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Sculpturing the future of water-soluble cyclodextrin branched polymers in pharmaceutical applications

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Water-soluble polymers of cyclodextrins (CyD) can be easily obtained in alkaline media following polycondensation of the naturally occurring monomers in the presence of a crosslinking agent. They can be further modified to customize specifically functionalized architectures. Compared to other macromolecules natural and not, the CyD polymers are endowed with a unique feature, the cone-shaped cavities where they can host guests of various nature. This element has solicited interest in this class of molecules for a wide range of applications including the biomedical field, in particular drug delivery. The CyD polymers display excellent behavior in terms of water solubility and solubilizing power towards drugs and therapeutic agents that are incompatible with biological fluids. Moreover, they can load more than one type of therapeutic agent in a single system thus allowing to implement combination therapy. In spite of some very promising results as delivery systems their potentialities remain limited by some intrinsic hurdles. Herein, we comment on their limits mainly related to the production process and the possible solutions to overcome them, giving an outlook on their assets for innovation in disease treatment.

Introduction

Cyclodextrins (CyDs) are natural products enzymatically derived from starch using CyD glycosyltransferases. They are water soluble, macrocyclic oligosaccharides, made of α -D-glucopyranose units joined by $\alpha(1-4)$ linkages (Figure 1A).^[1] The most common α , β and γ CyDs present 6, 7 or 8 glucopyranose units, respectively. CyDs have the shape of a truncated cone with the height of a glucose molecule, whereas the number of glucopyranoses determines the size of the cavity.^[2] This cavity has slightly hydrophobic character, while the external faces are more hydrophilic.^[3] This feature allows CyDs to host hydrophobic molecules within their cavity upon formation of supramolecular complexes, enabling solubilization and stabilization in aqueous media of otherwise insoluble substances. Technologies based on this principle have been exploited in the formulation of pharmaceutical active substances, in analytical separations, in food and cosmetic products, in agricultural treatments, in textile and environmental technologies, in wastewater treatments, etc.^[1, 4] CyD derivatives can be tailored exploiting the different reactivity of the hydroxyl groups in positions 2, 3 and 6 of the glucopyranose units affording hydrophilic, hydrophobic and ionizable CyDs. They can be selectively, randomly or fully substituted with one or more functional groups, resulting in very versatile substrates.^[5]

Thanks to their exceptional tunability, the interest has grown well beyond monomeric CyD derivatives and scientists have

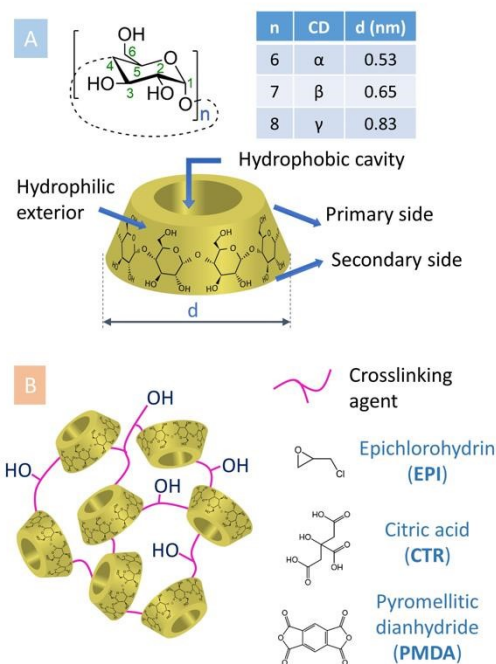


Figure 1: A) General and structural details regarding CyDs. B) Schematic representation of CyD-polymers obtained using different crosslinking agents.

moved towards systems incorporating various CyDs as one of the building blocks and in literature many reviews are available.^[6] Among them, CyD-based polymers (pCyD, Figure 1B) obtained upon a polycondensation reaction of the natural CyDs with a crosslinking agent in water have received considerable interest. They usually display:

- Enhanced CyD solubility: dissolution of pCyDs in water affords significantly higher CyD concentration compared to monomers: the polymerization process disrupts the network of

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intramolecular H-bonds in the monomers allowing more interactions between the -OH groups and the surrounding water molecules. Moreover, the chains connecting different CyD monomers often contain hydrophilic moieties, i.e. -OH, -COOH, etc.

