1 INTRODUCTION

1.1 Overview

This chapter will discuss about the background of the research including the materials used in the research, motivation and problem statement, objectives and scope of studies.

1.1.1 Carbamazepine (CBZ)

Carbamazepine (CBZ) which has an IUPAC name of 5H-dibenz[b,f]azepine-5-carboxamide and a molecular formula of C\textsubscript{15}H\textsubscript{12}H\textsubscript{2}O (MW 236.67). The molecular structure of CBZ as shown in Figure 1.1.

![Molecular structure of CBZ](image)

**Figure 1.1:** Molecular structure of CBZ

CBZ is an anticonvulsant that have been selected as the model drug having five different form which are four anhydrous forms and one dihydrate form as reported by Rustichelli and co-worker in 2000 (Rustichelli et al., 2000). Murphy et al. in 2002 stated that CBZ polymorphs were different in crystal structures and exhibits different melting points, chemical reactivity, solubility and compatibility (Murphy et al., 2002). Ceolin et al. in 1997 stated that polymorph II was a triclinic crystal with a prismatic morphology (Ceolin et al., 1997). Polymorph III and IV was different from the other polymorphs and they were fully describe in the literature. The International Centre for Diffraction Data has been reported that the polymorph III has a monoclinic crystal structure and this form is the most stable polymorph at a room temperature (Matsuda et al., 1994). Polymorph IV was presented as a needle-shape morphology and it will crystallize at high temperature (Lowes et al., 1987). Behme and Brooke in 1991 reported that the melting points for the all four polymorph was in the range 175-190°C (Behme and Brooke, 1991).
CBZ is classified as Class 2 according to the Biopharmaceutical Classification System (BCS) (Farias and Carneiro, 2014) which mean CBZ has low solubility in water and high permeability in human tissues. Since the absorption of CBZ is limited by its solubility, the dissolution characteristic improvement can increased the rate of absorption of CBZ and enhanced its oral bioavailability (Hu et al., 2003). The different packing of the four polymorphs form was shown in the Figure 1.2.

![Packing diagram of CBZ polymorphs form I, II, III and IV (Rodriguez-Spong et al., 2004)](image)

**Figure 1.2:** Packing diagram of CBZ polymorphs form I, II, III and IV (Rodriguez-Spong et al., 2004)

CBZ is a main model drug to study polymorphism and phase transition. CBZ also selected because of its low solubility to investigate process method to their ability to improve the solubility. CBZ was poorly compressible and its compatibility depends on the polymorphic form (Flicker, 2011).

Other than four polymorphs, CBZ also exist in dihydrate form which crystallizes in the orthorhombic system (McMahon et al., 1996). CBZ dihydrate shows the best compatibility form but it is not stable under compression (Lefebvre et al., 1986).
Dihydrate of CBZ was a stable form in an aqueous solution (Sehić et al., 2010) and its relative humidity was above 52% (McMahon et al., 1996). Other than that, CBZ dihydrate is the most common solvate with two molecules of water which has high relative humidity. Figure 1.3 shows the arrangement of the CBZ dihydrate (Rodriguez-Spong et al., 2004).

![Figure 1.3: The arrangement of the CBZ dihydrate (Rodriguez-Spong et al., 2004)](image)

1.1.2 Pharmaceutical Hydrate

Threlfall in 1995 state that approximately there were one third of active pharmaceutical ingredients (APIs) which capable of forming in hydrate form (Threlfall, 1995). Figure 1.4 shows that CBZ dihydrate formed a tunnel structure through the crystal and the water molecule were connected to each other by hydrogen bonding.

![Figure 1.4: Example of the channel hydrate CBZ dihydrate (Kogermann, 2008)](image)

The presence of water molecule can change the initial anhydrate or lower hydrate crystal structure such as the shape, symmetry, dimension and the capacity of a unit cell (Kogermann, 2008). The anhydrous forms have higher aqueous solubility and dissolution