

Cyclodextrin-based Combinatorial Polymers: Efficient Binders of Pharmaceuticals in Water

Patrick Shahgaldian* and Philippe F.-X. Corvini

*Correspondence: Prof. Dr. P. Shahgaldian, University of Applied Sciences and Arts Northwestern Switzerland, School of Life Sciences, Gründenstrasse 40, CH-4132 Muttenz, Tel.: +41 61 467 43 46, E-mail: patrick.shahgaldian@fnw.ch

Abstract: Cyclodextrins are cyclic oligomers of glucose; they are widely used in a large range of industrial applications because of their molecular inclusion properties. We used cyclodextrins to prepare different libraries of polymers and tested their ability to selectively recognize pharmaceuticals in water. It was demonstrated that the chemical composition of the polymer strongly influences its binding properties. The developed strategy can be used to produce selective sorbent nanomaterials of pharmaceuticals.

Keywords: Combinatorial library · Cyclodextrin · Nanoparticle · Pharmaceutical · Polymer

Cyclodextrins (CDs) are cyclic oligomers of glucose; they are composed of 6, 7 or 8 D-glucopyranosidic units, for α , β and γ cyclodextrins, respectively.^[1] They are bound *via* an α -(1,4) glucosidic linkage and are produced by the enzymatic degradation of starch by cyclodextrin glycosyltransferase (CGTase, EC 2.4.1.19); which is an α -amylase found in several micro-organisms (*e.g.* *Bacillus circulans*, *Bacillus macerans*, *Bacillus stearothermophilus*).^[2] Because of their use in a wide number of industrial applications, their production has been largely improved and optimized and the commercial price of one kilogram of β -cyclodextrin nowadays is approximately \$5 US. Indeed, cyclodextrins find applications in various fields such as separation materials (*e.g.* HPLC columns), cosmetics, agro-food, sensing and pharmaceutical formulations.^[3]

The main advantage that the cyclodextrin macrocyclic structure provides lies in the capacity of this water-soluble cyclic oligomer to form inclusion compounds with hydrophobic molecules, and yield water-soluble complexes. In addition, this complex can help to improve the chemical stability of the trapped molecule or limit its volatility (*e.g.* stabilization of fragrances, flavors). In the specific case of pharmaceuticals, CDs are widely used to solubilize poorly water-soluble drugs and thus improve their bioavailability. In our laboratories, we are interested in developing molecular recognition nanomaterials able to trap selectively target molecules, ranging from pharmaceuticals^[4] to viruses,^[5] in order to develop analytical tools to assess easily and rapidly the presence of those targets in waters. Because of the known capability of CDs to include pharmaceuticals, our choice went naturally in favor of using this macrocycle as a recognition element. Nevertheless, the large range of targets that are known to form inclusion complexes with CDs represented a weakness for this approach, as a good level of selectivity is needed. To overcome this, we decided to produce the materials combining the binding properties of CDs with additional recognition units through a combinatorial approach; it was expected to reach a

higher level of selectivity depending of the formulation used. A number of examples of cyclodextrin-based polymers (CDPs) have been previously published; it was then decided to produce cyclodextrins in a mixture with addition functional monomers.

In a preliminary work, we produced CD-based polyurethanes using α , β and γ -CD and toluene-2,4-diisocyanate as di-functional cross-linker.^[4a] The resulting nanoparticulate polymers exhibited a preferential affinity for aspirin compared to acetaminophen and levofloxacin (Fig. 1). We further demonstrated that the use of additional monomers and cross-linkers allowed tuning the recognition properties of the polymers for pharmaceuticals.^[4b]

