## Accepted Manuscript

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

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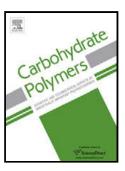
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## ACCEPTED MANUSCRIPT

1	Spray-dried voriconazole-cyclodextrin complexes: solubility, dissolution rate and chemical
2	stability
3	
4	ABSTRACT
5	
6	The present work investigates the effect of complexation with hydroxypropyl-beta-cyclodextrin
7	(HPBCD) and 2-O-methyl-beta-cyclodextrin (2-O-MBCD), on voriconazole solubility,
8	dissolution rate and chemical stability. Drug-cyclodextrin complexes were prepared as aqueous
9	solutions, which were spray-dried, and their properties were compared to wet ground samples
10	and physical mixtures. DSC analysis revealed absence of crystalline voriconazole from spray-
11	dried complexes. FTIR spectroscopy indicated changes in the H-bonding network of the
12	hydroxyl groups of cyclodextrin following drug inclusion. Dissolution rate of voriconazole was
13	significantly higher from spray-dried complexes with either cyclodextrin in comparison with free
14	drug, physical mixtures, or wet ground mixtures. However, two degradation impurities were
15	found in aged samples, with slightly higher impurity level with HPBCD. Performed solubility
16	studies suggested that 2-O-MBCD is more efficient solubilizer. Molecular docking simulations
17	showed a difference in the 1:1 binding affinities and sites, with HPBCD surprisingly forming
18	complexes of much lower energy, thus suggesting a multiple rather than a 1:1 complexation.
19	
20	Keywords: voriconazole, cyclodextrins, solubility, dissolution, stability, molecular docking
21	
22	1. Introduction
23	
24	As the number of new poorly soluble drugs is increasing (Dubin, 2006), exploring ways of
25	improving their solubility and bioavailability is becoming an essential part of formulation
26	development. Complexation of the drugs with cyclodextrins is one of the possible strategies for
27	enhancing the drug's solubility (Brewster & Loftsson, 2007). Some of the additional advantages
28	of cyclodextrins application include the potential for improvement of the drug's stability, safety,
29	organoleptic properties (Challa et al., 2005; Freitas et al., 2012; Hu et al., 2012). Among many
30	factors that can influence the character of drug-cyclodextrin interaction, the most important is the
31	nature of the cyclodextrin used (Redenti et al., 2000; Szejtli, 2004). Many chemically modified

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