapter 1 discuss on motivation and problem statement lead to this study. The objective and research scopes and work contribution also include in this chapter.

Chapter 2 provides a description on co-crystal design, focused on the intermolecular interactions theory that later will lead to the development of supermolecules. A general description on selection of co-crystal former, as well as the co-crystal properties and mechanism which co-crystal formation can enhance solubility are presented. This chapter also provides a brief discussion of the co-crystal screening techniques available and the co-crystal characterization. A summary of the previous experimental work on carbamazepine co-crystal is also presented.

Chapter 3 gives a review of the screening approach applied for co-crystal formation using non-stoichiometric method including the type of solvent used, and solution procedures through solid addition to saturated solution of CCF with selected solvents. The product crystals obtained were characterized using differential scanning calorimetry (DSC) in order to check on crystal's melting point and optical microscopy for it morphology.

Chapter 4 is devoted to a result and discussion where experimental data obtained using DSC characterization and optical morphology of crystal product presented. Result for confirmation of co-crystal formation analyzed using both of characterization technique compared against different solvent used. A detailed description in different melting point as well as morphology also outlined and compared with result obtained from previous studies.

Chapter 5 represents the summary of the work presented in this thesis and identified areas that can benefit from further research.

2 LITERATURE REVIEW

2.1 Overview

This chapter introduced co-crystals design, including the criteria for selecting co-crystal formers based on the synthon theory. The next section will focus on the pharmaceutical properties that can be altered by co-crystal approach for an API, including the stability, bioavailability, dissolution rate as well as mechanism of co-crystal which enhance solubility. The screening method i.e. solution and solid-state approaches in designing co-crystals and understanding the kinetics and mechanisms behind co-crystallization were discussed. Some of the characterization techniques used in co-crystal studies was as well discussed. The final two sections are devoted to the model compounds used in this experimental study which are CBZ and IBU. Final section discussed on several case studies from previous work of CBZ co-crystals formation.

2.2 Introduction

Co-crystals is crystalline structure consists of two or more neutral or organic components and solid in ambient conditions in their pure form. The intermolecular interaction occurred in co-crystal including hydrogen bonds, van der Waals, and π - π stacking and the most favourable geometry will lead to a supramolecular network. The co-crystals formation has an advantages of forming viable solid forms of APIs co-crystal even though without possess any ionisable functional groups and is believed to have better improvement in their pharmaceutical properties which unavailable in single component of API solid phases either in polymorphs or amorphous forms. Pharmaceutical co-crystal consists of an API together with a co-crystal former (CCF) which usually exists in the neutral state and mostly interact by hydrogen bonding. Tendency of hydrogen bonding interaction between various functional groups on API is often considered as a significant factor to a successful co-crystal formation (Childs et al., 2007; Reddy et al., 2009).

Pharmaceutical co-crystal's design that has multiple molecular components is important to control pharmaceutical properties without changing the molecular interaction. Lots of studies have been conducted, however, at determining new co-crystal form with different packing motif with no direct a priori ability to logically and reliable target

specific on physical properties of the pharmaceutical agents. Despite the fact that most studies discover new pharmaceutical co-crystal forms and their associated crystal structures, few addresses the strategic design principles that could possibly lead to the modification or enhancement of their physical and chemical properties. Therefore, design of co-crystals believed to enhance the variety of solid state forms of an API even for non-ionisable APIs, and improve their properties by alteration of solubility, dissolution rate, chemical stability, bioavailability and mechanical properties (Remenar et al., 2003; Rodríguez-Spong et al., 2003; Childs et al., 2004; Rodríguez-Spong et al., 2004; Zocharski et al., 2004; Trask et al., 2005; Nehm et al., 2006). Families of API co-crystals are being designed by considering the thermodynamic, molecular recognition, as well the kinetic theories to assemble hydrogen-bonded molecular of multiple components.

2.3 Co-crystal design

The intermolecular interactions understanding focused in crystal engineering lead to the development of supermolecules. The hydrogen bond has been the most important interaction in co-crystal formation due to its strength and directionality (Etter, 1990; Etter et al., 1991; Desiraju, 2002; Wenger et al., 2008). Important knowledge is gained to identify hydrogen-bond preferences and reliable synthons that lead to co-crystal formation by studying these hydrogen bond designs (Leiserowitz et al., 1969; Etter, 1990; Desiraju, 1995; Aakeroy et al., 2002; Wenger et al., 2008). Cambridge Structural Database (CSD) can be used to study on the occurrence of hydrogen bond motifs and other main interactions in crystal lattices based on the specific molecules, functional groups, and their synthons (Etter et al., 1991; Nangia et al., 1998; Allen, 2002). Some generally found synthons are shown in Figure 2.1.

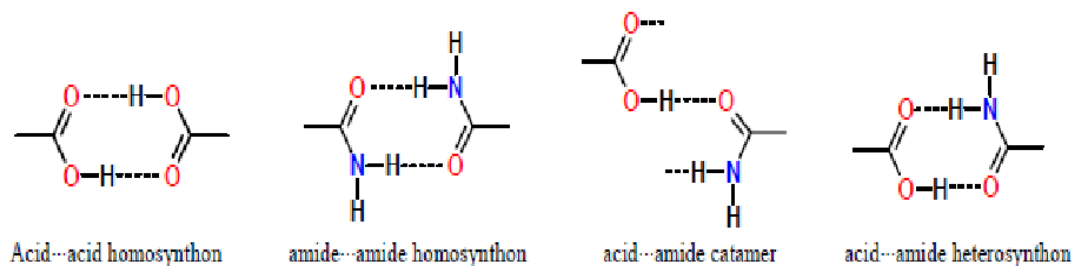


Figure 2-1: Common synthons found between carboxylic acid and amide functional groups. (Etter, 1991)

Parameters for preferred hydrogen bond patterns in crystals based on rigorous analysis of hydrogen bonds and packing motifs have been developed by Donohue in 1952 and Etter in 1991. These includes: (a) there are hydrogen bonding with the crystal structure of that compound for all hydrogen existing in molecule (Donohue 1952), (b) if there are available hydrogen-bond donors, each of good acceptors will be used in hydrogen bonding (Etter, 1991), and (c) the best hydrogen-bond acceptor and the best hydrogen-bond donor will preferentially form hydrogen bonds to one another (Etter 1991). Etter also studied on numerous of reasons at which this behaviour impossible to occur. These include the existences of multiple competitive hydrogen-bond sites, steric hindrances, or competing dipolar or ionic forces and conformational freedom. These common principles however create the basic for predicting for likely and unlikely structures. These principles of co-crystal formation were applied to carbamazepine (CBZ), an API which has the reliable carboxamide synthon.

CBZ of interest because it has low water solubility and it's well known four anhydrous polymorphs design and also exists as a dihydrate when exposed to moisture (Himes et al., 1981; Reboul et al., 1981; Lowes, Cairra et al., 1987; Murphy et al., 2002; Grzesiak et al., 2003) and solvates (water and acetone solvates) (Terrence et al., 1983; McMahon et al., 1996; Kobayashi et al., 2000; Fleischman et al., 2003). The crystal packing of CBZ in different forms of polymorphs and solvates explains the design of cyclic dimer, with the carboxamide group act as both of hydrogen bond acceptor and donor.

Examination of the crystal structures of solvates reveals hydrogen-bonding arrangements that can be applied to co-crystal formation. In many solvates, the solvent molecule is hydrogen-bonded to the API molecule. In case of CBZ, these solvates of CBZ confirm that the tendency of an API molecule exist as solvates is resulted from the molecular structures, hydrogen bond patterns, and crystal packing (Khankari et al., 1995; Nangia et al., 1998; Bingham et al., 2001; Infantes et al., 2002; Gillon et al., 2003). Supramolecular design strategies were utilized to prepare CBZ co-crystals using principle of the primary supramolecular synthon where molecular interactions either retain (strategy I) or disrupt the carboxamide dimer formation (strategy II) (Fleischman, Kuduva et al. 2003). Strategy I maintain the carboxamide homosynthon and uses of the external hydrogen bond donor and acceptor sites. While strategy II forms a heterodimer between the carboxamide and carboxylic groups by hydrogen bonds.

2.4 Co-crystal former selection

Selection of co-crystal former is most commonly based on the synthon theory (Desiraju, 1995) which builds within the co-crystal a supermolecules by consuming specific molecular fragments to create supramolecular synthons. The synthon theory proposes that for each functional groups present on the API and the co-crystal former will play a vital role for successful formation of co-crystals.

Although formation of the supermolecule may be favourable for supermolecule itself to be able pack into an ordered crystalline structure, however the disadvantage of the synthon theory is that it is not quantitative in so far. Additionally, other factors such as competition among the different functional groups present in API or the co-crystal former nor the steric density around the donor and acceptor does not considered in this theory. A study by Fabian and Fayos suggested that co-crystal formers selection based on shape and polarity would influence the success of co-crystal formation (Fabian, 2009; Fayos, 2009). On the other hands, Musemeci et al., in 2011 and Issa et al., in 2009 have proposed computational approaches in predicting the results of co-crystallization formation and Galek et al., in 2007 have developed a knowledge-based method for predicting the result of various co-crystallization reactions that may occur during the process.

The approach has been later used by Delori et al. for further research of the anti-malarial drug pyrimethamine (Delori et al., 2012; Delori et al., 2013). Abramov stated that, the influence of fluid-phase thermodynamics can be used for efficient and accurate screening technique of co-crystal formers for the co-crystallization of API. This finding is based on the comparison between excess enthalpy of an API and co-crystal former mixture virtual to the pure components (Abramov et al., 2012).

2.5 Co-crystal properties

Examples in the preceding section show that co-crystallization changes the interactions as well the composition of pharmaceutical materials. As such one can expect changes in physico-chemical properties such as chemical stability, melting points, hydrate formation, dissolution rates, bioavailability and solubility due to co-crystallization of pharmaceutical materials. This has been demonstrated for a few API co-crystals.

2.5.1 Chemical stability

Co-crystallization can improve the chemical stability of an API. For instance, carbamazepine is reported to undergo chemical degradation to cyclobutyl dimer after forming a hydrate (Matsuda et al., 1994; Rodriguez-Spong, 2005). The degradation reaction requires that the distance between the azepine rings of adjacent CBZ molecules be less than or equal to 4.1Å (Rodriguez-Spong, 2005). Co-crystallization of CBZ with co-crystal formers such as saccharin (SAC) or nicotinamide (NCT) alters the molecular interactions and packing arrangement of CBZ molecules. Hence, these co-crystals exhibit greater stability against hydration and degradation.

2.5.2 Melting points

It is a normal practice to check on the melting point of a compound for the characterization or purity identification; but, within pharmaceutical sciences, the determination on melting point is very important due to its relationships to aqueous solubility and vapour pressure (Abramowitz et al., 1990). In fact, the melting point has also been correlate to the Log of solubility, although assumptions on the entropy of fusion had to be drawn (Jain et al., 2001). Thus, in order to alter its aqueous solubility toward any particular purpose, being able to determine the melting point of a selected API before it was synthesized would be very beneficial. However, correlations relating chemical structure to melting point data remain indefinite. Factors contributing to the melting point of a crystal product such as the molecular arrangement within the crystal lattice, intermolecular interaction, molecular symmetry, and conformational degrees of freedom for a molecule, one clearly face the difficulties in trying to describe comparisons between molecular structure and crystalline lattice energy relate to the melting point. This situation becomes more complex when determining the multi-component's melting point because each of the components has its own characteristic properties and can influence the environment and intermolecular interactions around it (Katritzky et al., 1995). In addition, co-crystals with lower melting points can be advantageous during pharmaceutical processing, for instance when a melted state of a thermally labile API is needed during some processes such as hot melt extrusion, a co-crystal with a lower melting point than pure crystalline API will allow for melting at lower temperatures to avoid chemical degradation neighbours.

