Characterization of Carbamazepine- Hydroxypropyl-β-Cyclodextrin Inclusion Complex in Solid State Obtained by Freeze-Drying Process

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Complexation between Carbamazepine, an anticonvulsant drug used for the treatment of epilepsy, and hydroxypropyl-β-cyclodextrin (HPβCD) was studied in solid states. The inclusion complex was prepared in water solution of 1:1 molar and added with concentrated ammonium hydroxide to obtain true solution. The solid state of the inclusion complex was obtained by freeze-drying process. Complexation was characterized using infrared spectrophotometer, X-ray diffraction and Differential Thermal Analysis (DTA) compared to freeze-dried single compounds and their physical mixture. The result showed the different characteristic among inclusion complex, freeze-dried single compound and their physical mixture. It was assumed that there was an entrapment of the carbamazepine molecule into the molecule cavity of hydroxypropyl-β-cyclodextrin in the formation of the inclusion complex.

Keywords *: characterization, inclusion complex, carbamazepine, hydroxypropyl-β-cyclodextrin*

INTRODUCTION

Carbamazepine (CBZ), used for the treatment of epilepsy, has low water solubility approximately 200µg/mL. Due to the importance of immediate onset of action in the treatment of convulsive epileptic state, solubility enhancement is considerably needed to perform the better drug formulation particularly for injection dosage form (McEvoy, 2002; Koester *et al*, 2004; Loscher and Honack, 1997).

The enhancement of drug solubility can be attained by forming inclusion complex with cyclodextrin (Fig.1). During the complexation, the molecule of CBZ will be introduced into the hydrophobic cavity of cyclodextrin. As a result, the hydrophilic property in the surface of cyclodextrin molecules will enhance the water solubility of drug (Bekers *et al*., 1991; Peri *et al*., 1994).

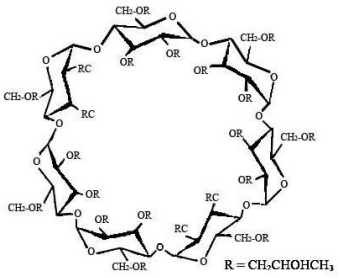

Figure 1. Molecular Structure of HPβCD

The possible type of cyclodextrin used for parenteral route is hydroxypropyl-β-cyclodextrin (HPβCD), which does not have such adverse reaction as nephrotoxic and hemolytic effect to human erythrocyte. Moreover, this cyclodextrin derivate perform the better water solubility at about 50 gram/100mL, 25ºC (Bekers *et al*., 1991; Peri *et al*., 1994).

There are several ways to obtain the solid state of inclusion complex, including freeze-drying, spray drying, co-precipitation, kneading, grinding and also melting (Bekers *et al*., 1991). Several study on the complexation methods performed freeze-drying as the most efficient method compared to others. None of the previous studies were carried out to characterize inclusion complex of CBZ-HPβCD in solid state obtained by freeze-drying process (Kurozumi *et al*., 1975; Shimpi *et al*., 2005; Isadiartuti and Suwaldi, 2005; Reddy *et al*., 2004).

The aim of the study is to determine the characteristic of CBZ – HPβCD inclusion complex in solid state using infrared spectrophotometer, X-ray diffraction and Differential Thermal Analysis (DTA).

MATERIALS AND METHODS

Carbamazepine (pharmaceutical grade) was donated by Novartis Biochemie, Ltd. HPβCD was supplied by Signa Husada, Ltd. A concentrated NH_4OH and distilled water was used throughout the study.

Preparation of inclusion complex. The inclusion complex was prepared in water solution of 1:1 molar ratio of CBZ and HPβCD, which then added with concentrated ammonium hydroxide to obtain true solution.The solid state of the complex is obtained through freeze-drying process using B-Braun Christ LMC-2 beta 1-8K freeze-dryer. CBZ and HPβCD both in aqueous solution were also dried to obtain the freeze-dried single compound. The physical mixture was gained by simply mixing the freeze-dried single compounds with spatula in 1:1 molar ratio.

Infrared spectroscopy studies. Samples were analyzed by IR-Spectrophotometer. 2 (two) mg of samples were introduced to about 300 mg dried potassium bromide (spectroscopy grade) and pressed to obtain transparent plate and put into sample holder. The infrared spectrums were obtained using JASCO FTIR 5300 spectrophotometer. The spectrums were traced within range 4000 to 400cm^{-1} wave number.

X-ray diffraction studies. Powder X-ray diffraction patterns were recorded using a JEOL JDX-3530 diffractometer with angle of 2θ from 5º to 40º.

Differential Thermal Analysis. Thermal analysis was performed on solid and freeze-dried samples using Differential Thermal Analyzer Metler Toledo. The range of thermal analysis covered temperatures from 50-250ºC and set up with rate 5ºC per minute.

RESULT AND DISCUSSION

Based on the infrared spectrums showed in Figure 2, the physical mixture showed carbonyl group absorbance (C=O) in 1678 cm^{-1}, aromatic ring doublet absorbance in 1604 cm^{-1} and aromatic ring single absorbance in 1489 cm^{-1} which were also demonstrated by freeze-dried CBZ. In contrast, these groups of specific absorbance were not performed in the inclusion complex spectrum, which is similar to the phenomena described in literature. In addition, while there was a peak superposition between CBZ and HPβCD in the fingerprint area of physical mixture spectrum, the complex spectrum showed the domination of HPβCD peaks in this area (Meislich *et al*., 1999; Silverstein *et al*., 1991; Jug *et al*., 2005).