- Enhanced hosting ability: thanks to the presence of many hydrophobic micro-environments, hydrophobic guests can reach higher concentrations with respect to the corresponding complexes with CyD monomers;
- Ability of pCyDs to self-organize in small nanoparticles (NPs) upon dissolution in aqueous/physiological environment.

Natural and synthetic CyD monomers have found applications in many fields, especially in drug development thanks to their good safety profile and ability to host lipophilic drugs in their cavity.^[7] Differently, pCyDs have only been proposed at lab level for biomedical applications in spite of their performance that is often superior to the monomers. In this perspective article, we give a concise overview on the state-of-the-art regarding the preparation, and drug delivery applications. We have selected few examples illustrated in detail to highlight the strengths and potential of this class of polymers. Moreover, we comment on the main hurdles blocking their progress and the main future perspectives in the field of pharmaceutical development.

Strengths and limits of straightforward synthesis

The first syntheses of pCyDs date back to 1960s.^[8] Since then, polycondensation in alkaline aqueous environment in the presence of a multifunctional crosslinking agent (CLA) has become the method of election to produce both water-soluble pCyDs as well as water-insoluble hydrogels. Discrimination among the two is achieved by attentively monitoring diverse reaction parameters: the initial concentration and molar ratio of reagents, the type of CyD, the reaction temperature and time, the base amount, the presence and quantity of catalyst, etc.^[9] All these parameters are relevant to rigorously control the overall molecular weight (MW) and degree of substitution (DS, number of substituents per CyD unit) which are ultimately essential to grant batch-to-batch reproducibility and the general quality and properties of the materials. Moreover, they also affect the availability of CyD cavities since, inevitably, the polycondensation reaction can occur on both rims of CyDs, involving different hydroxyl functionalities in position 2, 3 and 6 of the substrates at the same time. Thus, it is not trivial to obtain hyperbranched pCyDs with reproducible physico-chemical characteristics.

The most frequently used CLAs can be grouped in three main categories (Figure 1B):

- Bifunctional reactive species, e.g. epichlorohydrin (EPI)
- Molecules bearing more than two carboxylic acid groups, e.g. citric acid (CTR)
- Di-/poly anhydrides, e.g. pyromellitic dianhydride (PMDA).

EPI is the most widely used CLA in the synthesis of water-soluble pCyDs, thanks to its high reactivity, commercial availability and low price, overcoming its unfavourable toxicity profile. Polycondensation between EPI and CyDs takes place by heating the reagents in aqueous basic conditions allowing to obtain

after proper work-up neutral pCyDs with a CyD content up to 70% w/w and relatively high MW (Figure 2A). The seminal work of E. Renard et al. in 1997 reported a detailed analysis of the synthetic parameters enabling control over the production of water-soluble EPI-pCyDs when DS < 10, avoiding gelation occurring for DS > 12. The mean MW determined by the authors was 44 kDa for a 3 hrs reaction time. For longer reaction times MW of the polymer can increase up to 400 kDa.^[10]

The use of CLAs other than EPI came across more recently. The group of B. Martel published^[11] and patented^[12] a new synthesis for water-soluble pCyDs obtained with tri- and polycarboxylic acids, above all, citric acid (CTR, Figure 1B). They proposed a greener method in the dry state involving also a catalyst (i.e. phosphate salts) producing CTR-pCyDs with biodegradable ester linkages and overall negative charge. Due to the solid-state reaction requiring high temperature and the high number of esterifiable groups present on each CyD unit, it is very difficult to avoid gel formation and have strict control over batch-to-batch reproducibility. Hence, industrial scale up is more challenging compared to EPI-pCyDs.

