CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Co-crystal development has an increasing interest in the pharmaceutical field as it plays an important class of pharmaceutical material as it enhances the solubility, dissolution and consequent bioavailability of poor water-soluble drugs by forming a crystal and a co-former with specific stoichiometry composition, (Thakuria et al., 2012). CBZ is an insoluble drugs that has a high dose requirement (>100mg/day) for therapeutic effect and possess multiple challenges for oral drug delivery, including a narrow therapeutic window, auto induction of metabolism and dissolution-limited bioavailability, (Hickey et al., 2007; Bertilson and Thomson, 1986; Meyer et al., 1992).

This co-crystallization technique is an approach that allows binding active pharmaceutical ingredient (API) with one or more components of co-crystal former (CCF) without breaking or making new covalent bond within one periodic crystalline lattice, (Sheikh et al., 2009; Gagniere et al., 2009). This will then preserve the biological function of the drugs while increasing its solubility performance. Co-crystal can be prepared by several methods such as solvent based method and solid based method. The solvent based methods involve slurry conversion via solvent evaporation, cooling crystallization and precipitation while the solid based methods involve dry grinding and solvent-assisted grinding (Pandrela, 2010).

It has been reported that co-crystal commonly characterize using x-ray powder diffraction (XRPD) as stated by Qiao (2011). Besides that, fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) also can be used.
1.2 Motivation

Carbamazepine (CBZ) is classified as a class II compound with low aqueous solubility. It is one of the water insoluble drug that face issues regarding poor solubility, bioavailability, stability and mechanical properties. Co-crystallization technique currently has been widely used in the pharmaceutical industry in order to improve the solubility of drugs since the drug often discarded during commercial production due to their low solubility. Co-crystallization of CBZ with SAC has been successfully produces and shows a promising result as solubility of CBZ-SAC increase greatly compare to the CBZ. However, it has been reported that CBZ-SAC co-crystal has two different polymorphic form and Form II is said to have improves the solubility of the drugs as stated by Porter et. al. (2008), while solubility data for Form I are not yet reported. Due to the polymorphic properties of the CBZ-SAC co-crystal it is important for us to know which screening method can produce the desired co-crystal which is CBZ-SAC Form II.

1.3 Problem Statement

It is true that the CBZ-SAC co-crystal have indeed successfully produced more polymorphs and this shows that CBZ-SAC have the higher potential to produce varies properties in term of solubility, bioavailability and stability. As it has been reported that CBZ-SAC co-crystal has polymorph issues, screening study needed to be implemented. Therefore, to come out from this problem CBZ-SAC co-crystal production is being tailor by manipulating the crystallization technique in term of method of crystallization, solvent used, and the mol ratios of the component. Many possible methods in crystallization is being review in order to know which method would produce higher probability of forming co-crystal of CBZ-SAC Form II. The method of producing CBZ with other CCF from other research will be used as a guideline and for further study.
1.4 Objective

Based on the research background and problem statement, the objective of this study is:

1) To study the formation of carbamazepine-saccharin (CBZ-SAC) using varies solvent, solvent based crystallization method and concentration ratio [CBZ: SAC].

1.5 Scopes of Study

The scope of the research consists of:

1) Production of carbamazepine-saccharin (CBZ-SAC) co-crystal in ethyl acetate and formic acid solvent using cooling crystallization method, solvent evaporation method, slurry and stirring with different ratio of CBZ and SAC.

2) Characterizations of CBZ-SAC co-crystal using optical microscopic, powder x-ray diffraction (XRD), differential scanning calorimetry (DSC) and fourier transform infrared spectroscopic (FTIR).