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التوثيق الالكتروني والميكروفيلم

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A PHARMACEUTICAL STUDY FOR IMPROVEMENT OF ORAL BIOAVAILABILITY OF CERTAIN DRUGS

A Thesis
Presented by
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For the Degree of
Master in Pharmaceutical Sciences
(Pharmaceutics)

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ABSTRACT

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Antiepileptic drugs are those that are used mainly in the management of epilepsy, a case characterized by the chronic occurence of paroxysmal firing of neurons resulting in seizures. These seizures could be convulsive or non convulsive.

Carbamazepine (CBZ) is an antiepileptic drug used in the treatment of complex partial seizures, grand mal seizures, and simple partial seizures. It is practically insoluble in water, and has an erratic, slow, and unpredictable absorption in humans. This poor water solubility urged the trials to enhance its dissolution.

The work in this thesis is divided into three parts:

Part I: Preparation, Evaluation and Formulation of Carbamazepine Spherical Agglomerate Crystals in Different Dosage Forms.

Part II: Preparation and Evaluation of Carbamazepine Liquisolid Tablets.

Part III: Stability Study and Pharmacological Activity of the Prepared Carbamazepine Formulations.

Part I: Preparation, Evaluation and Formulation of CBZ Spherical Agglomerate Crystals in Different Dosage Form:

There are at least four polymorphic forms of CBZ and one dihydrate. The common form available in the market is known as the β-form or modification III. This form was obtained from CID Company. The other form commonly known is the α-carbamazepine or modification I which was prepared through this study, and which is characterized by its high stability at the different conditions.

The work in this part includes:

1. Preparation of Carbamazepine spherically agglomerated crystals:

This was carried out, by using ethanol as solvent, 200 ml distilled water as the crystallization solvent, and chloroform as the agglomerating solvent (bridging agent). The solution of carbamazepine at 50°C was added to water at 25°C, and the mixture was stirred for ten minutes using a two bladed mixer operated at 500 rpm. Then the bridging agent was added and stirring was continued for one or two hours. That bridging agent collects the crystals into agglomerates. Three amounts of the bridging agent were used, mainly, 1, 2.8, and 5 ml. The formed crystals were filtered and dried at 50°C for either two hours or two days.

2.Evaluation of Carbamazepine Spherical Agglomerate Crystals as Follows:

a) Microscopic Examination: Each of the carbamazepine powder and spherical agglomerates were microscopically examined to determine the shape of the crystals. Also a slide micrometer was used to determine the particle size of each crystal. Photomicrographs were taken for both CBZ powder (Cid) and the spherical agglomerates.

b) Melting Point Determination: The melting point of CBZ and its spherical agglomerate crystals was determined using a melting point apparatus, where each was placed in a capillary tube that was sealed at an end, and inserted in the apparatus. The melting process was viewed through a magnifying lense in the apparatus, and the melting point was recorded.

c) Differential Scanning Calorimetry (DSC): Accurately weighed carbamazepine powder and its spherical agglomerates were placed in aluminum sample cells and scanned thermally.

d) I.R. Spectroscopic Examination: Each of carbamazepine powder and its spherical agglomerate crystals were mixed with potassium bromide and compressed into discs that were then exposed to the Infra Red spectrum.

e) X-ray Diffraction Analysis: The analysis was performed on both Carbamazepine powder and its spherical agglomerates using an X-ray tube. The samples were scanned at a speed of 8.000 deg/min.

f) Equilibrium Solubility Studies: The study was done to determine the saturated solubility of carbamazepine and its spherical agglomerate crystals in distilled water, using a shaking water bath at 25°C±1°C that was operated until equilibrium was reached after 72 hours. The concentration of CBZ was calculated according to the K value obtained from the caliberation curve of CBZ in distilled water, which was prepared by dissolving CBZ in ethanol to prepare a stock solution. Samples of this stock solution were diluted with distilled water to obtain concentrations of 2-20 ug/ml. The absorbance of these solutions was measured spectrophotometrically at the predetermined λ-max.

g) Dissolution Studies: These were done using the USP Dissolution Tester Apparatus II with 900 ml distilled water as the dissolution medium that was maintained at 37±0.5°C. The paddle was rotated at 100 ±5 rpm, for a period of two hours. The samples were removed after 5, 10, 15, 30, 45, 60, 75, 90, 105, and 120 minutes, suitably diluted with the dissolution medium and their absorbance determined. The concentrations of the samples were calculated using the K value used in the previous test.

h) Stability of the Prepared CBZ Spherical Agglomerate Crystals: This study involved the follow up of the melting point, particle size, and dissolution rate of the spherical agglomerates stored at room temperature within a period of one year.