Also di- and polyanhydrides have been exploited as CLAs for the preparation of negatively charged pCyDs under physiological conditions. Trotta et al. optimized a synthesis based on pyromellitic dianhydride (PMDA) to obtain either water-soluble (up to 800 mg mL⁻¹) over a wide pH range and water-insoluble materials (named CyD-nanosponges) by modulating the PMDA: CyD ratio.^[13] Also in this case the limit of gelation during the reaction at room temperature is very subtle, thus complicating a scaled-up production.

Many other crosslinking agents have been tested, some of them showing promising results. However, being the use of EPI as straightforward as tunable, the neutral EPI-pCyDs are the only water-soluble ones currently commercially available and their industrial production reached the sub kg scale.

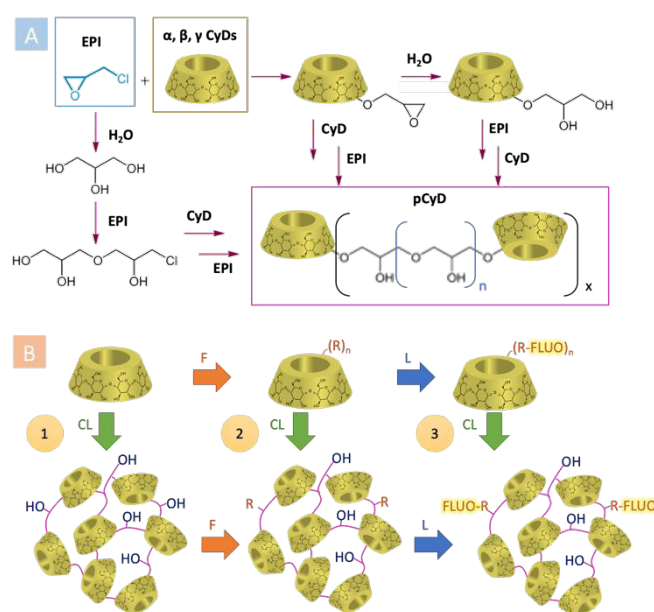


Figure 2: A) General synthetic scheme for the preparation of pCyDs using EPI as CLA; B) synthetic strategies for pCyDs functionalizations (CL= crosslinking, F = functionalization, L = labelling)



The pCyDs can also be further modified in order to afford materials with auxiliary features, like net charges or optical properties. These functionalizations can be achieved following three different strategies (Figure 2B):^[14]

1. Post-crosslinking functionalizations
2. Pre-crosslinking functionalizations
3. Sequential crosslinking and functionalizations

In this context, an important Achilles heel concerns the modification of CyDs as it often affords a mixture of isomers that are very hard to purify and separate. This has several consequences: i) proper characterization of the material according to GMP and ICH guidelines is challenging, ii) identifying by-products, degradation products and metabolites is demanding, iii) *in vivo* and/or side effects cannot be unambiguously linked to a single component or degradation product. Moreover, not all of synthetic approaches fit upscaling as, on large scales, they are too costly and/or hazardous, thus not compatible with GMP standards for drug production. So, it is necessary to face the challenges in the chemistry of *ad hoc* functionalized CyDs as single isomers creating new knowledge on sustainable, synthetic protocols for pCyDs polycondensation and functionalization, especially when targeting clinical applications.

pCyDs for the simultaneous delivery of multiple therapeutic agents

The first steps in the use of pCyDs as drug carriers date back to the 1980s' when Szejtli et al. highlighted the significantly higher concentration of CyDs obtained when dissolving the polymers and the better performance of the pCyDs in solubilizing guests also enhanced by the cooperativity of adjacent cavities in guest encapsulation.^[15]