2.5.3 Hydrate formation

APIs can be co-crystallized with co-crystal formers such that the API will not form a hydrate or a solvate. Since co-crystals are supramolecular assemblies and are designed based on functional groups and hydrogen bond complementarity, solvate formation that rely on this complementarity will be inhibited by the formation of co-crystals, given that the intermolecular interactions between the API and co-crystal former are stronger than between the solvent molecule and API. An example of this study is on the stability of CBZ co-crystals with nicotinamide (NCT) or saccharin (SAC) when exposed to high relative humidity (Rodríguez-Spong & Zocharski et al. 2003; Rodríguez-Spong 2005). Even though the pure CBZ anhydrous crystal transforms to carbamazepine dihydrate when exposed to high relative humidity, the co-crystals do not (Rodríguez-Spong 2005). A similar study on caffeine shows that the caffeine-oxalic acid co-crystal did not transform to caffeine hydrate under high relative humidity for seven weeks. However, other caffeine co-crystals dissociated and consequently, the hydrated form of the API resulted (Trask, Motherwell et al. 2005).

2.5.4 Dissolution Rate

Dissolution rate of different API co-crystal have been reported. The intrinsic dissolution rates of CBZ-SAC co-crystal in water are 1.7 and 2.3 times that of pure CBZ and close to the single component of anhydrous CBZ form III (Rodríguez-Spong, 2005). Childs et al formulated crystalline complexes with a salt form of an API and carboxylic acids. For example from previous work, fluoxetine hydrochloride, antidepressant drugs was crystallized with benzoic acid, succinic acid, and fumaric acid where the chloride ion acts as a hydrogen bond acceptor for carboxylic acid groups of the three ligands. Intrinsic dissolution studies were conducted at 10°C because at 25°C, the rates were so rapid that the dissolution rates of the co-crystal could not be distinguished from one another (Childs et al., 2007).

2.5.5 Bioavailability

Bioavailability studies need to be carried out if co-crystal were going to be a practical alternative for solid state forms of a drug. Bioavailability studies revealed the co-crystal achieved approximately three higher plasma concentrations for the same dose in dog (Mcnamara et al., 2006). Research of CBZ-SAC was reported to yield slightly higher

plasma levels when compared to dosing CBZ monoclinic, although the authors reported that the increase was not statistically significant (Hickey et al., 2006).

2.5.6 Mechanism by which co-crystal enhance the solubility

The strength of the crystal lattice and the solvation of co-crystal components are two independent factors that determine the solubility. One can lower the lattice energy or increase the solvent affinity in order to increase the solubility. Co-crystals capable to influence both factors to different extent (Serajuddin, 2007; Anderson et al., 1985). The solubility in solvents being controlled by the crystal lattice where there have little resistance to solvation, or when solvent–solute interactions match the solvent–solvent interactions, as in ideal solutions. In contrast, solvation will play an important role on the solubility of co-crystals as a result from the drug hydrophobicity (Liu, 2008; Yalkowsky, 1999).

Majority of hydrophobic drug co-crystals show this performance as the limitations imposed by the solvent–solute interactions (hydrophobicity) had reduced the solubility below that the determined by lattice energy (Maheshwari et al., 2012; Alalaweh et al., 2012). The solvation and lattice contributions to the solubility of carbamazepine co-crystals in organic and aqueous solvents (Gao et al., 2011; Good & Rodriguez-Hornedo, 2010) were based on the graphical method developed by Miyako and co-workers (Miyako et al., 2008). The solubility lowered by solvation by as much as an order of magnitude in organic solvents and orders of magnitude in water. In fact, solvation like hydrophobicity of the solute limited the melting point to be often poor parameter to determine aqueous solubility of co-crystals and not influence by the lattice energy (Gao et al., 2011; Bak et al., 2008).

The degree of the solvent–solute interaction in organic solvent is often proportional to the magnitude of the lattice strength, and thus enhance in co-crystal solubility are related with the decreases in melting point. However the situation is quite different in water where the solvation (hydrophobicity) limits the solubility to a larger extent than lattice strength and the magnitude of each factor is not proportional. Consequently, melting point will be a poor parameter of aqueous solubility for these co-crystals. Co-crystal solubility has also been influenced with co-crystal former solubility Childs et al., 2008; Gao et al., 2011). Decrease in the solvation barrier for a co-crystal to an extent

proportional to that of the pure co-crystal former resulted from the solubility behavior. While universal parameters of co-crystal solubility would be helpful, each case still needs a careful analysis on the factors that correlated with solubility.

2.6 Co-crystal screening

Throughout the co-crystalline literatures, numerous solution-based and solid-based mediated techniques have been used to screen the co-crystals. Current findings in solution-based technique to screen co-crystals include slow evaporation (Caira 1991; Etter et al., 1991; Ghosh et al., 1991; Fleischman et al., 2003; Walsh et al., 2003; Childs et al., 2004) from solutions with stoichiometric or equimolar concentrations of co-crystal components and solvo-thermal methods (Bettinetti & Caira et al. 2000; Rodríguez-Spong 2005), with the co-crystal former being more common. However all these processes suffer the risk of crystallizing the only single component phases, thus decreasing the opportunity to form the multiple component crystalline phases. Consequently, from these practically based approaches, numerous of experimental techniques are often tested and ability to larger the scale co-crystallization processes is limited (Morissette et al., 2004).

Co-crystallization product can occur during storage of solid mixtures of co-crystal components and solvent additive (Jayasankar et al. 2007). Co-crystallization in these solid co-crystal and solvent additive mixtures is assisted by moisture sorbed due to deliquescence of solvent additive at relative humidity above the deliquescent relative humidity (DRH). It is assumed that the water absorbed by the deliquescent material generates a medium for the co-crystal products to dissolve. The rate of co-crystal formation depends on the rates of moisture sorption, dissolution of co-crystal components and rate of nucleation as well as growth from solution phase.

Co-crystal formation in the solid state method is based on mechanical activation of materials by processes such as dry grinding or milling and studies done for these processes of co-crystal are abundant (Etter, 1990; Etter, 1991; Etter et al., 1991; Etter et al., 1993; Caira et al., 1995; Pedireddi et al., 1996; Oguchi et al., 2000; Trask et al., 2005; Trask et al., 2005; Jayasankar et al., 2006; Childs et al., 2008). Adding up of few drops of solvent in co-crystal grinding technique is becoming increasingly common (Trask et al., 2004; Wenger et al., 2008). Since grinding technique is quite highly

energetic process, co-crystal formation by co-grinding reactants with few drops of solvent continues throughout the development of amorphous phases of the reactants. This has been proven in studies by Jayasankar et al. using anhydrous form III CBZ and SAC (Jayasankar et al., 2006). Faster rate of co-crystal formation was observed during co-grinding at room temperature. Interestingly, CBZ-NCT and CBZ-SAC co-crystal were shown to spontaneously formed under a variety of storage conditions even when the two components were not grind together; suggesting that transformation from single components to multi-components was thermodynamically favourable (Maheshwari et al., 2009). However, most of these methods though simple to be apply within the laboratory scale, was not favourable when implemented to a bigger process scale used in industrial field.

Despite significant current studies in this pharmaceutical co-crystal study, there have been few experimental studies on the effectiveness of co-crystal screening approaches using both stoichiometric and non-stoichiometric method. The non-stoichiometric method, also known as reaction crystallization method categorized in solution based crystallization where saturated or nearly supersaturated solution of CCF in a solvent with high CCF solubility has been used as a crystallization medium. Solubility difference between the co-crystal and the selected pharmaceutical drug optimized by these conditions and hence allow for the creation and maintenance of a high activity for the co-former throughout the experiment.

Theoretically, the formation of single component crystals may exist if co-crystal components A and B have non-equivalent solubility solution co-crystallisation through evaporation of an equimolar solution due to supersaturation solution of CCF is generated with respect to less soluble reactant or both less soluble reactant and co-crystal. The reaction co-crystallisation (RC) technique has been accepted for this situation. RC technique are carry out by adding reactant B to a saturated or nearly supersaturated solution of reactant A and then the solution become supersaturated with respect to co-crystal AB, where co-crystallisation then can occur:



This technique is more efficient with non-stoichiometric solution concentrations and when solutions are saturated or nearly supersaturated with respect to reactants. In one of previous study, RC technique were carry out by adding CBZ to saturated or 18 nearly saturated solutions of co-crystal formers separately and several pure CBZ co-crystals were obtained (Childs et al., 2008).

2.6.1 *Others screening method*

Pharmaceutical co-crystals can also be formed by technique of supercritical fluids. Supercritical fluids play new role in screening of co-crystals. Supercritical fluid technology proposes a new screening development that allows a single-step generation of particles that are impossible or difficult to obtain by traditional techniques like salt formation especially for substances with thermal sensitivity or structure instability properties. The formation of pure and new co-crystals which is crystalline molecular complexes consist of an API and one or more conformers in single crystal lattice can be obtained due to distinctive properties of super critical fluids by using different supercritical fluid properties respectively (Padrela et al., 2009).

Another solution based method which has recently attracted much more interest for potential to scale up the co-crystal production is cooling crystallisation technique which involves difference in the temperature of the co-crystallisation system. Initially, very large quantities of reactants and solvent are mixed together in a reactor usually a jacketed vessel reactor, and then the system was heated to a higher temperature in order to make sure all solutes are totally dissolved in the solvent and then followed by a cooling down process. Hence, co-crystals will precipitate once the solution becomes supersaturated with respect to co-crystal as the temperature decreased (Mcnamara et al., 2006). For example, experiment of co-crystals between caffeine and p-hydroxybenzoic acid was screen through this cooling crystallization technique (He et al., 2010). The intermolecular interactions of caffeine and p-hydroxybenzoic acid in methanol solvent at different concentration ratios have been checked by cooling crystallisation, displaying that the effectiveness on co-crystal screening not only improved by understanding the details of the intermolecular interactions only but also provides a qualitative and predictive parameter for the final crystal products.

The cooling crystallisation technique can be also applied in combination with the tertiary phase diagrams (TPDs) in describing the regions of thermodynamic stability especially in a multi-component co-crystal system and in predicting for the possibility of co-crystals formation. In other research, cooling crystallisation on concentrated solution of CBZ-NCT slurry was observed by using an in situ FTIR spectroscopy probe, in which the development of the CBZ and NCT concentration solution explained the kinetic pathways of the co-crystallisation process giving useful information on nucleation and growth of the co-crystals as well on the proportion of each solid phase present in suspension. It is possible to determine the optimal operating conditions for a cooling co-crystallisation process through only analyzing the kinetic pathways and supersaturation levels of the components (Gagniere et al., 2009).

The hot stage microscopy technique has similar advantages to grinding over the solution based methods, which are the results are rapidly obtainable, the method avoids the formation of undesired products and is considered environmentally friendly. Yet its use is often limited to co-crystal formers with comparable melting points, to avoid molecular decomposition of one co-crystal former before the other has melted.

This method is based on the contact or mixed fusion approach (Kofler, 1980; Mccrone, 1987), which involves the melting process of one co-crystal former (the one with the higher melting point) between two microscope slides, which is then allowed to solidify. Second conformer was introduced between the same microscope slides and allowed to melt, consequently dissolving a proportion of the first co-crystal former at the region where they meet. This region is known as the zone of mixing. The system is next cooled down to room temperature and fully solidified, before being heated up again until all the components melt. This is observed using a microscope with crossed Polaroid filters. If co-crystallization is formed, a distinct new morphology with a different melting point to its components would be identified within the zone of mixing.

2.7 Characterization of co-crystal

Characterization of co-crystals is importance and there are different characterization methods starting from simple melting point determination to the complete structural determination through single crystal X-ray crystallography motif. Other analyzes such

as studying on the morphology of crystals by optical microscopic, observing changes in outer appearance of crystal forms.

DSC has recently been shown to be an efficient thermal method to synthesize co-crystals in situ (Lu, Rodríguez-Hornedo et al. 2008). In DSC, graph of heat flow versus temperature must be obtained where the heat flow to the sample must increase dramatically according to the setting temperature in order for the sample to melt completely and use the same heating rate for reference pan. Theoretically, if the heating curves showed two distinct melting peaks over the complete composition range, indicating that these materials was classified as semicrystalline or semicrystalline blends (Lukas et al., 2009). The heating rate appeared to affect the rate and extent of co-crystal formation, and solid phases were confirmed by inconsistent temperature X-ray diffraction (XRD).

