Feature Article

Cyclodextrin-based macromolecular systems as cholesterol-mopping therapeutic agents in Niemann-Pick Disease Type C

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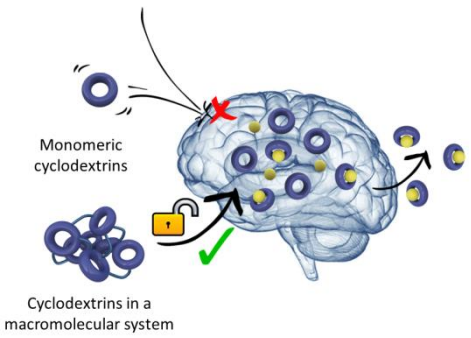
Over the last decade cyclodextrins (CDs) have gained considerable attention as a potential therapeutic intervention in the treatment of the rare genetic condition Niemann-Pick type C disease (NPC). However, the oligosaccharide in its monomeric form suffers from serious side effects especially from a pharmacokinetic and biodistribution standpoint. CD-based macromolecular systems hold great promises to overcome such limitations and might provide an improved therapeutic approach in reducing cholesterol accumulation in NPC. In the present article, we summarize the latest developments and synthetic strategies in the preparation of CD-containing polymers as cholesterol-mopping therapeutic agents in NPC.



1. Introduction

Cyclodextrins (CDs)[1, 2] are a family of naturally occurring, cyclic oligosaccharides consisting of D-glucose units joined together through α(1→4) linkages taking the characteristic tri-dimensional shape of a truncated cone. The best-characterised CDs are made up of 6, 7 and 8 glucopyranosidic units for α-, β- and γ-CD, respectively. A key feature of CDs is their water solubility due to the hydrophilic exterior surface and the presence, at the same time, of an internal hydrophobic cavity capable of hosting guest molecules.[3-5] CDs are highly biocompatible molecules and in their native forms are generally regarded as safe (GRAS) by US FDA.[6] Because of the ability to form inclusion complexes, they have become particularly attractive in pharmaceutical industry by enhancing water solubility and bioavailability of drugs.[2, 7-20] Native CDs can be chemically modified and its derivatives have found a range of remarkable biomedical applications. Sugammadex (tradename Bridion) for instance is a γ-CD derivative which irreversibly traps the steroid rocuronium, the most widely used neuromuscular blocking agent in general anaesthesia.[21] In Sugammadex the primary hydroxyl-groups of the upper rim are replaced with carboxyl thioether groups acting as negatively charged "fingers" providing at the same time an extended depth of the CD cavity and an electrostatic interaction to the positively charged ammonium group of rocuronium. More recently, CDs have shown therapeutic effect in a range of diseases with high social impact, such as Alzheimer's,[22] age-related macular degeneration[23] and atherosclerosis.[24] Over the last decade, CDs have gained considerable attention also as a potential therapeutic intervention in the treatment of the rare genetic condition Niemann-Pick type C disease (NPC).

NPC[25], also known as "childhood Alzheimer's", is a recessive, autosomal, and fatal metabolic genetic disorder caused by the accumulation of unesterified cholesterol in the brain, liver and spleen. Most cases are detected during childhood and progress to cause life-threatening complications by the second or third decade of life. In NPC the functional role of the protein

regulating cholesterol trafficking in the cell is compromised, and an excessive amount of unesterified cholesterol accumulates in endolysosomes.[26] The build-up of cholesterol causes brain damage, subsequent cognitive and mobility decline. Currently, there is no effective treatment for NPC, although potential therapies have shown some reduction of lipid storage in endolysosomes including Miglustat,[27] thiadiazole carbamates[28] and various histone deacetylase inhibitors (HDACi).[29, 30] A particular chemical modification of βCD, the 2-hydroxypropyl-β-cyclodextrin (HPβCD), has proved promising in the treatment of the condition HPβCD and has now entered NIH Phase 2b/3 clinical trial, and the FDA has granted orphan drug status for this CD derivative in NPC.[25, 31-33] However, the current use of HPβCD has significant shortcomings mainly due to its poor pharmacokinetics and bioavailability, particularly in the brain. Due its physicochemical properties, HPβCD does not passively cross the Blood-Brain Barrier (BBB) in substantial amounts.[34] Moreover, when systemically administered, high doses of HPβCD are typically required (2,000-4,000 mg/kg in mice)[32] in order to obtain a sufficient therapeutic effect because of short half-life in the bloodstream owing to rapid renal clearance.[35] However, when the concentration of HPβCD is high there are toxicity concerns due to haemolysis, cytotoxicity, ototoxicity, apoptosis induction, and tissue injury.[36-38] To obviate these limitations a number of different approaches have been suggested. For instance, active intracellular delivery to NPC cells via octa-arginine-appended βCD has shown to reduce intracellular cholesterol while significantly decrease the systemically administrated required dose compared with HPβCD.[39] PEG-lipid nanocarriers packaged with HPβCD have also been proposed showing cholesterol clearance from the lysosome in NPC cells.[40] Currently, in order to overcome the challenges associated to its systemic administration HPβCD therapy for treatment of brain in NPC patients is underway via intrathecal administration.[41]