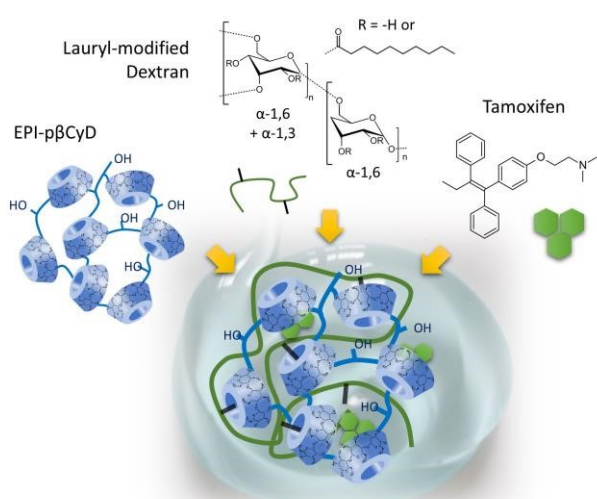


Figure 3: Self-assembly of lauryl-modified dextran and EPI-p β CyD affords hydrogels for the sustained delivery of Tamoxifen.

Later, a key work was carried out by P. Couvreur exploring the combination of EPI-p β CyD and a lauryl-modified dextran polymer as delivery system (Figure 3).^[16] EPI-p β CyD alone was

able to dissolve up to 0,7 mM of drug compared to 0,15 mM for β CyD thanks to the much higher amounts of β CyD dissolved in water as polymer, 100 mg/mL corresponding to 70 mg/mL of β CyD, compared to 17,5 mg/mL for the monomeric β CyD. Mixing the two polymers dissolved in high amounts allowed to obtain a gel used to load tamoxifen (TMX), a drug used in breast cancer treatment. The system showed at 37 °C a linear time-dependent release of TMX *in vitro*.^[17] The same group hypothesized the gel formation was due to inclusion of the hydrophobic alkyl chains in the CyD cavities and they demonstrated that the mixing of the same polymers in lower ratios could afford soluble nanoparticles (NPs) with dimension < 200 nm and size stability over 20 days.^[16, 18] In the case of the NP system they proved the crucial role played by the CyD cavity in ¹H-NMR experiments showing the inclusion of the lauryl moieties of the dextran polymer in the CyD cavities, yet leaving \approx 50% of the cavities empty. The remaining CyD units could then be exploited for TMX loading in dosage consistent with clinical application or benzophenone, a model compound, whose presence inside the CyD cavities was again proven by ¹H-NMR experiments.^[16] Their findings represented a first proof-of-principle that, differently from the monomers, pCyDs enable the contemporary encapsulation of two or more components in a unique system. They gave further credit to this hypothesis when testing the successful co-encapsulation of TMX and benzophenone (BP), into p β CyD NPs.^[19]

The contemporary delivery of multiple therapeutic agents was further pursued by Gref et al. who performed an in-depth investigation of the use of EPI-p β CyD for the loading of Ethionamide (ETH), a second line drug for tuberculosis, poorly soluble in water and inclined to crystallization, with a booster, an organic hydrophobic molecule that strongly increase ETH efficacy when co-administered (Scheme 1).^[20] Inclusion in EPI-p β CyD NPs increased the water solubility up to 25 mM for ETH and 1 mM for the booster, compared to 4 and 0,1 mM respectively for monomeric β CyD. Co-encapsulation of ETH with the booster, was achieved within the EPI-p β CyD NP confirming the same drug amounts as for single drug inclusion and ETH was found to reside not only in β CyD cavities, but also in other domains of the NPs.

The efficacy of this formulation was evaluated *in vitro* and *in vivo* in TB infected macrophages and mice, respectively. The suspensions of loaded NPs could be administered directly into mice lungs using a Microsprayer® system leading to a 3-log decrease of the pulmonary mycobacterial load after 6 administrations compared to untreated mice (Figure 4). The authors also discovered that unloaded EPI-p β CyD NPs (i) internalizes by means of phagocytosis in alveolar macrophages known as mycobacteria host impeding bacterial proliferation, (ii) is not causing cytotoxic effects in murine macrophages up to 5 mg/ml, (iii) neither induces gene toxicity in human macrophages nor solicits immune response and (iv) reduced the mycobacterial load, thus launching the polymeric CyD platform itself as most promising antibiotic agent.^[21]