Another rapid and efficient method to characterize co-crystal is to observe on the crystals morphology by optical microscopy. This feature reveals the outer appearance of crystals as unit cell repetition leads to crystal formations that can be observed by simple hand lens or microscope. Instead of using optical microscopy, for future morphology observation, polarizing optical microscopy, thermal microscopy and electron microscopy can be used. The geometry of crystal shape is almost proverbially anisotropic, in many cases even “faceted”. This implies that some orientation-dependent factor is active during crystal growth. If not, crystal grown under homogenous external condition would be sphere in shape (Van, 1995).

2.8 Model compound and co-crystal former

Carbamazepine and ibuprofen were chosen as the models drugs in this study. Carbamazepine is a class II compounds which is characterized by a high per-oral dose, in Biopharmaceutical Classification System (BCS) which has low aqueous solubility and high membrane permeability. Dissolution rate limited the bioavailability of such a class II drug (Rinaki et al., 2003). In contrast, ibuprofen is a class II compound with high permeability, has low bioavailability due to its low aqueous solubility in water but very soluble in various organic solvents (Patel et al., 2010).

2.8.1 Carbamazepine

Carbamazepine, an anti-convulsant drug, exists in four polymorphic forms from CBZ form I until IV (Lang et al., 2002; Grzesiak et al., 2003). The crystal structures of all four polymorphic forms of CBZ exhibit similar molecular conformations and hydrogen bonding patterns resulting in a carboxamide homodimer (Rodríguez-Spong et al., 2004). The primary difference between the different forms is in the packing arrangements that results in different crystallographic properties as illustrated in Table 2-1. The molecular structure of pure CBZ (Figure 2-2) shows an azepine ring with a primary amide functional group that has two hydrogen bond donors and two acceptors. The crystal structures of CBZ form III exhibits the carboxamide homodimer (Figure 2-3) due to hydrogen bonding between the amide groups of two CBZ molecules. Of the four polymorphic forms, monoclinic form III is the most stable form at room temperature (Behmi & Brooke, 1991). In addition to the four polymorphic forms, carbamazepine also forms a dihydrate and solvates (Fleishman et al., 2003; Fernandez et al., 2007; Johnston et al., 2007). The crystal structure of CBZ dehydrates exhibits the carboxamide dimer motifs similar to those observed in the CBZ polymorphs.

However, the anti-NH of carbamazepine amide forms hydrogen bonds with water molecules (Figure 2-4) that effects in the formation of water channels along the b-axis in carbamazepine dihydrate (CBZ(D)). As a result of these differences in the hydrogen bond patterns and packing arrangements, carbamazepine dihydrate shows different crystallographic and physico-chemical properties (Lowes et al., 1987; McMohan et al., 2005; Grzesiak et al., 2003; Lang et al., 2002). CBZ (D) is the thermodynamically stable form at high relative humidity (RH > 70%), and has the lowest solubility in water when compared to the anhydrous forms. Consequently, the anhydrous forms transform to CBZ (D) upon dissolution in water (Harris et al., 2005).

Table 2-1: Crystallographic properties of CBZ polymorphs (Grzesiak et al., 2003; Lang et al., 2002; Harrie et al., 2005; Lowes et al., 1987; Himes et al., 1981)

	CBZ I	CBZ II	CBZ III	CBZ IV	CBZ D
Crystal system	Triclinic	Trigonal	Monoclinic	Monoclinic	Monoclinic
Space group	P-1	R-3	P21/n	C2/c	P21/c
a (Å)	5.17	35.45	7.45	26.62	10.07
b (Å)	20.57	35.45	11.16	6.93	28.72
c (Å)	22.25	5.25	13.91	13.96	4.38
α (degree)	84.12	90	90	90	90
β (degree)	88.01	90	92.86	109.70	103.45
γ (degree)	85.19	120	90	90	90
Volume(cm ³)	2344.8	5718.3	1168.3	2421.9	1358.3
Density (g/cm ³)	1.34	1.24	1.34	1.29	1.33

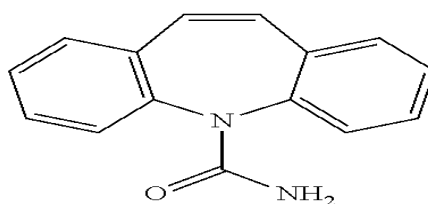


Figure 2-2: Molecular structure of CBZ

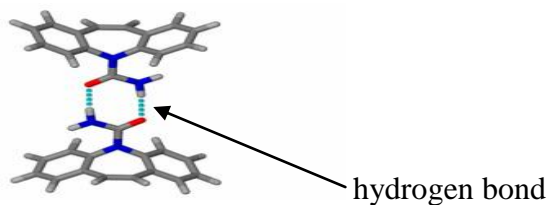


Figure 2-3: Hydrogen bonding pattern in CBZ form III (Himes et al., 1981)

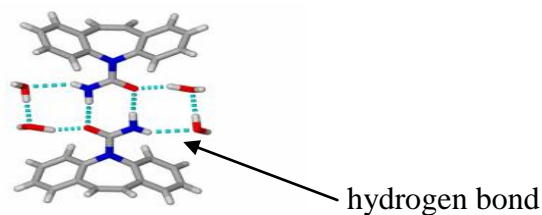


Figure 2-4: Hydrogen bonding pattern in CBZ (D) (Harris et al., 2005)

2.8.2 Ibuprofen

Ibuprofen (IBU) is a non-steroidal anti-inflammatory drug (NSAID) and a common analgesic drug with antipyretic action is widely administered orally and topically (Dollery, 1999). It is also used in the relief of rheumatoid arthritis and osteoarthritis symptoms (Pacheco et al., 2007). The physical and chemical studies of ibuprofen has been studied by a number of pharmacists (Rasenack and Muller, 2002; Nada et al., 2005). Ibuprofen has a hydrophobic property which gives low solubility in water. Ibuprofen have poor compressibility and compactibility under compaction process and most of the tablets produced at high speed were capped (Nokhodchi et al., 1995), hence a granulation step is necessary for most cases in production of solid dosage forms of IBU. These physico-mechanical problems such as growth temperature, solvent type, degree of supersaturation and addition of additives can be controlled by manipulating the crystallization conditions (Xie et al., 1998; Lang et al., 2002). The molecular structure of IBU shows in Figure 2-5.

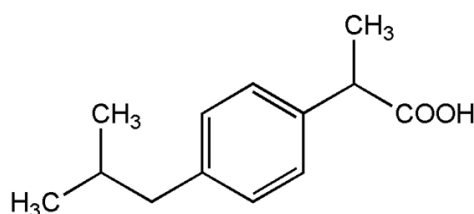


Figure 2-5: Molecular structure of IBU

2.9 Previous work on Carbamazepine co-crystal formation

Approximately 40 co-crystals of carbamazepine (CBZ) have been reported in previous study, and some of the CBZ co-crystal listed in Table 2.2.

Table 2-2: Examples of pharmaceutical co-crystals using Carbamazepine (Fleishman et al., 2003; McMohan et al., 2005; Childs et al., 2008; Babu et al., 2007; Lu et al., 2008; Vishweshwar et al., 2005; Desiraju, 2003)

API	Co-crystal Former	Ratio (API: Ligand)
Carbamazepine	Nicotinamide	1:1
	Sachcharin	1:1
	Benzoquinone	1:1
	Trimesic acid	1:1
	Terephthalaldehyde	1:1
	Formamaide	1:1
	Adamantane-1,3,5,7-tetracarboxylic acid	1:1
	4-aminobenzoic acid ³³	2:1 anhydrous 2:1:1 hydrate
	Malonic acid	2:1
	Succinic acid	2:1
	2,6-pyridinedicarboxylic acid	
	Aspirin	

Co-crystals of carbamazepine with saccharin (SAC), nicotinamide (NCT) and 4-aminobenzoic acid (4-ABA) among in interest as model systems in the current study since the crystallographic and physico-chemical properties of these co-crystals are reported (Fleishman et al., 2005, McMohan et al., 2005). Both CBZ-SAC and CBZ-NCT co-crystals exhibit polymorphism. Form I CBZ-SAC and CBZ-NCT were first identified in 2003 by slow evaporation technique of organic solvents containing the reactants in stoichiometric molar ratio (Fleishman et al., 2003).

Form II CBZ-SAC co-crystal polymorph was identified by polymer mediated nucleation technique (Porter et al., 2007). Differ from form I CBZ-SAC co-crystal, form II CBZ-SAC co-crystal does not maintain the CBZ amide homodimer however forming the CBZ amide forms heterosynthon by hydrogen bonding with the SAC amide (Porter et al., 2008) as shown in Figure 2-6. Based on thermal analysis and stability study of form II CBZ-SAC co-crystal, form I was reported to be the thermodynamically stable phase

at room temperature (Porter et al., 2007). However, form I CBZ-SAC co-crystal transforms to CBZ (D) upon dissolution in water due to higher aqueous solubility or moisture content in the co-crystal (Rodríguez-Spong et al., 2005).

Polymorphic form II of CBZ-NCT co-crystal was produced using melt-quenching form I co-crystal and reheating the resulting amorphous phase (Seefeldt et al., 2007) as well as by polymer mediated nucleation and growth from the solutions (Porter et al., 2008). Form I CBZ-NCT is relatively stable at room temperature, and is monotropically corresponded to form II co-crystal. Form II exhibits an exothermic transformation to form I at melting point of 83-90°C (Seefeldt et al., 2007). Upon dissolution in water, form I CBZ-NCT transforms to CBZ (D) due to higher aqueous solubility or moisture content of the co-crystal. The crystal structures of CBZ-NCT co-crystals are shown in Figure 2-7.

Carbamazepine-4-aminobenzoic acid (CBZ-4ABA) co-crystal is reported to form in the anhydrous and hydrated form (Mcmohan et al., 2008). The crystal structures of the two co-crystals of CBZ-4ABA are shown in Figure 2-8 and Figure 2-9. The 2:1 ratio of anhydrous structure shows the expected acid amide heterosynthon as well as an unexpected amide-amide homosynthon. Two acid-amide heterosynthons was connected through N-H \cdots O hydrogen bonds to form a tetrameric unit. These tetramers are hydrogen bonded to CBZ homodimers on each side via amino N-H \cdots O hydrogen bond shows in Figure 2-8 (Mcmohan et al., 2005). Whereas, in the 2:1 hydrated structure, presence of water molecule interrupts the expected acid amide heterosynthon. A second CBZ molecule interacts with the water interrupted the dimer via O-H \cdots O and N-H \cdots O hydrogen bonds to form a tetramer. These tetramers are in turn connected by amino N-H \cdots O hydrogen bond to form an eight molecule discrete unit which shows in Figure 2-9 (Mcmohan et al., 2005). Both the anhydrous and hydrated co-crystals were discovered by slow evaporation technique of organic solvents containing CBZ and 4ABA in 1:1 or equimolar mol ratio (Mcmohan et al., 2005). However, the relative thermodynamic stabilities of these two co-crystalline phases are not studied. Identifying the factors influence the formation and thermodynamic stability of these two co-crystalline phases will enable expectation of phase transformation, and is therefore an issue of interest in the current study.

CBZ-SAC, CBZ-NCT and CBZ-4ABA co-crystals were also selected in the current study as the co-crystal formers (SAC, NCT and 4ABA) in these co-crystals exhibit difference pharmaceutical properties like stability, hygroscopicity, solubility and melting points. Nicotinamide (NCT) has four polymorphic forms and with a melting point in the range of 126-128°C (Hino et al., 2001). It has high aqueous solubility, and well known to it self-associate in aqueous solutions (Coffman & Kildsig, 1996). In addition, NCT has been proven to improve the solubility of several drugs significantly by forming complexes in solution (Hussain et al., 1993; Rasool et al., 1991). During storage at high relative humidity, NCT can sorbs more than 50% water and deliquesces (Rodríguez-Spong et al., 2005). In contrast, saccharin (SAC) and 4-aminobenzoic acid (4-ABA) are non-hygroscopic and have low aqueous solubility and both are ionisable (Gracin & Rasmuson, 2004; O'Neil, 2001). SAC is a weak acid with a pKa value of 1.8 (Zubair & Hassan, 1984) while 4-ABA is amphoteric with 2 value of pKa which is 2.45 and 4.85 respectively (Robinson, 1956). The melting point of SAC and 4-ABA are higher when compared to NCT. SAC melts at 229.5°C (Basavoju et al., 2008) while 4-ABA melts at 187-189°C (Gracin & Rasmuson, 2004).