While treatment with monomeric HPβCD remains a promising therapeutic approach in NPC, there is a growing interest in finding alternative way for treating the condition with an improved pharmacokinetic and biodistribution profile. CD-based macromolecular systems hold great promises to overcome some of the limitations outlined. This Feature Article will focus on the latest developments in CD-based macromolecular systems for the treatment of NPC with a particular attention to the synthetic strategies and methodologies for preparing such systems, while we remand to more comprehensive reviews on CD-containing polymers with pharmaceutical applications.[42-44]

2. CDs embedded into polymeric structure

Since the 1980s CDs have been incorporated into macromolecular architectures in order to enhance pharmaceutical and biomedical properties of polymers.[45-49] CD-Containing Polymers (CCPs) exhibit unique mechanical properties, stimuli-responsiveness and drug release characteristics that are extremely appealing in bioscience. CCP have been employed in designing assemblies (hydrogels, micelles and nanoparticles) with a range of bio-applications, from complexing disinfecting drugs for control release in wound and burn treatments[47] to delivery vehicles for nucleic acids,[50] from the construction of biosensors for cocaine[51-53] to sophisticated host-guest assemblies for regenerative medicine.[54] In general, CCPs offer several advantages over the simple monomeric CDs, such as: i) improved water solubility for the presence of several CD units[55], ii) higher catalytic effect [56-60] and iii) greater drug-loading capacity.[61-63] The improved binding abilities are essentially due to the cooperation of several adjacent CD moieties to bind guest molecules that are too large to be accommodated in a single CD cavity.[58, 64, 65] An important example of CCP with important medical applications is the anticancer system CRLX101. CRLX101 is a novel nanoparticle-drug conjugate based on a linear CD-containing polymer bearing camptothecin (CPT), a potent inhibitor of topoisomerase I which is currently in Phase 1/2a clinical trial.[66] Through CRLX101 the payload is released

inside cancer cells augmenting antitumor activity while reducing toxicity. CPT is linked covalently through a glycine link to the linear copolymer which in turn consists of alternating subunits of βCD and poly(ethylene glycol) (PEG) (Figure 1).

