importance of β-cyclodextrin substitution level and type for solubilization and stabilization of poorly soluble APIs in parenteral dosage forms

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Introduction:

Parenteral formulations often contain higher concentrations of excipients than active ingredients. These excipients enhance safety, provide solubility, better stability, increase bioavailability, improve patient compliance, or generally improve drug performance[1,2]. Each year an increasing number of novel APIs demonstrate poor aqueous solubility, in certain therapeutic areas 90% of new drugs are poorly water soluble[3]. As therapies shift toward more challenging molecules, more sophisticated methods of solubilizing and stabilizing than can be afforded by traditional excipients must be explored in the formulation and processing[4]. Cyclodextrins such as Cavitron™ hydroxypropyl β cyclodextrin (HP-β-CD) are cyclic oligosaccharides of varying ring diameter capable of solubilizing pharmaceutical actives while having a favorable toxicological profile. Cyclodextrins aid in solubilization via complexation of the active molecule within the hydrophobic cavity formed between the ring of glucose units, the size of the cavity helps guide the interaction between the host and guest molecule[5]. The work detailed here explores the complexation efficiency of hydroxypropyl substituted β cyclodextrins (HP- β CD's) of varying substitution levels and sulfobutyl ether substituted β cyclodextrin with both large and small molecules (table 1).

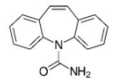
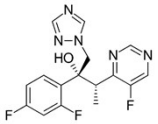
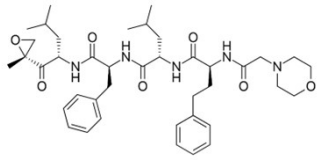
Carbamazepine marketed by Baxter as Carnexiv™	**Voriconazole** marketed by Pfizer as VFEND®	**Carfilzomib** marketed by Amgen as Kyprolis®
		
MW: 238.1 pKa = 15.96	MW: 349.3 pKa = 2.01	MW: 719.91 pKa = 3.5

Table 1: API Characteristics and Structures

Methods:

A rational step-by-step formulation aproach was used to determine the solubility isotherms for, 2 small molecule API's (carbamazepine, voriconazole) and one large molecule API (carfilzomib) respectively. Each isotherm was determined in water at relevant pHs using both Cavitron™ W7 HP5 (HP-β-CD HP5) and W7 HP7 Pharma (HP-β-CD HP7) as marketed by Ashland Inc. with hydroxypropyl groups replacing the hydroxyl groups on 5 and 7 of the glucose units respectively, as well as sulfobutylether β-cyclodextrin (SBE-β-CD) to test the impact of degree of substitution and substituent type on complexation efficiency. Assay was analyzed via HPLC. Voriconazole and carfilzomib samples were lyophilized via a standard.

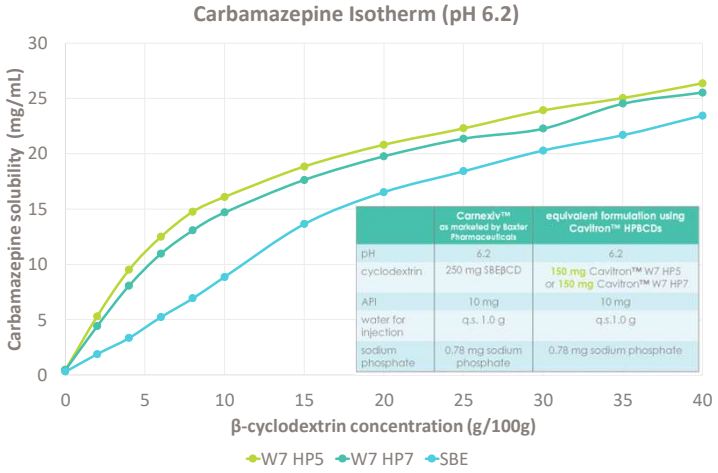


Figure 1: Carbamazepine Isotherm

Results:

Small Molecules: For carbamazepine both Cavitron™ W7 HP5 and Cavitron™ W7 HP7 significantly increase solubility. The degree of HP-β-CD substitution did not impact complexation and Cavitron™ W7 HP5 and Cavitron™ W7 HP7 demonstrated better solubility (26 mg/ mL and 25 mg/ mL respectively) than SBE-β-CD (23 mg/ mL) and the mechanism of complexation seems to be the same for both Cavitron™ W7 HP5 and HP7. Other excipients such as PEG400, propylene glycol and citric acid had little impact on the solubility. Formulating a generic version of Carnexiv™ (10 mg / mL carbamazepine with 250 mg/ml SBEβCD) with Cavitron™ W7 HP5 or Cavitron™ W7 HP7 reduced the required cyclodextrin by 100 mg/ml which amounts to a 2 g reduction of cyclodextrin per dose.