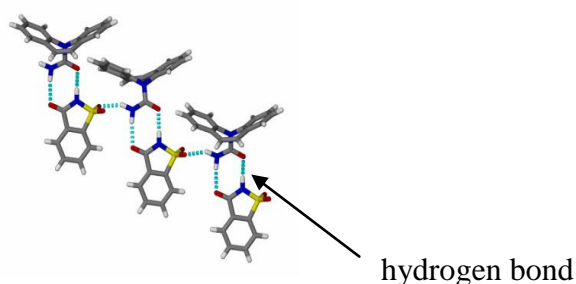


Figure 2-6: Hydrogen bonding in form II CBZ-SAC co-crystal (Porter et al., 2008)

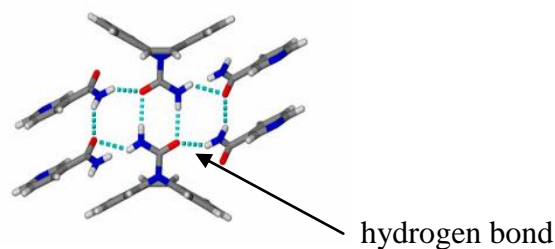


Figure 2-7: Hydrogen bonding pattern in CBZ-NCT co-crystal (Fleishman et al., 2003)

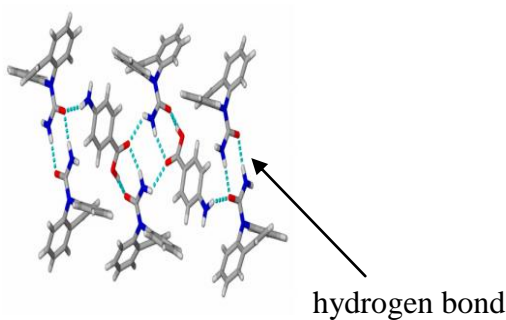


Figure 2-8: Molecular assemblies in 2:1 anhydrous CBZ-4ABA co-crystal (Mcmohan et al., 2005)

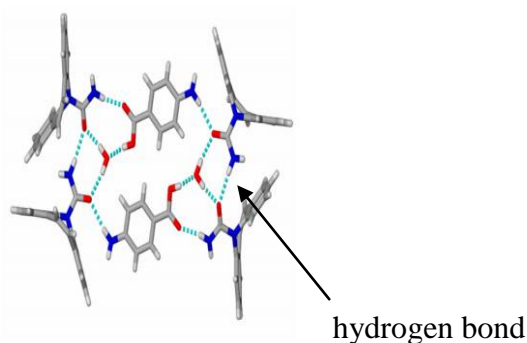


Figure 2-9: Molecular assemblies in 2:1:1 CBZ-4ABA co-crystal hydrate (Mcmohan et al., 2005)

2.10 Summary

This chapter describe about the methods used in the screening of pharmaceutical co-crystals, beginning with a description of the crystal engineering guidelines that are practically used in the selection of suitable API and co-crystal formers to be included in such experimental screens and the standard characterization techniques. Crystal engineering design is frequently based on examining existing structures provided in the Cambridge Structural Database (CSD) in order to discover robust supramolecular synthons. Co-crystals have the advantage that they can be formed regardless of the API's ionisable status. Instead, their formation relies on complementary functional groups between the API and a biologically safe partner molecule, termed the co-crystal former, to allow for hydrogen bonding or other form of interactions in the solid. Significant physiochemical properties of an API such as its bioavailability, stability and processability features can be considerably improved upon co-crystallization, thus allowing for optimal drug formulation. Various methods and tools have been recommended for the preparation of co-crystals in line with the increased interest in the area to the researcher. The co-crystal preparation or screening processes can be divided into solid-state or solvent-based methods. Characterization of co-crystals can be carried out using X-ray

diffraction, DSC, optical microscopy, SEM, TGA in order to determine whether a co-crystalline material has been generated. As CBZ and IBU has been chosen as a model compound, several cases from previous research focusing in CBZ co-crystal has been presented throughout this paper.

3 MATERIALS AND METHODS

3.1 Overview

In this chapter, a method is reported for the formation of co-crystals by applying reaction crystallization technique under ambient conditions. Reaction crystallization technique carried out by mixing reactant's solutions or co-crystal components in non-stoichiometric concentrations according to the degree of solubility of the product. The carbamazepine-ibuprofen (CBZ-IBU) was selected as a model compound to study the screening process using reaction crystallization in organic solvents. In the same solvent, CBZ-IBU co-crystal was prepared by mixing solutions of CBZ and IBU. Solvents selected in this study included: acetonitrile, ethanol, ethyl acetate, formic acid and propanol. Co-crystals were believed to form within 24 hours after manually mixing of an ethanol solution of IBU and solid CBZ. Other solvent (acetonitrile, ethyl acetate, formic acid and propanol) observed a similar findings. The reaction crystallization method was extended to high-throughput screening of co-crystals using environmentally friendly solvents.

3.2 Introduction

This chapter presents a study of co-crystal screening method of carbamazepine-ibuprofen using non-stoichiometric method. Carbamazepine, a class II drug in BCS is anti-convulsant drug with low solubility and auto induced metabolism. CBZ together with CCF can form co-crystals through the interaction of hydrogen bonding at the primary amide group. While ibuprofen, a pharmaceutically acceptable co-crystal former, has one hydrogen bond donors and two hydrogen bond acceptors. To prove on these relationships, the solvents selected in this study consist of have different functional groups as well as different molecular sizes. In this way, ethanol, acetonitrile, ethyl acetate, formic acid and propanol were used as representative solvents, with distinctive surface interaction characteristics. Screening of CBZ-IBU co-crystal using non-stoichiometric crystallization was done through solid addition to saturated solution of CCF with these solvents. After that, co-crystal analysis or characterizations need to be done in order to determining the chemical as well as physical properties. Characterization of co-crystal is utmost importance after the screening. There are

different characterization methods of product crystal, from simple melting point determination through X-ray crystallography, to study the outer appearance or morphology of crystal by microscopic methods, to observe the changes in crystal forms vary with temperature and phase transition using thermal methods.

3.3 Chemicals

The solvents used for screening process comes from various sources namely Merck Malaysia (ethanol gradient grade), Fisher Chemical (acetonitrile HPLC grade, acetone analytical reagent grade) and Sigma-Adrich (propanol, ethyl acetate, formic acid) and Carbamazepine and Ibuprofen were obtained from ACA International Corporation and Shasun Pharmaceutical respectively. All chemicals that were used were of high grade (purity > 99%).

3.4 Non-stoichiometric crystallization

Saturated solutions of the CCF were prepared in 160 ml of acetonitrile, ethanol, ethyl acetate, formic acid and propanol separately in 200 ml beaker at ambient temperature. The CCF solid was added in fixed amount of the solvents. All of the system was mixed using a set of hot plate with magnetic stirrer until the entire solid was dissolved without heat it. More and more CCF solid was added manually to the solution until no further CCF could dissolve. Then, the solution was left to equilibrate for about 24 hours in room temperature. After that, all of the final solution was withdrawn from the beaker using 10ml plastic syringe and filter using 0.22 μm syringe filter to remove any excess solid in the solution.

The co-crystal was prepared by adding 1.2-1.8 g of solid API or CBZ in 10 ml filtered saturated solution of CCF and solvents in 50 ml conical flask. The amount of CBZ added varied depend on CCF while for saturated solution of CCF. The system then was left to equilibrate for about 3 days in 3 conditions at room temperature; in stagnant, manually agitated every 6 hours and shaken in automated shaker with 150 rpm approximately at 25°C. To separate the solid co-crystal, the final solution slurry was filtered using vacuum filter and dried at room temperature.

3.5 Co-crystal analysis and characterization

Differential Scanning Calorimetry (DSC) is used to determine the melting point of product crystal. The samples (2.0-2.5 mg), fixed in meshes were crimped in aluminium pan and lid, then heated 200°C using ramp method with flowrate 50 ml/min at a heating rate of 10°C/min using nitrogen purge.

The morphology of the crystal is observe using microscopy. In this study, a Dino-eye microscope eye-piece and Carl Zeiss model microscope at 771.7x magnification with scale of 1 cm represent 25 μm . The sample (a little) was placed on glass slide and then place in the optical microscope. The microscope images showing the morphology of different co-crystal obtained.

3.6 Summary

The procedures presented here revealed that reaction co-crystallization allows for the successful and rapid formation of co-crystals under ambient conditions, in either organic solvents or solutions. This chapter also identify the mechanism for co-crystal formation from solutions or solid-liquid systems (wet solid phases or slurries), where co-crystallization is formulated by the effect of non-stoichiometric concentrations of co-crystal components on decreasing the solubility of the molecular complex to be crystallized. These will lead to the findings that can give a influential approach to develop logical screening processes for co-crystal development, and in situ co-crystallization techniques, and to develop batch or continuous co-crystallization processes.

4 RESULT AND DISCUSSIONS

4.1 DSC Analysis

DSC experiments were carried out to study the thermal behaviour of the crystal form in relation to the individual components. The melting point, the onset temperature and heat of fusion can be obtained from the thermograms. Section 4.1.1 is discussing about DSC analysis in pure component while section 4.1.2 discussing about the screening process.

4.1.1 Pure component

Figure 4-1 shows a two endothermic peaks where the small endothermic peak in the range of 155-165 °C represent the melting point of pure carbamazepine (CBZ) form III, while the large and sharp peak at 190.75°C represent the melting point form I. These two endothermic peaks represent the characterization of CBZ form III, the most stable form of CBZ in room temperature (Grzesiak et al., 2003). Whereas Figure 4-2 show only one sharp endothermic peak obtained at 76.33°C pointed to the melting point of pure ibuprofen (IBU). The melting temperature for both of CBZ and IBU are in good agreement with the literature value reported by Childs et al., (2008) and Bailey et al., (2003) which is in the range of 190-192 °C for CBZ and 76-78 °C for IBU.

