Therapeutic Cyclodextrin Nanocavities:
Novel Uses of Empty Cyclodextrins

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Cyclodextrins have long been known and used as solubilizing and stabilizing excipients in different pharmaceutical dosage forms. (1) These enzyme-modified starch derivatives with less than 1 nm size central cavities are made up from D-glucopyranose units.

The last 35 years in cyclodextrin technology has witnessed the successful uses of these nanocavities for molecular encapsulation of poorly soluble APIs to increase their solubility, bioavailability, stability or to reduce their side effects.

Recently, more and more emphasis is put to the therapeutic application of "empty" non-occupied cyclodextrin nano cavities. The first such application was published 1983 where parenterally administered empty methyl-β-cyclodextrin cavities were used to selectively bind and remove toxic retionoids from the systemic circulation after A vitamin intoxication. Based on this recognition, huma clinical trials proved the clinical usefulness of cyclodextrin-assisted detoxication concept. Years later, Organon Biosciences started a program aiming at the selective removal of neuromuscular blocking agent from anesthetized patients via selective cyclodextrin complexation. These efforts have resulted in the approval and marketing of a tailored γ-cyclodextrin derivative (called ***Sugammadex***®) for binding and remove rocuronium, the neuromuscular blocking API by complex formation. The empty γ-cyclodextrin derivative with 0.9 nm size cavity diameter has alredy been marketed as a drug active in the USA, EU and Japan under the tradename ***Bridion***^{TM} by Schering Plough.

The chemically modified hydroxypropyl-β-cyclodextrin (HPBCD) as solubilising excipient is listed in both the US and European Pharmacopoeias, as a parenterally safe additive for injectable products. This compound has also been reputed to have certain affinity to cholesterol forming a non-covalent inclusion complex with the lipid.This interaction is manifested in the solubilisation of cholesterol in water. It has recently been found that this HPBCD applied intravenously will improve the clinical status of a lethal genetic disorder called Nieman Pick Type C (NPC) disease. In April 2009, HPBCD was approved under by the US FDA to treat NPC. This is the second time in the United States that cyclodextrin by itself has been administered in an attempt treat a fatal disease. Over 20 years ago, cyclodextrin was used in a medical case involving a boy suffering from severe hypervitaminosis A. On May 17, 2010, the FDA granted HPBCD orphan drug status and designated HPBCD as a treatment for NPC disease.