Cyclodextrins for parenteral use

A comparison of Hydroxypropyl and Sulfobutyl Betadex

As a result of thorough development work, CycloLab Ltd (Budapest, Hungary) has established and validated the production of USP-complying Betadex Sulfobutyl Ether Sodium formulation excipient (SBECD, Dexolve^{TM}) in 2008. This cyclodextrin (CD) derivative is the main component of several commercial drug formulations worldwide acting as a solubility and stability enhancer. SBECD is one of the two parenterally applicable cyclodextrin derivatives besides Hydroxypropyl Betadex (HPBCD), nevertheless both of these substances are just as suitable in drug products of various administration routes.

In order to highlight the special properties of SBECD it is worth comparing these two injectable composite substances.

Both CD derivatives are resultant of substituting neat beta-cyclodextrin at maximum 21 possible hydroxyl moieties in a random manner, i.e. both end products are complicated mixtures of modified CD species of different average degree of substitution (DS) as well as vast number of regioisomers. However, it is possible to characterize the distribution of such species which is an important quality parameter of both composites. Thorough toxicological safety studies were performed for both HPBCD and SBECD meeting specific compositional profiles, which are by now standardized regulatory wise to overcome the said variability. HPBCD has a monograph in both United States Pharmacopoeia (USP) and European Pharmacopoeia (EP), while SBECD is listed only in USP. It is noteworthy that while the pharmacopoeial specification for average DS permits the wide range of 2.8-10.5 in the case of HPBCD, SBECD must meet the strict requirement of 6.2-6.9. Unlike HPBCD, SBECD is not only a solubilizing but a definitive osmotic agent, too. Their pharmaceutically and physico-chemically relevant properties are shown below:

Comparison of relevant physico-chemical properties of HPBCD and SBECD

	HPBCD	SBEBCD
Crystallinity /amorphousness	Amorphous	Amorphous
Color	white	white
Solubility in water	> 1200 mg/ml	> 1200 mg/ml
Administration route (typical examples)	Oral, intravenous, intramuscular, ophthalmic, nasal and suppository	Oral, intravenous, intramuscular, subcutaneous, ophthalmic, nasal and inhalation
Acceptable DS according to pharmacopoeias	2.8-10.5	6.2-6.9
Charge	Neutral	Polyanionic (Na^+ salt)
Suitability for taste masking	Suitable	Not suitable due to salty taste

Thresholds above which adverse effects may occur (based on suggestion by EMA document EMA/CHMP/333892/2013)	300 mg/kg/day	300 mg/kg/day

Both HPBCD and SBECD may interact with neutral drugs to improve solubility and chemical stability, but SBECD owing to its polyanionic nature binds especially well to cationic, nitrogen containing compounds.

Osmolality of aqueous HPBCD and SBECD solutions

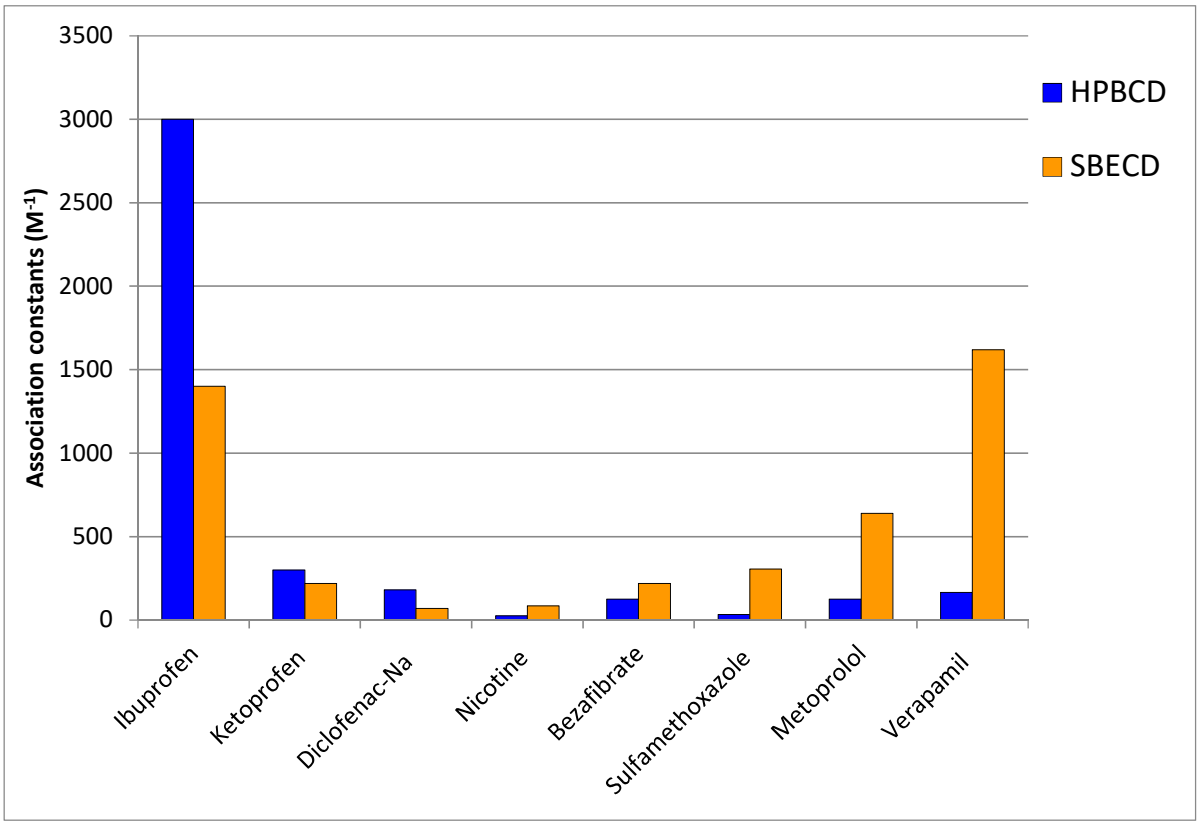
Concentration (w/w%)	Osmolality (mOsm/kg)	
	HPBCD (average DS=4.6)	SBECD (average DS=6.5)
5	37	135
10	81	286
15	129	501
20	196	785

Viscosity of aqueous HPBCD and SBECD solutions at 25°C

Concentration (w/w%)	Viscosity (cP)	
	HPBCD (average DS=4.6)	SBECD (average DS=6.5)
5	1.16	1.17
10	1.34	1.37
15	1.60	1.68
20	2.00	2.10
25	2.60	2.85
30	3.38	4.09

In conclusion as the above tables show, the strength of HPBCD in comparison with SBECD lies mainly in its taste and low osmolality. Otherwise – strictly from physico-chemical point of view- the two cyclodextrins are theoretically interchangeable. There is no significant difference between the applicable routes, toxicological profile and the viscosities of their aqueous solutions up to 25 w/w%. Consequently, the choice still must be made based on experimental assessment of otherwise rather unpredictable molecular interaction strength between a drug (or drug candidate) and HPBCD or

SBECD. The following chart illustrates how the interaction strength (quantified by complex association constant) of HPBCD and SBECD between drugs of various character might differ.



These results show that the application of SBECD might be suggested to solubilize (typically nitrogen-containing) basic drugs, whereas HPBCD performs the best when acidic or neutral substances are to be dissolved.