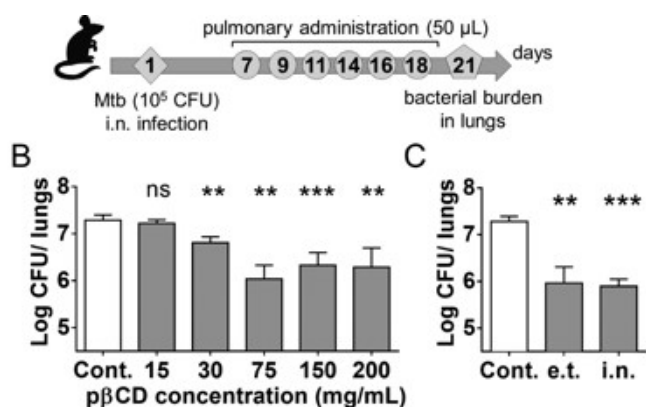


Figure 4: (A) Mice were i.n. inoculated with 105 CFU of Mtb H37Rv strain in 20 µL of PBS. At days 7, 9, 11, 14, 16, and 18, mice received administrations of 50 µL of suspensions via the e.t. route using a microsyringe delivering aerosol directly into the lungs. At day 21, lungs were harvested for determination of bacterial burden by CFU counting. (B) Bacterial load at day 21 postchallenge after 6 inoculations of 50 µL of different EPI-pβCyD concentrations by the e.t. route. (C) Comparison of the impact of EPI-pβCyD (6x50 µL at 150 mg/mL) on Mtb pulmonary load administered by the i.n. route or by the e.t. route after i.n. infection. Symbols ** and *** denote $p < 0,01$ and $p < 0,001$, respectively. Reprinted from ref. 21 with permission from American Chemical Society.

Most recently the superior ability of the polymer in drug solubilization and co-encapsulation was demonstrated by different groups using pCyD platforms for the contemporary delivery of three therapeutic agents to implement combination therapy, in particular chemotherapy with phototherapy.

S. Sortino et al. investigated pβCyD platforms for bimodal light-activated therapies of cancer and bacterial infections. They combined a nitroaniline NO donor activated upon blue light irradiation triggering NO radical release with a photosensitizer (PS), such as Zn(II) phthalocyanine, for the formation of 1O_2 upon NIR irradiation.^[22] Both the NO radical and 1O_2 are cytotoxic species generated locally and attacking multiple targets, not suffering from any kind of resistance mechanism. Noteworthy, conservation of the light-activated properties of the NO donor and PS when confined in a restricted space is not trivial, as self-quenching can occur. Clear-cut evidence was provided of a synergistic mechanism in killing neoplastic cells by comparison of the performance of the NPs loading both NO donor and PS with the NPs containing a single component.^[23]

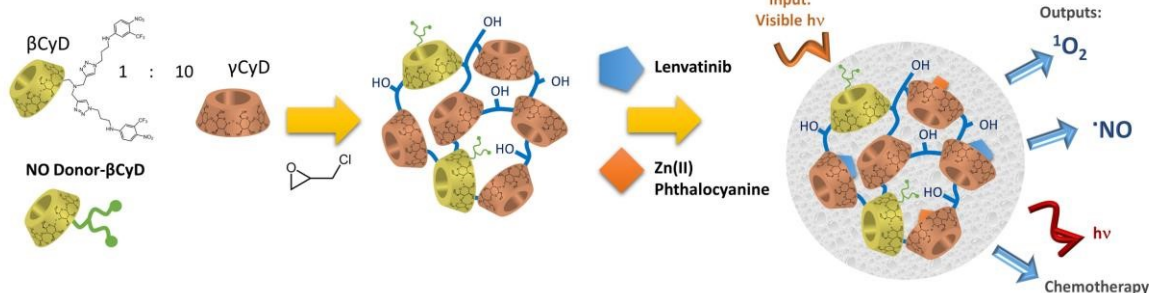
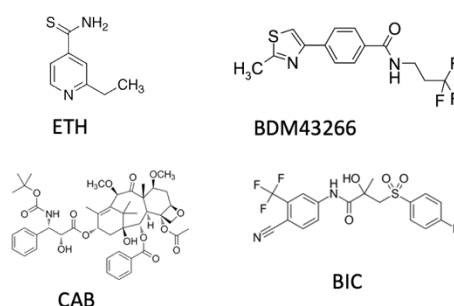