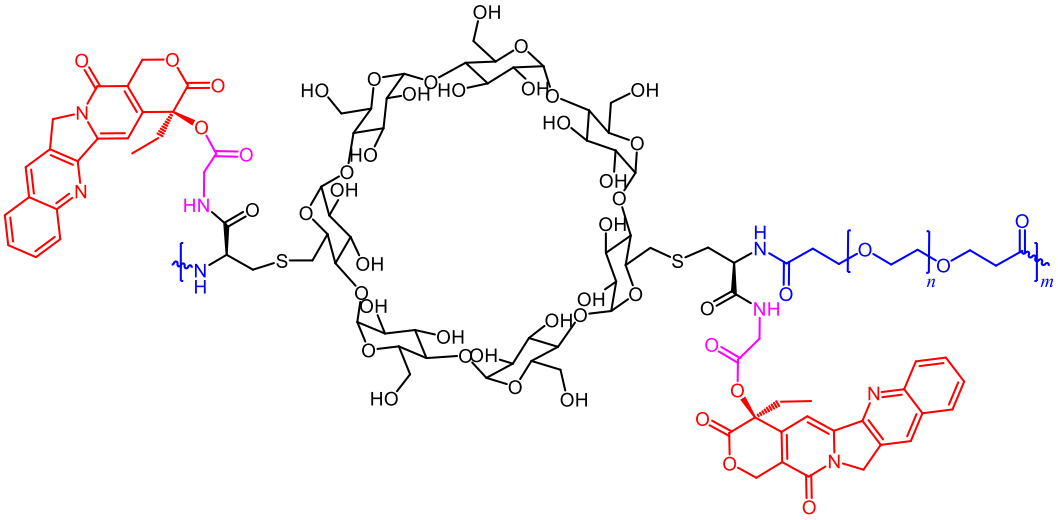


Figure 1 – Schematic representation of CRLX101

From a pharmacokinetic standpoint, CCPs present at least three highly desirable characteristics in NPC treatment: 1) the higher molecular weight of the polymer potentially translates into retardation of renal clearance, thus prolonging blood half-life of the system,[67-72] 2) oligomers of CDs are more easily excreted through the renal tubules without degradation[73] and 3) when assembled into nanoparticles, they have shown to exploit carrier-mediated transcytosis pathway found in the BBB for brain drug delivery via systemic administration.[74] CD-containing macromolecular architectures which have been proposed in treating NPC are essentially of two types (Figure 2): a) with CDs either covalently linked or b) physically assembled through threading onto polyrotaxanes.

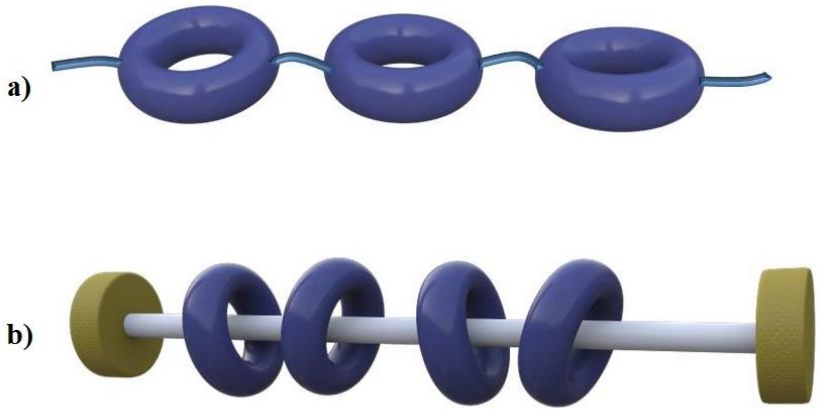


Figure 2 - Schematic representation of the different types of CD-containing macromolecular systems which have been proposed so far in NPC

Kulkarni et *al.*[75] first reported a linear polymer prodrug (ORX-301) based on βCD monomer units linked together by a short pH-degradable ketal linkage. The synthesis of ORX-301 was achieved through 1,3 dipolar click reactions between A-D diazide βCD-monomer and difunctionalised ketal linker. Subcutaneous injections of ORX-301 demonstrated extension of the mean lifespan of NPC mice at a dosage 5-fold lower (800 mg/kg, body weight) the HPβCD dose proven efficacious (4000 mg/kg[32]). Moreover, ORX-301 showed to penetrate the BBB and counteracts neurological impairment.

