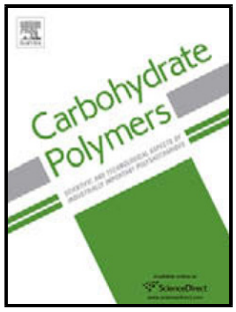

Title: Spray-dried voriconazole-cyclodextrin complexes: solubility, dissolution rate and chemical stability

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Spray-dried voriconazole-cyclodextrin complexes: solubility, dissolution rate and chemical stability

ABSTRACT

The present work investigates the effect of complexation with hydroxypropyl-beta-cyclodextrin (HPBCD) and 2-O-methyl-beta-cyclodextrin (2-O-MBCD), on voriconazole solubility, dissolution rate and chemical stability. Drug-cyclodextrin complexes were prepared as aqueous solutions, which were spray-dried, and their properties were compared to wet ground samples and physical mixtures. DSC analysis revealed absence of crystalline voriconazole from spray-dried complexes. FTIR spectroscopy indicated changes in the H-bonding network of the hydroxyl groups of cyclodextrin following drug inclusion. Dissolution rate of voriconazole was significantly higher from spray-dried complexes with either cyclodextrin in comparison with free drug, physical mixtures, or wet ground mixtures. However, two degradation impurities were found in aged samples, with slightly higher impurity level with HPBCD. Performed solubility studies suggested that 2-O-MBCD is more efficient solubilizer. Molecular docking simulations showed a difference in the 1:1 binding affinities and sites, with HPBCD surprisingly forming complexes of much lower energy, thus suggesting a multiple rather than a 1:1 complexation.

Keywords: voriconazole, cyclodextrins, solubility, dissolution, stability, molecular docking

1. Introduction

As the number of new poorly soluble drugs is increasing (Dubin, 2006), exploring ways of improving their solubility and bioavailability is becoming an essential part of formulation development. Complexation of the drugs with cyclodextrins is one of the possible strategies for enhancing the drug's solubility (Brewster & Loftsson, 2007). Some of the additional advantages of cyclodextrins application include the potential for improvement of the drug's stability, safety, organoleptic properties (Challa et al., 2005; Freitas et al., 2012; Hu et al., 2012). Among many factors that can influence the character of drug-cyclodextrin interaction, the most important is the nature of the cyclodextrin used (Redenti et al., 2000; Szejtli, 2004). Many chemically modified