Figure 5: Sketch of a NP achieved upon self-assembly of EPI-pβCyD, zinc phthalocyanine as red emitting 1O_2 PS, lenvatinib as chemotherapeutic agent and the tailored molecular conjugate as green emitting NO donor.

Encouraged by these positive findings they recently used a mixed β and γCyD polymer to implement the loading of 3 different therapeutic agents in NPs: the NO donor in this case was covalently linked to the pCyD, and the functionalized polymer was subsequently loaded with Zn(II) phthalocyanine as PS and Lenvatinib (LVB) as chemotherapeutic drug (Figure 5). The NP system maintained high water solubility, increased the solubility of all therapeutic agents and preserved the photophysical properties of both NO donor and PS as well as the anticancer activity of LVB. In particular, this mixed polymer increases the solubility of LVB 30-fold compared to the free drug and 2-fold compared to a similar polymer with only βCD.^[24]

Recently, Pancani et al. reported an EPI-pβCyD system also loaded with 3 agents for combination therapy with: i) Cabazitaxel as chemotherapeutic agent; ii) Bicalutamide as androgen receptor; iii) Chlorin e6 as PS for photodynamic therapy. Combination of cabazitaxel with bicalutamide was proposed as the androgen receptor can reverse resistance acquired by the tumor to the taxane (Scheme 1).^[25] Stable NPs were obtained while increasing significantly the solubility of both drugs in water, with PS properties being intact in the presence of the other two agents.

Noticeably, in an era where multidrug resistance (MDR) is advancing rapidly in the treatment of cancer as well as microbial infections compromising the output of conventional therapies, the potential of the pCyD platforms to load multiple agents is of utmost importance and fostering further research to bring them to the clinics.



Scheme 1: Structure of Ethionamide (ETH), Booster BDM43266, Cabazitaxel (CAB) and Bicalutamide (BIC).



Hurdles on the way to the clinics

Looking for CyD applications in the clinics we immediately take note that we are looking at a signboard "Work in progress". While the potential of CyD monomers as excipients in pharmaceuticals is widely accepted and many CyD-based substances have been approved for drug formulations, only few CyDs have been unveiled as Active Pharmaceutical Ingredient (API). Sugammadex was approved as antidote for rocuronium, a neuromuscular blocking agent used as anaesthetics, working upon selective encapsulation of the target.^[26] 2-Hydroxypropyl- β CyD (HP β CD) was found effective for the treatment of Niemann Pick type-C diseases.^[27] These discoveries triggered several researches aimed at developing CyD-based therapies in different lysosomal storage and neurodegenerative diseases, cardiovascular dysfunctions, infections and various types of cancer. Most recently, M. Anderson et al. patented a β CyD dimer for the selective capture of the metabolite 7-ketocholesterol considered responsible for plaque formation in arteries,^[28] while M. Agnes et al. patented metal-binding CyDs as potentiators of antibiotics.^[29]

Despite their huge potential, at the moment there are no pCyDs tested or commercialized as API or delivery tools and their clinical applications are not taking off. We discern several reasons for this gridlock. The polymers have not yet been approved by Drug and Food agencies for clinical applications. This is subject to strict product quality requirements and full toxicologic screening at high costs, a risk that pharmaceutical companies have not run yet. Few research groups have addressed the latter topic with encouraging findings suggesting a lack of cytotoxicity in normal cells, but the available data need to be integrated.^[21] Additionally, the analytical challenges associated with quantifying any potential reactive groups remaining post-synthesis that might pose risks by alkylating and binding to proteins or DNA in the body, further complicates the development process and increases the associated costs for complying with the necessary quality requirements and safety parameters.^[21] If pCyDs will be formally approved, an escalation of their clinical use is expected thanks to the possibility to use them in combination with already FDA approved drugs targeting different diseases. Moreover, the search for new sustainable production processes of amphiphilic CyDs, proposed at lab level for gene delivery, is also expected to drive innovation as gene delivery is a very hot topic for treatment innovation in many pathological conditions.