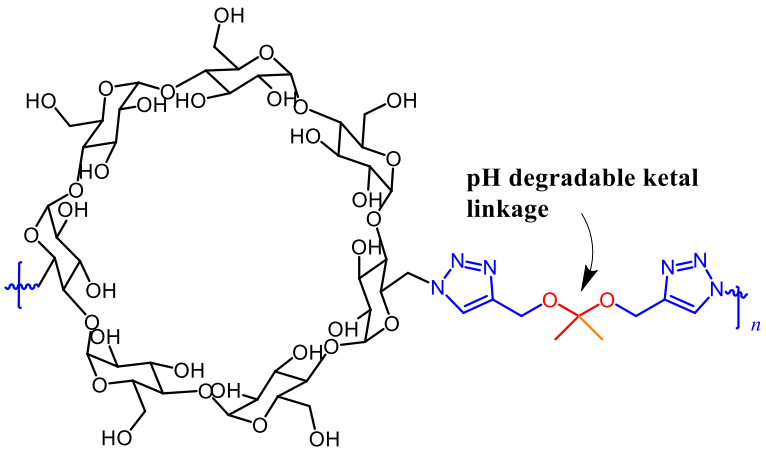


Figure 2 Schematic representation of ORX-301

Polyrotaxane (PRXs) have been vastly investigated as CD-containing macromolecular systems in NPC. PRXs are physically assembled polymeric systems whose formation is driven by the inclusion of guest macrocycles onto a polymer chain.[76-79] PRXs are endowed with unique architectures and highly desirable properties such as water-solubility and functionality while characterised at the same time by low cytotoxicity (masking the effect of CDs in the PRX) and controllable size. For this reasons PRXs, are being particularly successful in the realm of bioscience with applications ranging from drug to gene delivery, from tissue engineering to biosensor applications.[80-83] CDs rings have been tethered onto linear polymeric chains capped with bulky end-groups (*stoppers*) giving rise to CD-based PRXs (CD-PRXs). CD-PRXs have been suggested as excellent candidates for sophisticated drug delivery systems.[84, 85] The mobility with which threaded rings can rotate and slide along the axe in fact represents a key feature for potentially enhancing multivalent interactions with biological receptors with modified CDs or for improving endocytosis in drug delivery (Figure 3).[86] Besides the multivalent ligand-receptor interaction translates into very strong and selective binding.[87]

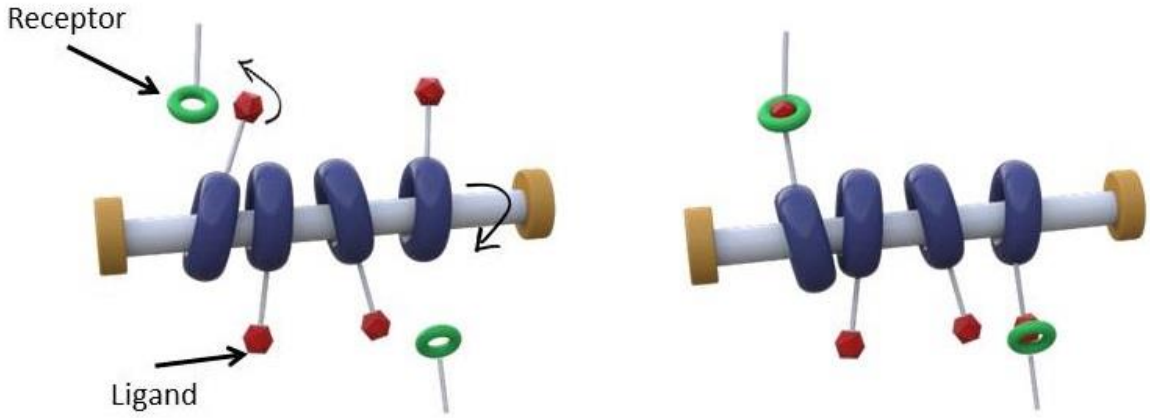


Figure 3 - schematic representation of a CD-PRX and its potential multivalent interactions

As highly polyfunctional systems CD-PRXs are particularly suited for drug delivery with the unique characteristic that the drug loaded to a PRX can be released all at once as soon as the

stoppers have been cut off at the desired destination. The loading of several CDs threaded into a PRX has also been suggested as a way to deliver multiple CD macrocycles with their cholesterol activity in the treatment of NPC. Tamura et *al*. developed a CD-PRX with acid cleavable stoppers to allow dissociation at lysosomal pH and release the loaded βCDs (Figure 4). The system prolonged the life span and suppressed neurodegeneration in mice model of NPC disease even at 500 mg/kg dose, significantly lower dose compared to HPβCD.[88, 89]