Solubility of voriconazole was significantly increased with both Cavitron™ W7 and Cavitron™ W7 HP7. Changing the degree of substitution of HPβCD and substituent type had only a modest effect, with the lower degree of substitution Cavitron™ W7 HP5 (41 mg/mL) performing much better and the higher degree of substitution Cavitron™ W7 HP7 (35 mg/mL) performing slightly better than SBEβCD (33 mg/mL) in 40 w/w % solutions of solubilizer. Cavitron™ W7 HP5 could be considered an alternative solubilzer to SBEβCD for formulating voriconazole solutions thus requiring less cyclodextrin for obtaining a clear solution, which can be lyophilized and easily reconstituted.

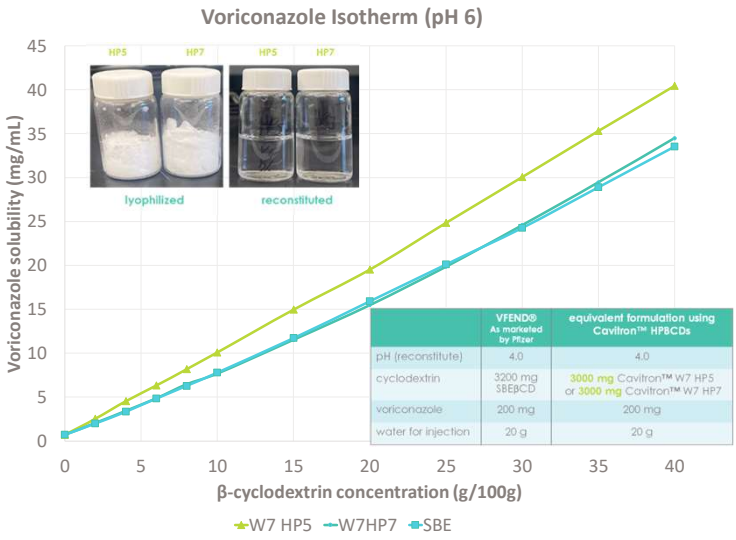


Figure 2: Voriconazole Isotherm

Results:

Large molecules: Cavitron™ W7 HP5 and Cavitron™ W7 HP7 significantly increase solubility of carfilzomib especially at higher concentrations, lower concentrations of SBEβCD showed higher solubility of carfilzomib then tapered off. Degree of substitution of HPβCD plays a role in solubilizing carfilzomib, the lower degree of substitution performing better. Cavitron™ W7 HP5 demonstrated better solubilization than SBEβCD, while Cavitron™ W7 HP7 demonstrated similar solubility compared to SBEβCD. Cavitron™ W7 HP5 could be considered an alternative solubilizer for carfilzomib formulations. Requiring less cyclodextrin for obtaining a clear solution, which can be lyophilized and easily reconstituted at a higher concentration that is currently formulated, allowing for lower volume injections.

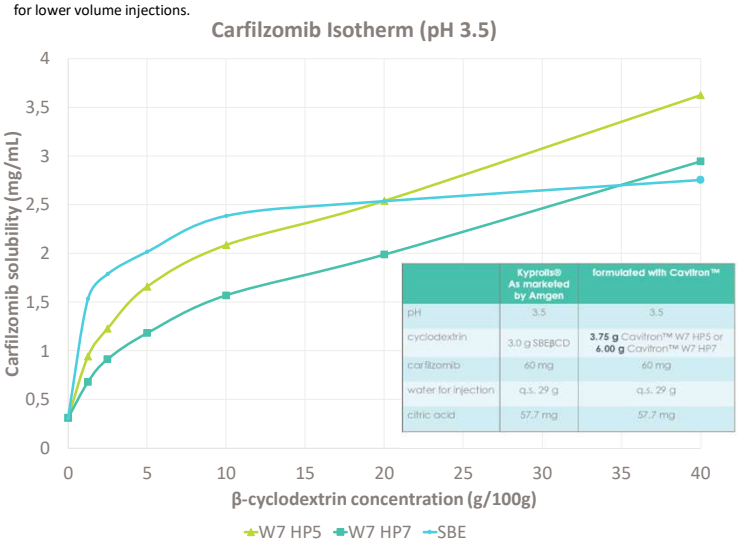


Figure 3: Carfilzomib Isotherm

Conclusion:

Cavitron™ hydroxypropyl b cyclodextrins are valuable ingredients for pharmaceutical formulations of otherwise insoluble API's by providing a wide range of benefits including improved solubilization and stabilization of both small and large molecules. Cyclodextrins can provide solutions to formulating insoluble drug products containing active ingredients with very low solubility, opening the door to otherwise inaccessible treatments.

References:

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