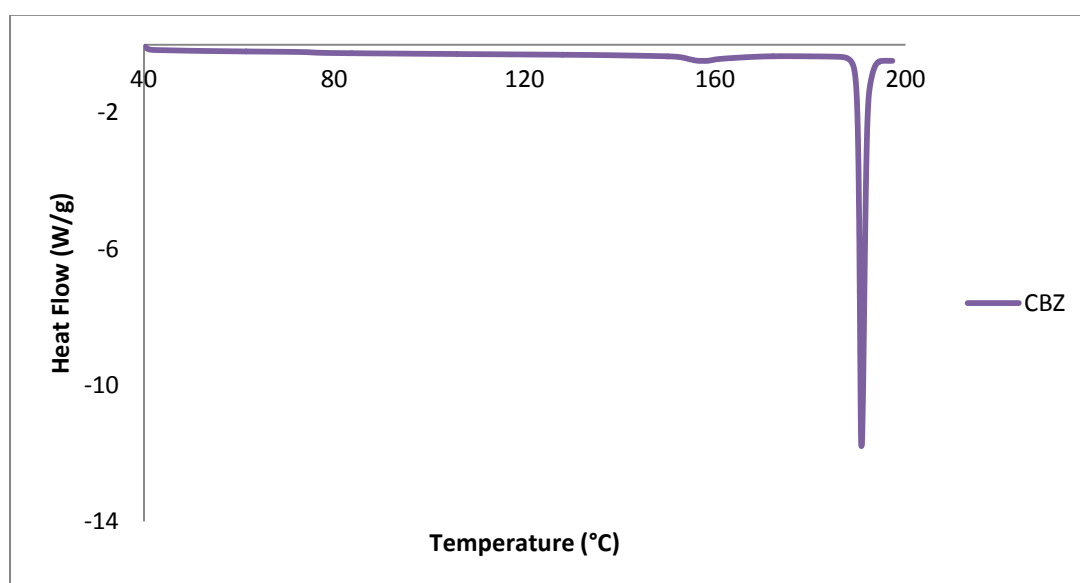


Figure 4-1: DSC heating curve of pure CBZ

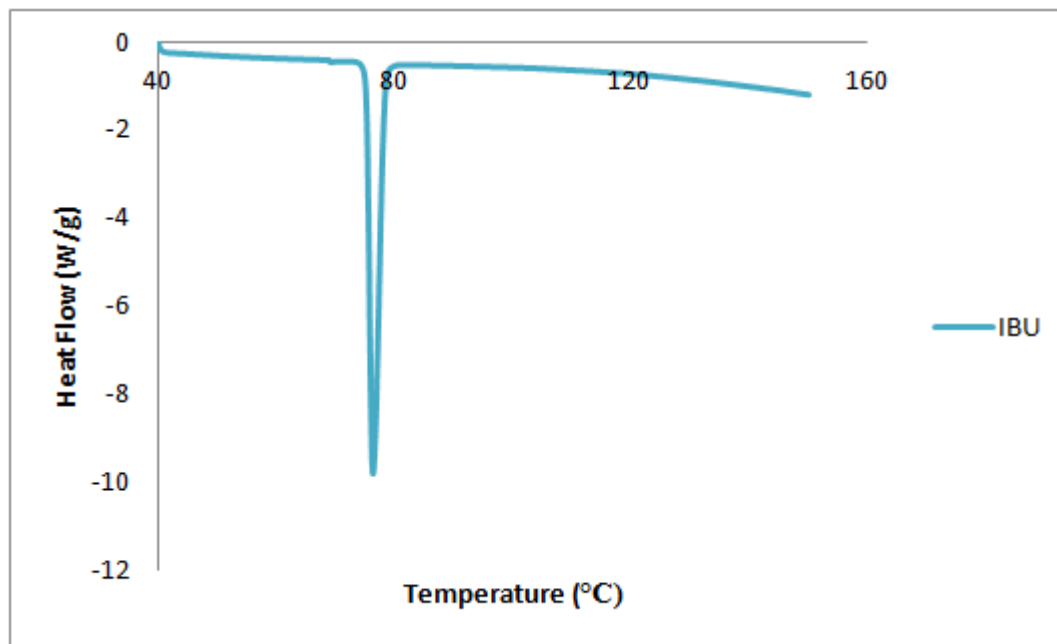


Figure 4-2: DSC heating curve in pure CBZ

4.1.2 Screening results

The thermal behaviour of crystal produce from the screening is listed in Table 4-1. Crystal produced using acetonitrile and propanol as a solvent has a small peak showing a melting point in the range of 160.98-162.44 °C corresponds to form II of CBZ, follow by another peak with melting point in the range of 183-187.32 °C. These two melting points shows that after CBZ form II melt, it has simultaneously recrystallized to CBZ form IV. For ethanol and ethyl acetate solvents, the melting point of crystal produced has a melting point in the range of 178.3-182.51 °C on average represent the melting point of CBZ form IV. This shows that no co-crystal or pure IBU produced, however CBZ form III have changed to form IV indicated by melting point obtained (Grzesiak et al., 2003). On the other hand, for screening from formic acid for stagnant, it seemed like crystal produce prone to form hydrate crystal of CBZ due to humidity or water content at the melting point of 75.59 °C (Elqidra et al., 2004). While for shaking and manually agitated condition, the melting point obtained in the range of 118-121 °C correspond to co-crystal. This shows that, the crystal produce is mixture of co-crystal, API (CBZ form I) and CCF (IBU). Further confirmation of the co-crystal obtained from this solvent need to be characterized using XRPD. Due to limitation access of this equipment, for this technical report, XRPD characterization can't be proceed. However for publication

purposes, this characterization is a must. The example of thermograms showed in Figure 4-3 until Figure 4-7.

Table 3-1: Melting point from CBZ-IBU screening using DSC

Samplpe/ Condition	Melting Point in Stagnant Solution (°C)	Melting Point in Manually Agitated (°C)	Melting Point in Shaking at 150 rpm (°C)
CBZ-IBU (Acetonitrile)	162.64, 189.16	164.82, 185.28	162.86, 187.51
CBZ-IBU (Ethanol)	180.11	181.25	173.54
CBZ-IBU (Ethyl Acetate)	182.35	180.08	185.11
CBZ-IBU (Formic Acid)	75.59, 181.59	118.61, 188.98	121.93, 187.10
CBZ-IBU (Propanol)	161.18	160.77, 185.23	178.18

4.2 Morphology

The morphology of pure CBZ, IBU and the product crystal obtained from solid addition to saturated saturation of co-crystal former is summarized in Table 4-2 and 4-3. From Table 4-2, pure CBZ have thin plate like morphology while pure IBU have a needle-like structure (Mahalaxmi et al., 2009; Nokhodchi et al., 2010). Morphology from Table 4-3 shows a clear difference between the samples. The agglomerates morphology of crystal was observed in acetonitrile and propanol. On the other hand, mixture of rod-like and prismatic morphology obtained from crystal produced in ethanol and ethyl acetate solvents which correspond to morphology of CBZ form IV and III (Marcus, 2009). In contrast, crystal produce from formic acid in stagnant condition exhibits narrow needle morphology reflects the hydrate form CBZ crystal (Elqidra et al., 2004) while in shaking and agitated conditions, both have needle like morphology. In comparison to the pure morphology of CBZ and IBU, it seemed like most of the morphology observed in the screening behaving more likely to CBZ morphology in different form either form I and II (needle-like), form III (prismatic) or form IV which has rod-like morphology (Marcus, 2009).

Table 4-2: Morphology of pure CBZ and IBU


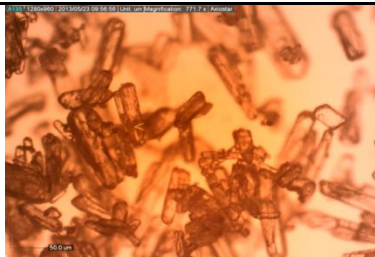
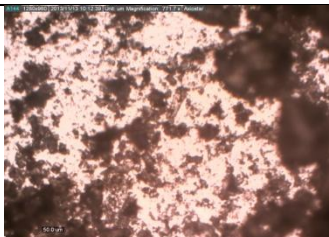
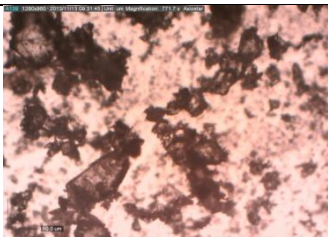
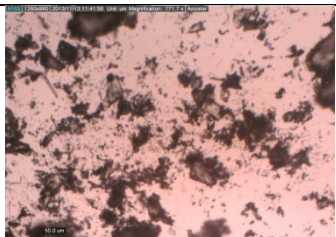
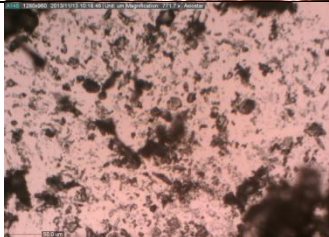
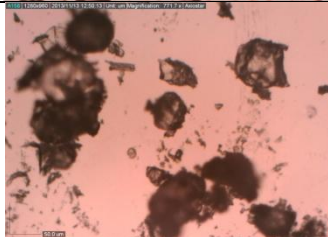

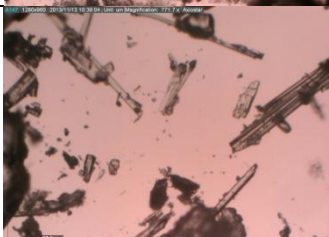
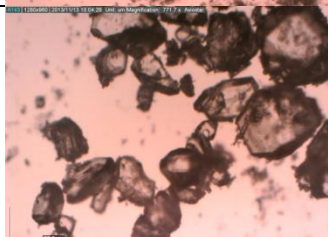
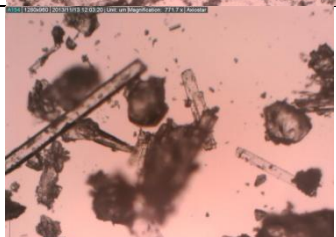


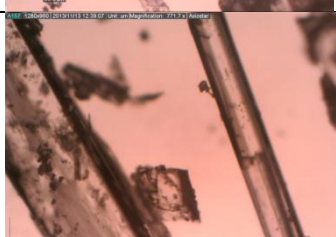
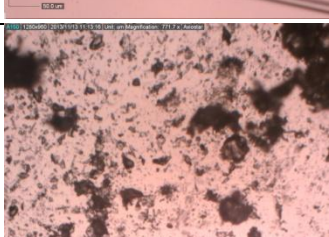
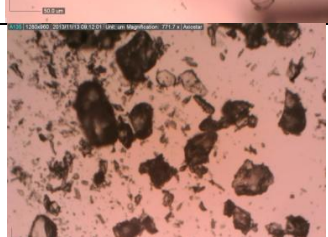
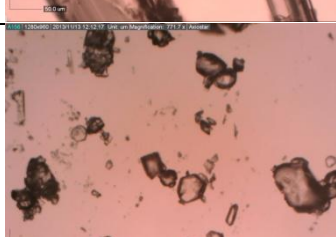
Sample/condition	CBZ	IBU
		

Table 5-3: Morphology image of co-crystals

Sample/Condition	Stagnant solution	Manually agitated	Shaking at 150 rpm
CBZ-IBU (Acetonitrile)			
CBZ-IBU (Ethanol)			
CBZ-IBU (Ethyl acetate)			
CBZ-IBU (Formic acid)			
CBZ-IBU (Propanol)			

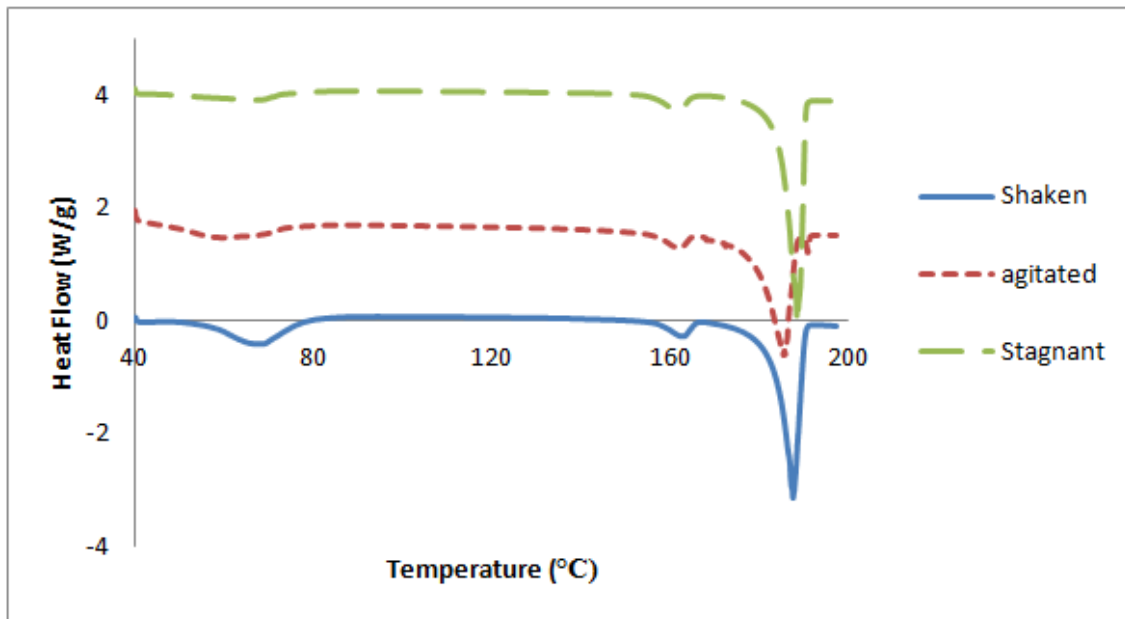


Figure 4-3: DSC heating curve in different crystallization conditions of CBZ-IBU co-crystal in acetonitrile

