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Research Article

Physico-chemical characterization, In-vitro Dissolution behavior of Simvastsatin poorly water soluble drugs

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Abstract. The objectives of this research were to prepare and characterize inclusion complexes of clonazepam with β-cyclodextrin and hydroxypropyl-β-cyclodextrin and to study the effect of complexation on the dissolution rate of clonazepam, a water-insoluble lipid-lowering drug. The phase-solubility profiles with both cyclodextrins were classified as A_P-type, indicating the formation of 2:1 stoichiometric inclusion complexes. Gibbs free energy $(\Delta G_{tr}{}^{o})$ values were all negative, indicating the spontaneous nature of clonazepam solubilization, and they decreased with increase in the cyclodextrins concentration, demonstrating that the reaction conditions became more favorable as the concentration of cyclodextrins increased. Complexes of clonazepam were prepared with cyclodextrins by various methods such as kneading, coevaporation, and physical mixing. The complexes were characterized by Fourier transform infrared spectroscopy and differential scanning calorimetry studies. These studies indicated that complex prepared kneading and coevaporation methods showed successful inclusion of the clonazepam molecule into the cyclodextrins cavity. The complexation resulted in a marked improvement in the solubility and wettability of clonazepam. Among all the samples, complex prepared with hydroxypropyl-β-cyclodextrin by kneading method showed highest improvement in *in vitro* dissolution rate of clonazepam. Mean dissolution time of clonazepam decreased significantly after preparation of complexes and physical mixture of clonazepam with cyclodextrins. Similarity factor indicated significant difference between the release profiles of clonazepam from complexes and physical mixture and from plain clonazepam. Tablets containing complexes prepared with cyclodextrins showed significant improvement in the release profile of clonazepam as compared to tablet containing clonazepam without cyclodextrins.

KEY WORDS: β-cyclodextrin; clonazepam; hydroxypropyl-β-cyclodextrin; inclusion complexation; *in vitro* dissolution studies; mean dissolution time.

INTRODUCTION

Clonazepam (CLZ) belongs to a class of anticonvulsants that enhances gamma-aminobutyric acid (GABA) receptor responses. Anticonvulsants used for several types of seizures, including myotonic or atonic seizures, photosensitive epilepsy, and absence seizures. CLZ exerts its action by binding to the benzodiazepine site of the GABA receptors, which causes an enhancement of the electric effect of GABA binding on neurons resulting in an increased influx of chloride ions into the neurons. This results in an inhibition of synaptic transmission across the central nervous system (1,2). CLZ is a light yellow crystalline powder which is practically odorless. It is freely very soluble in methanol, ethanol, and acetone, and practically insoluble in water (at 25°C<0.1 mg/ml). It is generally considered that compounds with very low aqueous solubility will show dissolution rate-limited absorption and, hence, poor absorption, distribution, and target organ delivery (3). Improvement of aqueous solubility in such a case is a valuable goal to improve therapeutic efficacy.

Cyclodextrins (CDs) form a group of structurally related oligosaccharides with cylinder-shaped cavities that have the capacity to form inclusion complexes with many drugs by taking a whole drug molecule, or a part of it, into the cavity (4,5). Because of the large number of hydroxyl groups on CDs, they are water-soluble. They are known for their ability to molecularly encapsulate a wide variety of drugs into their hydrophobic cavity without the formation of any covalent bonds. CDs have widespread pharmaceutical applications mainly because of their effect on enhancing the solubility and bioavailability of many drug formulations. Complexation with cyclodextrins has been reported to enhance the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs (6–9). CDs first came to the fore in marketed products as drug delivery technologies that enabled the development of various prostaglandins (10).

β-cyclodextrin (β-CD) has ideal dimensions to complex a range of commonly used drugs. Unfortunately, it has a limitation of high affinity for cholesterol, which may lead to crystallization of poorly water-soluble β-CD–cholesterol complex in the kidney, and thereby causing nephrotoxicity.

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