CARBAMAZEPINE-AMINO ACID PRODRUGS TO IMPROVE PHYSICOCHEMICAL PROPERTIES AND BIOAVAILABILITY OF CARBAMAZEPINE

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ABSTRACT

Carbamazepine (CBZ) is the first-line treatment of epilepsy, including BCS II which is characterized by high membrane permeability and low solubility in water. The limited solubility of CBZ causes the low dissolution rate of this drug hence results in the low absorption and low bioavailability of CBZ when given orally. One strategy that can be done to overcome the problems associated with limited solubility of CBZ is the formation of prodrug to enhance its solubility. Therefore, this research is aimed to increase solubility of carbamazepine by the formation of CBZ prodrug with promoeity group of amino acid glycine (GLY), alanine (ALA) and lysine (LYS). The formation of prodrug PD-CBZ-GLY, PD-CBZ-ALA and PD-CBZ-LYS are done by adding diisopropylcarbodiimide (DIC) followed by reaction at 0 °C. Identification of the formed compounds are conducted by using DTA, FTIR and NMR. The results obtained show formation of the prodrug PD-CBZ-GLY, PD-CBZ-ALA and PD-CBZ-LYS. Furthermore, the physicochemical characterization of the prodrug is done by using DTA, PXRD and optical microscope. From the results obtained, the prodrug compounds have different characteristics with the CBZ. The melting point of prodrug compounds are 179.6 - 188.8 °C. These values are lower than CBZ which has melting point 192.6 °C. Solubility of the prodrugs in distilled water (pH 6.8 ± 0.05 and T = 37 ± 0.5 ºC) are 533.44 - 748.38 µg/mL higher compared to the solubility CBZ (278.62 µg/mL). Dissolution efficiency within 30 min of the CBZ also increases from 13.69 % for CBZ to 37.90 - 64.27 % for the prodrug compounds. The partition coefficient values (log P) of the prodrugs in octanol/ water at 37 ± 0.5 °C are 1.13 - 1.89. Those values are lower than the log P of CBZ (2.41). The bioavailability study is conducted on male New Zealand Rabbits demonstrated that the formation of prodrug compounds are able to shorten the t_{max} from 6.14 hours for CBZ to 1.63 - 2.77 hours; increase the maximum plasma concentration (C_{max}) of CBZ from 2.56 µg/mL for CBZ to 4.38 and 6.75 µg/mL for PD-CBZ-ALA and PD-CBZ-LYS, respectively and also increase the AUC_{0-12} from 20.59 µg hrs/mL to 21.99 dan 34.48 µg hrs/mL, respectively. From the results obtained, it can be concluded that the formation of prodrug CBZ-amino acid with promoeity group of GLY, ALA and LYS are able to increase the solubility and the dissolution rate of CBZ, and also reduce the value of log partition coefficient. Based on the bioavalability study, prodrug of PD-CBZ-ALA and PD-CBZ-LYS are able to increase the bioavailability of CBZ. Furthermore, PD-CBZ-LYS is the chosen prodrug which is promising for the further development in order to improve solubility as well as bioavailability of CBZ. Additionally, careful consideration has to be given when choosing the proper promoeity group for the formation of prodrug of CBZ-amino acid therefore a safe and effective CBZ prodrug can be obtained.

Key words: prodrug, carbamazepine, glysine, alanine, lysine, physicochemical and bioavailability

Proverbs 21 : 30

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