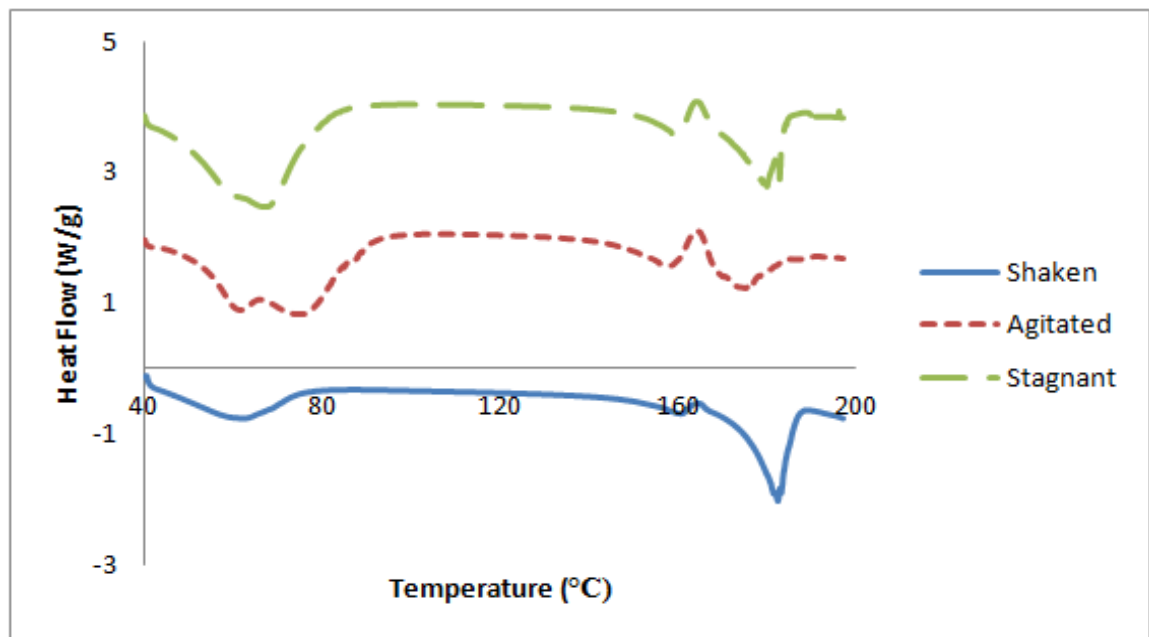


Figure 4-4: DSC heating curve in different crystallization conditions of CBZ-IBU co-crystal in ethanol

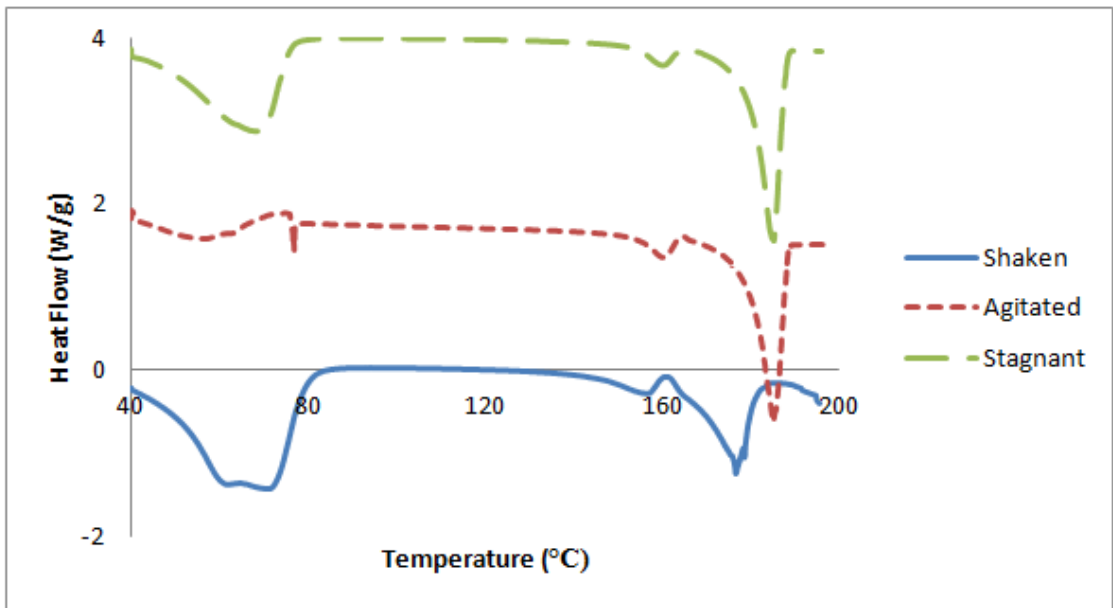


Figure 4-5: DSC heating curve in different crystallization conditions of CBZ-IBU co-crystal in propanol

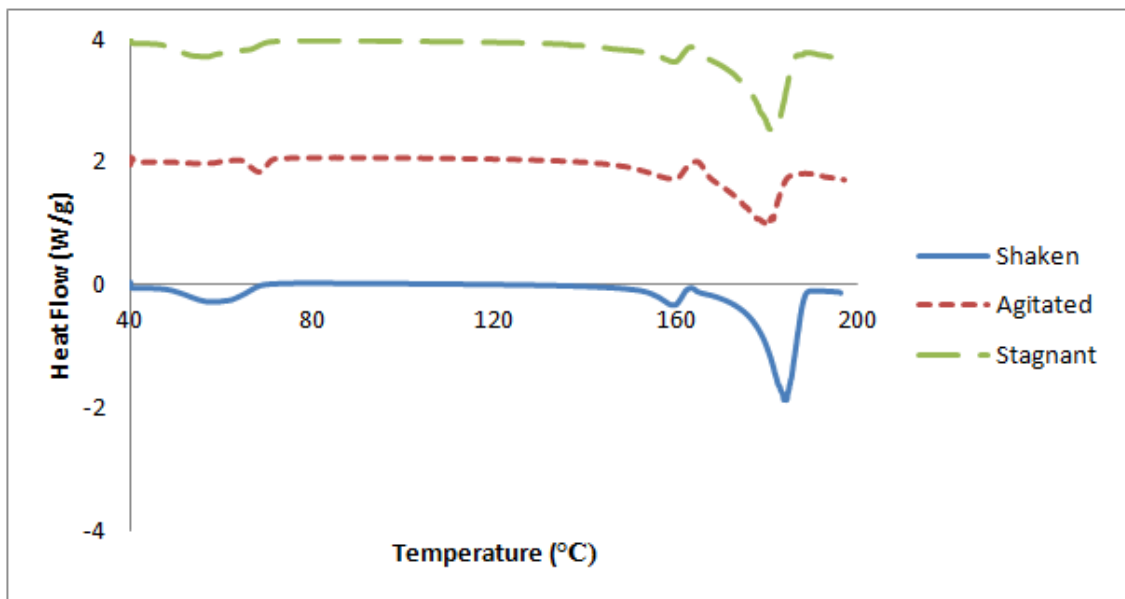


Figure 4-6: DSC heating curve in different crystallization conditions of CBZ-IBU co-crystal in ethyl acetate

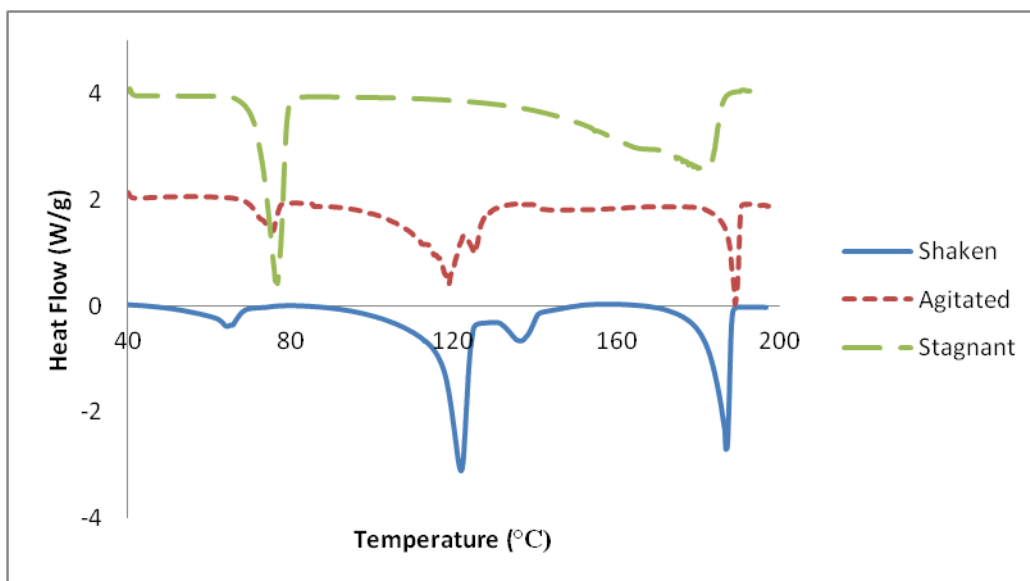


Figure 4-7: DSC heating curve in different crystallization conditions of CBZ-IBU co-crystal in formic acid

4.3 Summary

The formation of CBZ-IBU co-crystal was achieved from formic acid using reaction crystallization method. These samples were analyzed with the optical microscopy to observe the morphology of co-crystal. Analysis showed that the entire three samples in acetonitrile solvent were agglomeration powder whereas a mixture of rod-like and prismatic morphology in ethyl acetate and ethanol was obtained. In contrast, thermograms obtained from screening using formic acid showed three different peaks representing the mixture of CBZ-IBU co-crystal, IBU and CBZ. This finding agreed with the needle-like morphology obtained. From the screening, only formic acid indicated co-crystal has successfully formed. In other solvents (acetonitrile, ethyl acetate, ethanol and propanol), only CBZ is formed due to the peaks obtained corresponded to the melting point of pure CBZ in different polymorph form.

5 CONCLUSION

5.1 Conclusion

This thesis has studied on the co-crystals formation between CBZ-IBU which comprises of a screening using non-stoichiometric method (stage I) prior to product characterization (stage II). The formation of co-crystal with non-stoichiometric method is dependent on co-crystal former concentration. CBZ-IBU co-crystal was synthesized by varying the co-crystal former concentration along using the reaction crystallization method. From the characterization, in most cases product crystal were found to belong to either pure component, which include a potentially new form of CBZ. Currently, the DSC and optical microscopy used for characterization for physical properties study providing unconvincing evidence for co-crystal confirmation. Hence, this study has illustrated the need for further improvements in the characterization of the product crystal formed to check the crystal structure such as XRPD. However, this study still has provided considerable evidence that can be used to give more insight into the formation of co-crystals, and serve as complementary tools to experimental efforts targeting for pharmaceutical co-crystal.

5.2 Future work

In this study some aspects should be improved in order to obtained better result. First, during carry out the experiment, then characterization of the crystal produced and lastly on preparation method of the co-crystal. During the experiment, there are some precautions steps that need to be considered. The sample must weight accurately to obtain the better results. Other than that, the acetone solvent is used for cleaning of apparatus in order to prevent any impurities present in the sample. Apparatus used need to be cleansed thoroughly before being used again to avoid any sample contaminant. Besides, to get the best results for the analysis, the product crystal produced need to be confirmed by others characterization such as PXRD for the structure, and for thermal properties, FTIR and TGA can be use. Once confirm the co-crystal, further study on thermodynamic and kinetic should be conducted. Moreover, if the co-crystal was not able be formed, varying type of screening methods should be used such as slow evaporation, dry grinding or cooling crystallization technique that yield a high

percentages of successful rate to co-crystallized the APIs and co-crystal former.