In term of X-ray diffraction pattern, It can be seen in Figure 3 that the physical mixture powder (C) showed crystalline peaks in 2θ ; 12,120º; 13,020º; 18,340º; and 19,740º even though considerably lower than those in freeze-dried CBZ profile (A) which clearly demonstrated crystalline state. While, the complex (D) showed relatively amorphous state as well as the freeze-dried HPβCD performed, showing the state of complexation between the drugs and the HPβCD (Isadiartuti and Suwaldi, 2005).

Thermal analysis profiles, shown in Figure 4, presented a different pattern among the samples. DTA profile of the freeze-dried CBZ (A) showed a sharp melting point pattern, presenting the crystalline state of substance. While the dull peak was presented by the DTA profile of freeze-dried HPβCD (B), showing an amorphous state of the particles (Nalluri *et al*., 2003).

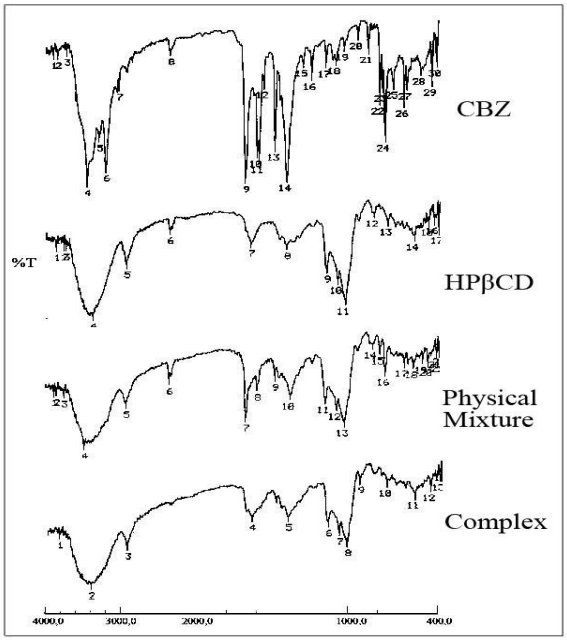

Fig. 2. Infrared spectrums of the freeze-dried CBZ, the freeze-dried HPβCD, the physical mixture and the complex traced within range 4000 to 400cm^{-1} wave number.

The melting point pattern of the physical mixture demonstrated a slight shift to the higher temperature compared to the freeze-dried single compound (C). On the other hand, DTA profile of inclusion complex CBZ- HPβCD showed a considerable change in melting point which is shifting 24ºC higher than the freeze-dried CBZs' melting point (D). The significant change may represent the massive interaction during the complexation between CBZ and HPβCD (Nalluri *et al*., 2003).

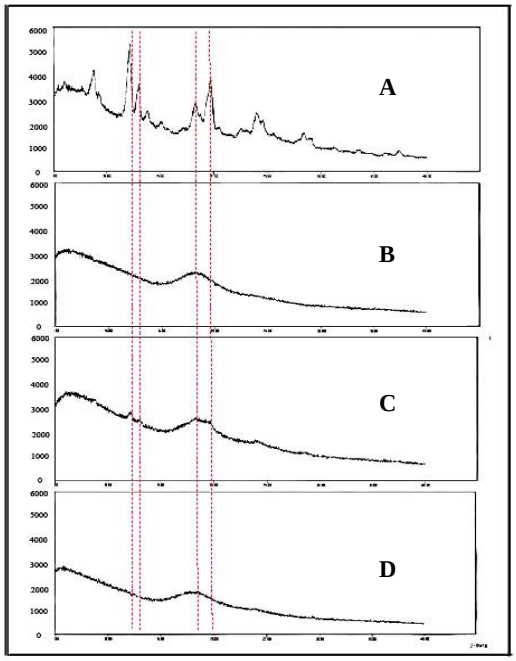

Fig. 3. Diffractograms of the freeze-dried CBZ (A), the freeze-dried HPβCD (B), the physical mixture (C) and the inclusion complex (D).

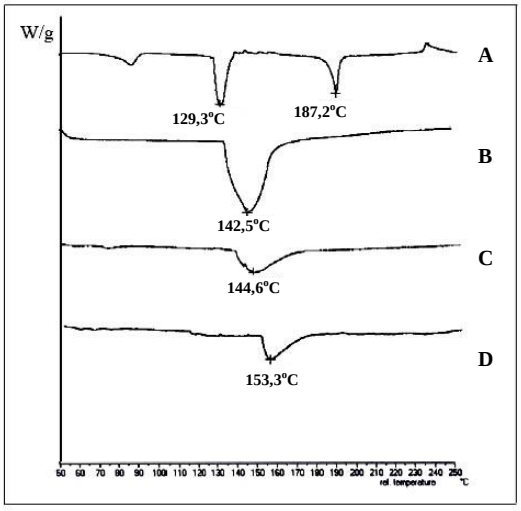

Figure 4. DTA profiles of the freeze-dried CBZ (A), the freeze-dried HPβCD (B), the physical mixture (C) and the inclusion complex (D).

Conclusion

From the result of infra-red spectrum, it was assumed that there was an interaction in carbonyl groups of CBZ showed by the disappearance of carbonyl specific spectrum in the infra-red spectrum of inclusion complex. The compared diffractogram demonstrate a decrease of crystallization in inclusion complex compared to their physical mixture. The Differential Thermal Analysis (DTA) profile expressed the shifting melting point of CBZ in the DTA profile of inclusion complex. It was suggested that the different characteristic performed by inclusion complex, compared to the freeze-dried single compound and their physical mixture, was occurred possibly because of entrapment of CBZ molecules into the molecule cavities of HPβCD during the formation of the inclusion complex. Thus, the complex may perform as a highly soluble substance when compared to the single drug compound since it may lowers the hydrophobic properties of CBZ.

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