While the release kinetics of the loaded cargo has been addressed by several groups, less information is available on premature leakage of the cargo *in vivo* that may cause undesired side effects. In this frame we need to keep in mind that this issue is not always pertinent as it depends on the type of administration. When local treatment applies, as in the case of long infections and skin diseases, evidence is already available on the feasibility of pCyD systems for *in situ* pulmonary application by means of microsyringe systems and gel preparations with antibiotic activity, respectively. Differently, when systemic administration is required, the retainment of the cargo is crucial and some authors addressed this topic by mixing

pCyDs with other polymers such as the hydrophobic dextrans to form more stable NPs.^[16, 30]

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Similarly, another aspect still to be better explored is the target specificity of the polymeric system. Again, this feature strongly depends on the route of administration. Addition of a targeting ligand is feasible and expected to become straightforward being available several synthetic routes to functionalize pCyDs. As to p β CyDs, an example is available where folic acid, specifically recognized by the folate receptor present on the cell membrane of many tumors, was covalently linked to the β CyD units. Unfortunately, the approach did not afford an improvement of the IC₅₀ value of the loaded cis-Pt prodrug compared to the system lacking the folic acid functionalization.^[31] Another interesting example concerns the functionalization of p β CyDs with histidine or carbinine (β -alanyl-histamine) moieties, both ligands with important physiological roles in Cu(II) metabolism in mammals. The functionalized p β CyDs formed Cu(II) complexes *in situ* thus simulating superoxide dismutase (SOD) activity and protecting cells from oxidative damage.^[32] Note that a critical point for further deployment remains the presence of single functionalized β CyD isomers in the polymers. Translation to the clinics also implies use of sterile products. The correct timing of the sterilization phase needs to be defined as it can occur at two stages, either before or after drug loading. In a very informative paper Bilensoy *et al.* compared gamma radiation, micro-filtration and autoclaving to sterilize formulations of amphiphilic CyDs organizing in NPs.^[33] Sterilization by gamma irradiation appeared the best as particle size, drug loading and release profile were not altered. Filtration was no option as the NPs were too large and autoclaving caused NP aggregation. Few reports on sterilization of the CyD polymers object of this paper are available up to now. Von Recum et al investigated the effect of autoclaving at 120°C, gamma radiation and ethylene oxide on crosslinked polymers obtained with β CyD and diisocyanate.^[34] Ethylene oxide or gamma radiation sterilized, antibiotic-loaded polymers displayed the same bactericidal activity compared to non-sterilized polymers. Autoclaving was discarded as lower drug amounts were loaded due to crosslinking to higher extents. While autoclave sterilization with heating is feasible for pCyDs, in the case of loaded pCyDs the production of by-products can occur and needs to be checked.^[35] Gref et al. proposed microfiltration with 0.22 μ m filters, a very common method, to sterilize p β CyDs loading ETH and booster assessing with HPLC the full recovery of the NPs measuring few tens of nm.^[20b] Couvreur et al performed sterilization by means of a high hydrostatic pressure system particularly suited for soft materials such as the mixed gel of p β CyD and alkyl-modified dextran.^[36] Finally, UV sterilization is feasible, with little risk for the unmodified pCyDs that are totally transparent to UV light, but the cargo may be light-responsive thus requiring a check on the photostability of the loading.^[37] Whatever method is selected for sterilization, a rigorous control of the effects of the method used on the formulation composition and behaviour is mandatory in all cases.