REFERENCES

- Aakeroy, C. B., A. M. Beatty, et al. (2002). "A High-Yielding Supramolecular Reaction." *Journal of the American Chemical Society*, 124, 14425-14432.
- Abramov, Y.A., Loschen, C., Klant, A. (2012). "Rational coformer or solvent selection for pharmaceutical cocrystallization or desolvation." *J. Pharm. Sci.*, 101, 3697.
- Abramowitz, R.; Yalkowsky, S.H.(1990). "Melting Point, Boiling Point, and Symmetry." *Pharm. Res.*, 7, 9, 942–947.
- Adivaraha, J. (2008). "Understanding the Mechanisms, Thermodynamics and Kinetics of Cocrystallization to Control Phase Transformations (dissertation)." University of Michigan.
- Alhalaweh, A., Roy, L., Rodriguez-Hornedo, N., Velaga, S.P. (2012). "pH-dependent sol-ubility of indomethacin-saccharin and carbamazepine-saccharine cocrystals in aqueous media." *Mol. Pharm.* 9, 2605–2612.
- Allen, F. H.(2002). "The Cambridge Structural Database: a quarter of a million crystal structures and rising." *Acta Crystallographica B58*, 380-388.
- Almarsson, O. and Zaworotko M. J. (2004). "Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines?" *Chemical Communications*, 1889-1896.
- Anderson, B.D., Conradi, R.A., (1985). "Predictive relationships in the water solubility of salts of a nonsteroidal anti-inflammatory drug." *J. Pharm. Sci.* 74, 815–820.
- Babu, N. J., Reddy, L. S., Nangia, A. (2007). "Amide-N-Oxide Heterosynthons and Amide Dimer Homosynthons in Cocrystals of Carboxamide Drugs and Pyridine N-Oxides." *Mol. Pharm.*, 4, 417-434.
- Bak, A., Gore, A., Yanez, E., Stanton, M., Tufekcic, S., Syed, R., Akrami, A., Rose, M., Sura-paneni, S., Bostick, T., King, A., Neervannan, S., Ostovic, D., Koparkar, A. (2008). "The co-crystal approach to improve the exposure of a water-insoluble compound: AMG 517 sorbic acid co-crystal characterization and pharmacokinetics." *J. Pharm. Sci.* 97, 3942–3956.
- Basavoju, S., Bostrom, D., Velaga, S. P.(2008). "Indomethacin-Saccharin Cocrystal: Design, Synthesis and Preliminary Pharmaceutical Characterization." *Pharm. Res.*, 25, 530-541.

- Behme, R. J., Brooke, D. (1991). "Heat of Fusion Measurement of a Low Melting Polymorph of Carbamazepine That Undergoes Multiple-Phase Changes During Differential Scanning Calorimetry Analysis." *J. Pharm. Sci.*, 80, 986-990.
- Bettinetti, G., M. R. Caira, et al. (2000). "Structure and Solid-State Chemistry of Anhydrous and Hydrated Crystal Forms of the Trimethoprim-Sulfamethoxypyridazine 1:1 Molecular Complex." *Journal of Pharmaceutical Sciences* 89, 478-489.
- Bingham, A. L., D. S. Hughes, et al. (2001). "Over one hundred solvates of sulfathiazole." *Chemical Communications*, 7, 603-604.
- Caira, M. R. (1991). "Molecular complexes of sulfonamides. Part 1. 1:1 complexes between sulfadimidine [4-amino-N-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide] and 2- and 4-aminobenzoic acids." *Journal of Crystallographic and Spectroscopic Research* 21, 641-648.
- Caira, M. R., L. R. Nassimbeni, et al. (1995). "Selective formation of hydrogen bonded cocrystals between a sulfonamide and aromatic carboxylic acids in the solid state." *Journal of the Chemical Society, Perkin Transactions 2*, 2213-2216.
- Childs, S. L. and K. I. Hardcastle. (2007) "Cocrystals of piroxicam with carboxylic acids." *Crystal Growth & Design*, 7, 1291-1304.
- Childs, S. L., L. J. Chyall, et al. (2004). "Crystal Engineering Approach to Forming Cocrystals of Amine Hydrochlorides with Organic Acids. Molecular Complexes of Fluoxetine Hydrochloride with Benzoic, Succinic, and Fumaric Acids." *Journal of the American Chemical Society*, 126, 13335-13342.
- Childs, S. L., Rodríguez-Hornedo, N., Reddy, L. S., Jayasankar, A., Maheshwari, C., McCausland, L., Shipplett, R., Stahly, B. C. (2008). "Screening Strategies Based on Solubility and Solution Composition Generate Pharmaceutically Acceptable Cocrystals of Carbamazepine." *CrystEngComm*, 10, 856-864.
- Coffman, R. E., Kildsig, D. O. (1996). "Hydrotropic Solubilization - Mechanistic Studies." *Pharm. Res.*, 13, 1460-1463.
- Delori, A., Galek, P.T.A., Pidcock, E., Jones, W. (2012). "Quantifying homo- and heteromolecular hydrogen bonds as a guide for adduct formation." *Chem. Eur. J.*, 18, 6835-6846.

- Delori, A., Galek, P.T.A., Pidcock, E., Patni, M., Jones W. (2013). "Knowledge-based hydro-gen bond prediction and the synthesis of salts and cocrystals of the anti-malarial drug pyrimethamine with various drug and GRAS molecules." *CrystEngComm*.
- Desiraju, G. R. (1995). "Supramolecular Synthons in Crystal Engineering--A New Organic Synthesis." *Angewandte Chemie International Edition in English*, 34, 2311-2327.
- Desiraju, G. R. (2003). "Crystal Engineering: From Molecules to Materials." *J. Mol. Struct.*, 656, 5-15.
- Dollery C. (1999). "Therapeutic drugs." *Churchill Livingstone Press*, 2, 11–13.
- Donohue, J.(1952). "The Hydrogen Bond in Organic Crystals." *Journal of Physical Chemistry* 56, 502-510.
- Elqidra R., Unlu N., Capan Y., Sahin G., Dalkora T., Hincal A.A. (2004). "Effect Of Polymorphism on In Vitro-In Vivo Properties of Carbamazepine Conventional Tablets." *J Drug Del. Sci. Tech*, 14, 147-153.
- Etter, M. C. (1990). "Encoding and Decoding Hydrogen-Bond Patterns of Organic Compounds." *Accounts of Chemical Research*, 23, 120-126.
- Etter, M. C. and S. M. Reutzel (1991). "Hydrogen Bond Directed Cocrystallization and Molecular Recognition Properties of Acyclic Imides." *Journal of the American Chemical Society* 113, 2586-2598.
- Etter, M. C.(1991). "Hydrogen Bonds as Design Elements in Organic Chemistry." *Journal of Physical Chemistry* , 95, 4601-4610.
- Etter, M. C., S. M. Reutzel, et al. (1993). "Self-organization of adenine and thymine in the solid state." *J. Am. Chem. Soc.* 115, 4411-4412.
- Fábián, L.(2009). "Cambridge structural database analysis of molecular complementarity in cocrystals." *Cryst. Growth Des.*, 9, 1436–1443.
- Fayos, J. (2009). "Molecular crystal prediction approach by molecular similarity: data mining on molecular aggregation predictors and crystal descriptors." *Cryst. Growth Des.*, 9, 3142–3153.
- Fernandes, P., Bardin, J., Johnston, A., Florence, A. J., Leech, C. K., David, W. I. F., Shankland, K. (2007). "Carbamazepine Trifluoroacetic Acid Solvate." *Acta Crystallogr.* E63, O4269-U2927.

- Fleischman, S. G., S. S. Kuduva, et al.(2003). "Crystal Engineering of the Composition of Pharmaceutical Phases: Multiple-Component Crystalline Solids Involving Carbamazepine." *Crystal Growth & Design*, 3, 909-919.
- Gagniere E., Mangin D., Puel F., Rivoire A., Monnier O., Garcia E. and Klein J.R. (2009). "Formation of co-crystals: kinetic and thermodynamic aspects." *J.Cryst. Growth.*, 311, 2689–2695.
- Galek, P.T.A., Fábíán, L., Motherwell, W.D.S., Allen, F.H., Feeder, N. (2007). "Knowledge-based model of hydrogen-bonding propensity in organic crystals." *Acta Cryst.*, B63, 768–782.
- Gao, Y., Zu, H., & Zhang, J. (2011). "Enhanced dissolution and stability of adefovir dipivoxil by cocrystal formation." *J. Pharm. Pharmacol.*, 63(4), 483-490.
- Ghosh, M., A. K. Basak, et al. (1991). "Structure and Conformation of the 1:1 Molecular Complex of Sulfaproxyline-Caffeine." *Acta Crystallographica* C47, 577-580.
- Gillon, A. L., N. Feeder, et al.(2003). "Hydration in molecular crystals--a Cambridge Structural Database analysis." *Crystal Growth and Design*, 3, 663-673.
- Good, & Rodriguez-Hornedo, N. (2010). "Cocrystal Eutectic Constants and Prediction of Solubility Behavior." *Cryst. Growth Des.*, 10 (3), 1028–1032.
- Gracin, S., Rasmuson, Å. C. (2004). "Polymorphism and Crystallization of P-Aminobenzoic Acid." *Cryst. Growth Des.*, 4, 1013-1023.
- Grzesiak, A., Lang, M., Kim, K., Matzger, A. J. (2003). "Comparison of the Four Anhydrous Polymorphs of Carbamazepine and the Crystal Structure of Form I." *J. Pharm. Sci.*, 92, 2260-2271.
- Harris, R. K., Ghi, P. Y., Puschmann, H., Apperley, D. C., Griesser, U. J., Hammond, R. B., Ma, C., Roberts, K. J., Pearce, G. J., Yates, J. R., Pickard, C. J. (2005). "Structural Studies of the Polymorphs of Carbamazepine, Its Dihydrate, and Two Solvates." *Org. Process Res.Dev.*, 9, 902 - 910.
- He G., Chow P.S. and Tan R.B.H. (2010). "Investigating the intermolecular interactions in concentrationdependent solution cocrystallization of caffeine and p-hydroxybenzoic acid." *Cryst Growth Des.*,10, 3763–3769.
- Hickey, M. B., M. L. Peterson, et al. (2006). "Performance comparison of a co-crystal of carbamazepine with marketed product." *European Journal of Pharmaceutical Sciences* 67: 112 -119.

- Himes, V. L., A. D. Mighell, et al.(1981). "Structure of carbamazepine-5H-benz[b.f]azepine-5-carboxamide." *Acta Crystallographica*, B37, 2242-2245.
- Hino, T., Ford, J. L., Powell, M. W. (2001). "Assessment of Nicotinamide Polymorphs by Differential Scanning Calorimetry." *Thermochim. Acta.*, 374, 85-92.
- Hussain, M. A., DiLuccio, R. C., Maurin, M. B.(1993). "Complexation of Moricizine with Nicotinamide and Evaluation of the Complexation Constants by Various Methods." *J. Pharm. Sci.*, 82, 77-79.
- Infantes, L. and S. Motherwell.(2002). "Water clusters in organic molecular crystals." *Crystal Engineering Communications*, 4, 454-461.
- Issa, N., Karamertzanis, P.G., Welch, G.W.A., Price, S.L.(2009). "Can the formation of pharmaceutical cocrystals be computationally predicted? I. Comparison of lattice energies." *Cryst. Growth Des.*, 4, 442–453.
- Jain, N., Yalkowsky, S. H. J. (2001). "The estimation of aqueous solubilities of organic nonelectrolytes" *Pharm. Res.*, 90, 234–252.
- Jayasankar, A., A. Somwangthanaroj, et al. (2006). "Cocrystal formation during cogrinding and storage is mediated by amorphous phase." *Pharmaceutical Research*, 23, 2381-2392.
- Jayasankar, A., D. J. Good, et al. (2007). "Mechanisms by which moisture generates cocrystals." *Molecular Pharmaceutics* 4, 360-372.
- Johnston, A., Florence, A. J., Fernandes, P., Shankland, A., Kennedy, A. R. (2007). "10,11- Dihydrocarbamazepine-Form-Amide Solvate (1/1)". *Acta Crystallogr. B*, E63, O3888-U3750.
- Katritzky, A. R., Lobanov, V. S., Karelson, M. (1995). "QSPR: The Correlation and Quantitative Prediction of Chemical and Physical Properties from Structure." *Chem. Soc. ReV.*, 279-287.
- Khankari, R. K. and D. J. W. Grant.(1995). "Pharmaceutical Hydrates." *Thermochemica Acta*, 248, 61-79.
- Kobayashi, Y., S. Ito, et al.(2002). "Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate." *International Journal of Pharmaceutics*, 193, 137-146.
- Kofler L. and Kofler A. (1980). "Thermal micromethods for the study of organic compounds and their mixture." McCrone Research Institute, Chicago.