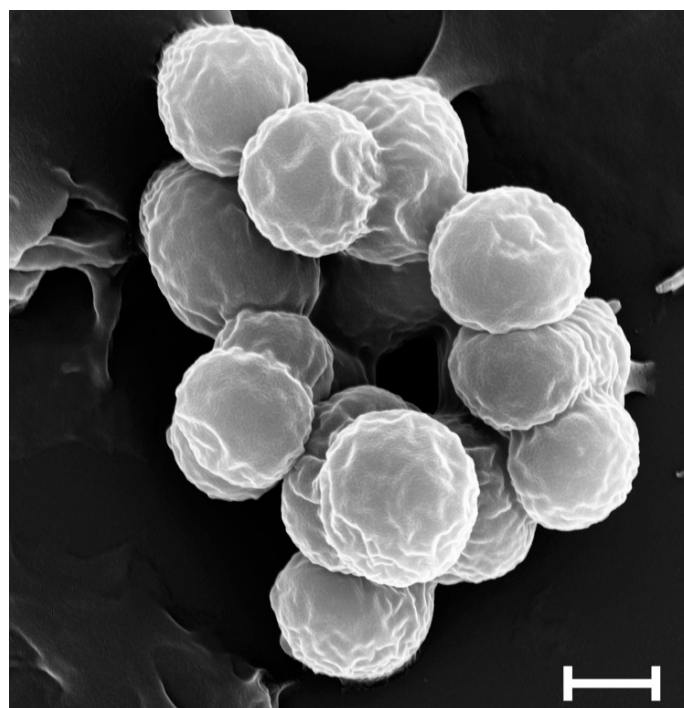
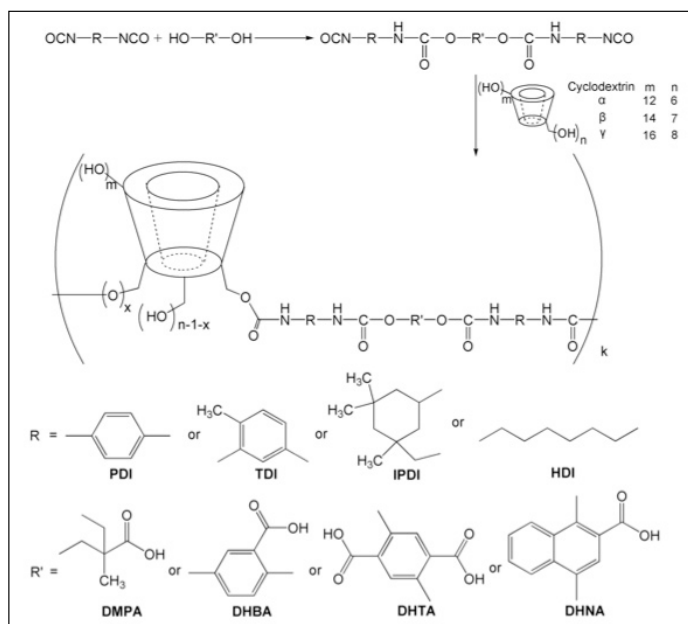


Fig. 1. Scanning electron micrograph of a cyclodextrin-based polymer [scale bar: 1 μ m].

These initial promising results prompted us to produce a library of CDPs increasing the number of monomers and cross linkers.^[4c] This approach allowed the production, in less than 24h, of a series of 51 different CDP polyurethanes that were further tested for their molecular recognition properties; the synthesis was carried out in a well plate format (Scheme 1).

To study the molecular recognition properties of the produced CDPs, they were first incubated in an aqueous mixture of nine pharmaceuticals of interest, namely acetaminophen, atenolol, ofloxacin, ciprofloxacin, tetracycline, sulfamethoxazole, chloramphenicol, propranolol and diclofenac. After an incubation of 120 min, the polymers were spun down and the supernatants were analyzed using an automated high-performance liquid chromatography system. The results demonstrated that the composition of the polymer has a strong influence on its recognition properties. For instance, one polymer prepared with β -CD, hexamethylene diisocyanate and 2,5-dihydroxyterephthalic acid



Scheme 1. Synthetic route to CD-based polyurethanes.

was shown to have a relevant specificity for diclofenac. The next step consisted in showing that the polymers that were produced in the library format, with quantities not exceeding few milligrams, could be produced in a larger scale without affecting their binding selectivity. This was done for two selected polymers that were further investigated for their ability of molecular recognition. The results confirmed that these polymers produced at the gram scale retained the selectivity observed for the library polymers.

In parallel we developed another approach to produce CDP using photopolymerization.^[4d] In order to use β-CD as

monomer, the native macrocycle was chemically modified in order to introduce in the structure acryloyl functions that can be further polymerized. Eight different additional co-monomers and three cross-linkers were used. As for polyurethanes, the photopolymers were produced in a high-throughput fashion that allowed producing 46 different polymers in less than 24 h. The assessment of the binding properties of those CDPs revealed a formulation-dependent behavior. Here again, the synthesis at the gram scale did not show any relevant differences with the polymers produced at the milligram scale.

The work is underway to use the produced polymers for two different types of applications, first as recognition elements in an environmental diagnostic kit and also as removal/recovery material for biotechnological and environmental applications.

Acknowledgements

Financial supports from the Swiss Commission for Technology and Innovation (CTI/KTI; grant PharmaInAqua II) and the FHNW research fund are gratefully acknowledged.

Received: April 30, 2013

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