Conclusions/ Outlook

In conclusion, pCyDs stimulated great interest for many applications and the more they got used and known, the more their profiles could be adopted for specific targets, pharmacological and not.

Enzymatic starch digestion is a sustainable process that affords the natural monomers as building blocks in very large amounts at inexpensive costs. Further research is expected to provide new knowledge on sustainable, synthetic protocols for CyD functionalization. The actual polycondensation procedure has high atom economy and requires a very low number of reagents with accessible costs keeping the synthesis cheap. Further exploration of CLAs other than EPI and systematic investigation of the reaction conditions to optimize parameters is expected to boost sustainable pCyDs production on large scale.

Translation of the pCyDs to the clinics as drug delivery systems or API implies however much more than sustainable synthesis at accessible costs with mandatory batch-to-batch reproducibility. In-depth inquiries need to be performed on the toxicological profile of each new pCyD-based product proposed for the clinics. Also, as more information is becoming available on the ability of pCyD-based systems to interact with different biological players, not only the identified target, we need more research to unveil their biological profile. In this context, actual research and innovation activity carried out worldwide on this class of polymers is of utmost importance to foster further progress.

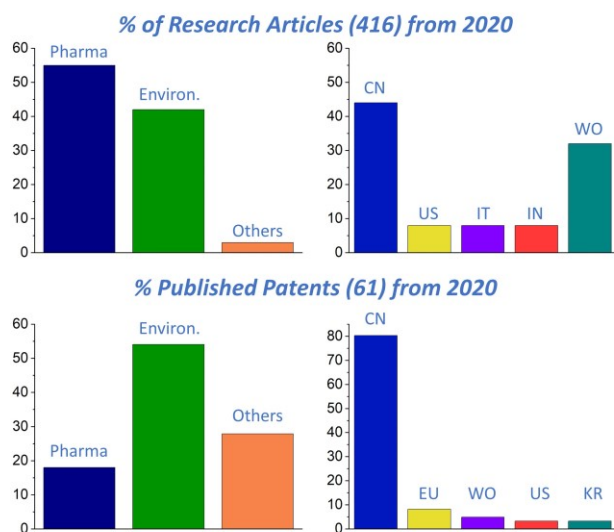


Figure 6: Summary of Web of Science and Espacenet outcomes ("cyclodextrin polymer" in the title and ">= 2020" as publication date). The research articles were 416, the patents 61. Article topics: 55% pharmacological, 42% environmental and 3% other applications. Patent topics: 11% pharmacological, 33% environmental and 17% other applications. Country of Origin of Articles: 44% China (CN), 8% USA (US), 8% Italy (IT), 8% India (IN), 32% from the rest of the World (WO). Country of Origin of patents: 80% China (CN), 8% Europe (EU), 5% World applications (WO), 3% USA (US), 3% South Korea (KR).

An inquiry on Web of Science (WoS) and Espacenet (EN) confirms the great interest in pCyDs for many different fields of applications which is a driving force in the development of these materials and their conquest of concrete industrial and clinical

applications. A comparison between the research articles (Web of Science®) and patents (Espacenet®) containing "cyclodextrin polymer" in the title and published from 2020 (Figure 6) afforded some interesting information. While the published research articles are more in the field of medical and pharmaceutical applications, the patents are mostly about environmental applications. In both cases, China is the place where most of the research outputs are produced. The gap between research and patents regarding pharmacological applications is probably due to the limitations mentioned above. Hopefully, thanks to the wide number of developing patents regarding other uses of pCyDs, we expect increasing interest in these materials and this will attract more investments enabling to fulfil the gap on missing toxicological and regulatory information regarding pCyDs.

Author Contributions

IManet: funding acquisition, conceptualization, writing original draft, and review, supervision; MAgnes: conceptualization, writing original draft, and review, supervision; MMalanga: writing original draft, and review, literature analysis; AMazza: literature analysis and editing.

Conflicts of interest

There are no conflicts to declare.

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Notes

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In faith,

Roberto Marzetti