- Lang, M.; Kampf, J. W.; Matzger, A. J. (2002). "Form IV of Carbamazepine." *J. Pharm. Sci.*, 91, 1186-1190.
- Leiserowitz, L. and G. M. J. Schmidt.(1969). "Molecular Packing Modes. Part III. Primary Amides." *Journal of the Chemical Society (A): Inorganic, Physical, Theoretical*, 2372-2382.
- Liu, R., (2008). "Water-insoluble Drug Formulation." *CRC Press, Boca Raton, FL*.
- Lowes, M. M. J., Caira, M. R., Lotter, A. P., Vanderwatt, J. G. (1987). "Physicochemical Properties and X-Ray Structural Studies of the Trigonal Polymorph of Carbamazepine." *J. Pharm. Sci.*, 76, 744-752.
- Lowes, M. M. J., M. R. Caira, et al. (1987). "Physicochemical properties and X-ray structural studies of the trigonal polymorph of carbamazepine." *Journal of Pharmaceutical Sciences*, 76, 744-752.
- Lu, E., N. Rodríguez-Hornedo, et al. (2008). "A rapid thermal method for cocrystal screening." *Crystal Engineering Communications*, 10, 665-668.
- Lukas K. and Peter LeMaire K. (2009). "Differential scanning calorimetry: Fundamental Overview" Department of Physics, Central Connecticut State University, New Britain.
- Mahalaxmi R., Ravikumar, Shivanand P., Arun S., Annie S. (2009). "Effect of Recrystallization on Size, Shape, Polymorphs and Dissolution of Carbamazepine." *J.Pharm-Sci*, 3, 725-732.
- Maheshwari, C., A. Jayasankar, et al. (2009). "Factors that influence the spontaneous formation of of pharmaceutical cocrystals by simply mixing solid reactants." *Crystal Engineering Communications* (published online Nov. 2008).
- Maheshwari, C., André, V., Reddy, L.S., Roy, L., Duarte, T., Rodríguez-Hornedo, N. (2012). "Tailoring aqueous solubility of a highly soluble compound via cocrystallization: effect of cofomer ionization, pHmax, and solute-solvent interactions." *CrystEngComm*, 4801–4811.
- Marcus O'Mahony. (2009). "Carbamazepine: A Solution Mediated Polymorphic Transformation." University of Limerick.
- Matsuda, Y., Akazawa, R., Teraoka, R., Otsuka, M. (1994). "Pharmaceutical Evaluation of Carbamazepine Modifications - Comparative Study for Photostability of Carbamazepine Polymorphs by Using Fourier Transformed Reflection-Absorption Infrared Spectroscopy and Colorimetric Measurement." *J. Pharm. Pharmacol.* 1994, 46, 162-167.

- McCrone W. C. (1957). "Fusion methods in chemical microscopy." *Wiley Interscience Publication, New York 1957*.
- McMahon, J. A., Bis, J. A., Vishweshwar, P.; Shattock, T. R., McLaughlin, O. L., Zaworotko, M. J. (2005). "Crystal Engineering of the Composition of Pharmaceutical Phases. 3. Primary Amide Supramolecular Heterosynthons and Their Role in the Design of Pharmaceutical Cocrystals." *Z. Kristallogr.*, 220, 340-350.
- McMahon, L. E., P. Timmins, et al. (1996). "Characterization of Dihydrates Prepared from Carbamazepine Polymorphs." *Journal of Pharmaceutical Sciences*, 85, 1064-1069.
- McNamara, D.P., Childs, S.L., Giordano, J., Iarriccio, A., Cassidy, J., Shet, M.S., Mannion, R., O'Donnell, E., Park, A. (2006). "Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API." *Pharm. Res.* 23, 1888–1897.
- Miyako, Y., Tai, H., Ikeda, K., Kume, R., Pinal, R. (2008). "Solubility screening on a series of structurally related compounds: cosolvent-induced changes on the activity coefficient of hydrophobic solutes." *Drug Dev. Ind.*, 499–505.
- Morissette, S. L., O. Almarsson, et al. (2004). "High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids." *Advanced Drug Delivery Reviews* 56, 275-300.
- Murphy, D., F. Rodríguez-Cintron, et al.(2002). "Solution-mediated phase transformation of anhydrous to dihydrate carbamazepine and the effect of lattice disorder." *International Journal of Pharmaceutics*, 246, 121-134.
- Musumeci, D., Hunter, C.A., Prohens, R., Scuderi, S., McCabe, J.F. (2011). "Virtual cocrystal screening." *Chem. Sci.*, 883–890.
- Nada H.A., Al-Saidan M.S., Mueller W.B. (2005). "Crystal Modification for Improving the Physical and Chemical Properties of Ibuprofen." *Pharm. Technol.*, 29, 90–101.
- Nangia, A. and G. R. Desiraju.(1998). "Supramolecular Synthons and Pattern Recognition." *Topics in Current Chemistry*, 198, 57-95.
- Nehm, S., B. Rodríguez-Spong, et al.(2006). "Phase Solubility Diagrams of Cocrystals Are Explained by Solubility Product and Solution Complexation." *Crystal Growth & Design*, 6, 592-600.
- Nokhodchi A., Amire O., Jelvehgari M. (2010). "Physico-mechanical & Dissolution Behaviours of Ibuprofen Crystals in the Presence of Various Additives." *Daru*, 2.

- Nokhodchi A., Rubinstein M.H., Larhrib H., Gyout J.C. (1995). "The effect of moisture on the properties of ibuprofen tablets." *Int. J. Pharm.*, 118, 191–197.
- Oguchi, T., K. Kazama, et al. (2000). "Specific complexation of ursodeoxycholic acid with guest compounds induced by co-grinding." *Physical Chemistry Chemical Physics* 2, 2815-2820.
- O'Neil, M. J. (2001). "The Merck Index." 13th Merck & Co., Inc: New Jersey.
- Pacheco P.D., Manrique J.Y., Martinez F. (2007). "Thermodynamic study of solubility of ibuprofen and naproxen in some ethanol + propylene glycol mixtures." *Fluid Phase Equilibria.*, 262, 23–31.
- Padrela, L., Rodrigues, M., Velaga, S. P., Matos, H. A., Azevedo, E. G. (2009). "Formation of indomethacin-saccharin cocrystals using supercritical fluid technology." *Eur. J. Pharm. Sci.*
- Patel Rajanikant P., Nirav P., Patel N.M., Patel M.M. (2010). "A novel approach for dissolution enhancement of Ibuprofen by preparing floating granules." *Int J Res Pharm Sci. 1*, 57, 322-323.
- Pedireddi, V. R., W. Jones, et al. (1996). "Creation of crystalline supramolecular arrays: a comparison of co-crystal formation from solution and by solid-state grinding." *Chemical Communications*, 987-988.
- Porter III, W. W., Elie, S. C., Matzger, A. J. (2008). "Polymorphism in Carbamazepine Cocrystals." *Cryst. Growth Des.*, 8, 14-16.
- Rasenack N., Muller B.W.(2002). "Ibuprofen crystals with optimized properties." *Int. J. Pharm*, 245, 9–24.
- Rasool, A. A., Hussain, A. A., Dittert, L. W. (1991). "Solubility Enhancement of Some Water-Insoluble Drugs in the Presence of Nicotinamide and Related Compounds." *J. Pharm. Sci.*, 80, 387-393.
- Reboul, J. P., B. Cristau, et al.(1981). "5H-5-Dibenzyl[b,f]azepinecarboxamide (carbamazepine)." *Acta Crystallographica*, B37, 1844-1848.
- Reddy, L. S., S. J. Bethune, et al.(2009) "Cocrystals and Salts of Gabapentin: pH dependent cocrystal stability and solubility." *Crystal Growth & Design*.
- Remenar, J. F., S. L. Morissette, et al.(2003). "Crystal Engineering of Novel Cocrystals of a Triazole Drug with 1,4-Dicarboxylic Acids." *Journal of the American Chemical Society*, 125, 8456-8457.

- Rinaki E., Valsami, G., and Macheras, P. (2003). "Quantitative biopharmaceutics classification system: The central role of dose/solubility ratio." *Pharm. Res.*, 20, 1917-1925.
- Robinson, R. A., Biggs, A. I.(1956). "The Ionization Constants of P-Aminobenzoic Acid in Aqueous Solutions at 25°C." *Aust. J. Chem.*, 10, 128-134.
- Rodríguez-Hornedo, N., Nehm, S. J., Seefeldt, K. F., Pagán-Torres, Y., Falkiewicz, C. J. (2006). "Reaction Crystallization of Pharmaceutical Molecular Complexes". *Mol. Pharm.*, 3, 362-367.
- Rodríguez-Spong, B. (2005). "Enhancing the Pharmaceutical Behavior of Poorly Soluble Drugs through the Formation of Cocrystals and Mesophases. Ph.D. Thesis." University of Michigan, 2005.
- Rodríguez-Spong, B., C. P. Price, et al. (2004). "General principles of pharmaceutical solid polymorphism: A supramolecular perspective." *Advanced Drug Delivery Reviews*, 56,241-274.
- Rodríguez-Spong, B., P. Zocharski, et al.(2003) ."Enhancing the Pharmaceutical Behavior of Carbamazepine Through the Formation of Cocrystals " *The AAPS Journal* 5.
- Schultheiss N. and Newman A.(2009) "Pharmaceutical Cocrystals and Their Physicochemical Properties." *Cryst. Growth Des.*, 9, 2950-2967.
- Seefeldt, K. J., Miller, J., Alvarez-Núñez, F., Rodríguez-Hornedo, N. (2007). "Crystallization Pathways and Kinetics of Carbamazepine-Nicotinamide Cocrystals from the Amorphous State by in Situ Thermomicroscopy, Spectroscopy and Calorimetry Studies". *J. Pharm. Sci.*, 96, 1147-1158.
- Sekhon B.S.(2012). "Drug-drug Co-crystal." *DARU Journal of Pharmaceutical Sciences*, 20-45.
- Serajuddin, A.T.M. (2007). "Salt Formation to Improve Drug Solubility." *Adv. Drug Delivery Rev.*, 603–616.
- Ter Horst, J. H.; Deij, M. A.; Cains, P. W. (2009). "Discovering New Co-Crystals." *Crystal Growth & Design*, 9(3), 1531.
- Terrence, C. F., M. Sax, et al.(1983). "Effect of Baclofen enantiomorphs on the spinal trigeminal nucleus and steric similarities of carbamazepine." *Pharmacology*, 27, 85-94.

- Trask, A. V., W. D. S. Motherwell, et al. (2005). "Pharmaceutical Cocrystallization: Engineering a Remedy for Caffeine Hydration." *Crystal Growth & Design*, 5, 1013-1021.
- Trask, A., V., W. D. S. Motherwell, et al. (2004). "Solvent-drop grinding: green polymorph control of cocrystallisation." *Chemical Communications*, 890-891.
- Van S. J. (1995). "The geometry of crystal growth." *Terra Scientific Publishing Company*.
- Vishweshwar, P., McMahon, J. A., Oliveira, M., Peterson, M. L., Zaworotko, M. J.(2005). "The Predictably Elusive Form II of Aspirin." *J. Am. Chem. Soc.*, 127, 16802- 16803.
- Walsh, R. D. B., M. W. Bradner, et al. (2003). "Crystal Engineering of the Composition of Pharmaceutical Phases." *Chemical Communications*, 186-187.
- Wenger, M. and J. Bernstein. (2008). "An alternate crystal form of gabapentin: a cocrystal with oxalic acid." *Crystal Growth & Design*, 8, 1595-1598.
- Xie, Y.C., Liu, H.Z., Chen, J.Y.(1998). "Candida rugosa lipase catalyzed esterification of racemic ibuprofen with butanol: racemization of R-ibuprofen and chemical hydrolysis of S-ester formed." *Biotechnology Letters*, 20, 455-458.
- Yalkowsky, S.H. (1999). "Solubility and Solubilization in Aqueous Media." American Chemical Society, Oxford University Press, New York, USA.
- Zaworotko M.,(2006) "Pharmaceutical co-crystals: do they represent a new path to improved medicines?." *J. Pharm. Pharmacol.*, 58, A91.
- Zocharski, P., S. Nehm, et al.(2004). "Can Solubility Products Explain Cocrystal Solubility and Predict Crystallization Conditions?" *The AAPS Journal* 6.
- Zubair, M. U., Hassan, M. M. A.(1984). "Saccharin. In Analytical Profiles of Drug Substances." Academic Press: Orlando, Florida, 487-519.

APPENDICES