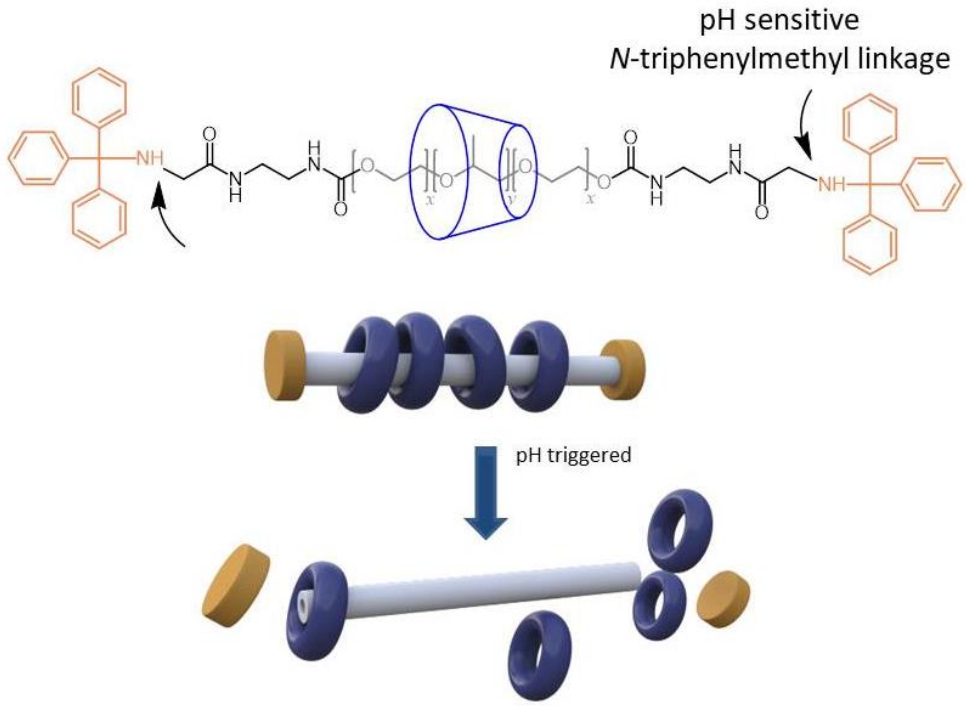


Figure 4 - Disassembling of a CD-PRX triggered by the cleavage of the stoppers

Such CD-PRX was synthesised from pluronic P123 (PEG-b-PPG-b-PEG triblock copolymer) as the axle polymer, the threaded βCDs were modified with 2-(2-hydroxyethoxy)ethyl carbamate (HEE) to improve water-solubility and *N*-triphenylmethyl (N-Trt) selected as acid-cleavable bulky stoppers.[90] The high molecular weight of CD-PRX translates into prolonged blood half-life and therefore a higher accumulation of CDs in tissues and more effective cholesterol lowering activity in comparison to CD derivatives.[91] A similar approach has been proposed to prepare nonviral gene carrier systems based on CD-PRXs with cytocleavable

disulfide-terminal groups consisting of PEG chain and cationic α-CDs forming stable DNA polyplexes.[92, 93] Mondjinou *et al*[94] also reported pluronic-based CD-PRX containing HPβCD as potential NPC therapeutics. The polyrotaxanes were synthesized under heterogeneous conditions with triblock polymers of various composition by threading HPβCDs onto ditriethylenediamino-terminated pluronics and finally end-capped with 2,4,6-trinitrobenzene groups. Treatment of NPC type 2-deficient fibroblasts with such CD-PRXs showed substantial reductions in cholesterol accumulation in the cells. Collins *et al*. showed the first use of pluronic-based CD-PRX[95, 96] *in vivo* for treatment of NPC using LC/MS/MS.[97]

3. Conclusions

CD-based macromolecular systems are gaining considerable interest as an improved therapeutic approach over the use of monomeric CDs in NPC. The embedding of the CD macrocycle into a larger macromolecular architecture shows therapeutic activity while providing several advantages over the current administration of HPβCD especially under the pharmacokinetic and the biodistribution profile. We anticipate that CD-based macromolecular systems represent an emerging tool in the treatment of the neglected disease by providing a better and more effective therapy for NPC. Moreover, such approach may also contribute towards the treatment of other neurodegenerative disorders exhibiting impaired cholesterol metabolism such as Alzheimer's, Parkinson's and Huntington's diseases.[98]

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Conflict of Interest

The authors declare no conflict of interest

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TOC

Cyclodextrins (CDs) have proved promising in the treatment of the rare genetic condition Niemann-Pick type C disease (NPC). In order to improve its pharmacokinetic and biodistribution profile CD-based macromolecular systems are being investigated to improve its therapeutic approach in reducing cholesterol accumulation in NPC.

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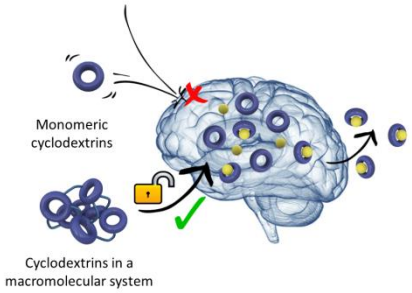
Cyclodextrin-based macromolecular systems as cholesterol-mopping therapeutic agents in Niemann-Pick Disease Type C



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