SELECTED APPLICATIONS OF CYCLODEXTRIN POLYMERS

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ABSTRACT

The review consists of two parts. In the first part selected properties of CD polymers which are useful for their application are presented; their network and gelation properties, along with their adsorption capacities and stabilities, are described here. In the second part, various applications of CD polymers of commercial interest, as well those which are promising in the medicinal field, are shown.

Keywords: crosslinker, gelation, inclusion, nanosponge, network, stability

1. INTRODUCTION

Cyclodextrin (CD) polymers have valuable properties which are useful in many fields. Therefore, research in the aspect of their chemistry as well as due to their various potential applications, is very intensive. Starting with the characterization of CD monomers, the authors will proceed to that of CD polymers in this paper.

CD monomers are macrocycles, widely used in various areas, *e.g.,* in the pharmaceutical industry, in analytical chemistry, in separation processes or

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catalysis [1, 2], their relatively simple, environmentally friendly preparation being an advantageous feature. Also worth noting is the application of CDs in the food processing [3-5] and cosmetic [6] industries. The ability of CD molecules, having hydrophobic cavities and hydrophilic outer cores, to form inclusion complexes plays a crucial role in their application [7-9].

CD polymers are obtained by crosslinking CDs with polyfunctional compounds, *e.g.,* epichlorhydrin (EP) or hexamethylene diisocyanate (HMDI). It is worth noting that the properties of CD polymers depend strongly on their crosslinking degree.

Growing attention is being paid to CD polymers due to their application in various fields [10-19]. CD polymers serve in the medicinal area for drug delivery [20-24] and for designing new tissue engineering materials [25, 26]. They are employed in environmental protection [27-31], for the removal of organic [32, 33] and inorganic [34] as well as heavy metal [35-38] pollutants**.** Also the use of CD polymers in the pharmaceutical [39-42] and cosmetic [40, 43] industries is worth mentioning.

CD nanosponges are a new kind of CD polymers: they are promising in designing new materials with special properties [44, 45]. The present review is a continuation of our efforts dealing with CD polymers [10, 12, 13, 46].

2. PROPERTIES OF CD POLYMERS

2.1. Network properties of CD polymers

The network properties of CD nanosponges, a new class of crosslinked CD polymers, were investigated using inelastic light-scattering techniques. Raman and Brillouin scattering experiments were performed for a detailed inspection of the vibrational dynamics of such polymers in order to provide physical descriptors correlated with their crosslinking degree and elastic properties.

The CD nanosponges are amorphous crosslinked polymers obtained from CDs and polyfunctional compounds, *e. g.,* pyromellitic anhydride (PMA) or carbonyldiimidazole (CDI) as crosslinkers (Fig. 1). The formed polymers are highly crosslinked nanoporous materials with interesting inclusion/release properties [47]. Due to the presence of hydrophobic cavities in CDs and hydrophilic channels in the porous structure, the CD nanosponges are able to encapsulate a large variety of compounds.

The type of crosslinker and its amount may strongly affect the properties of CD nanosponges, such as swelling capacity and hydrophilicity/hydrophobicity, therefore, it is possible to modulate the properties of CD nanosponges. It is worth noting that the above properties are important in their application in drug delivery [48], agriculture and environmental protection [49] as well as in biocatalysis [50].
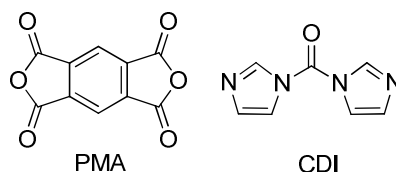
Fig. 1. Structures of crosslinkers PMA and CDI

The structural data of CD nanosponges obtained by using the crosslinkers PMA [51] and CDI [52] are crucial in the aspect of their degree of crosslinking as well as of their swelling ability which, in the presence of aqueous solutions, results in gel-like properties.

The vibrational dynamics of the two considered systems of nanosponges was investigated with the use of Raman and Brillouin light-scattering experiments over two different frequency ranges: terahertz (for Raman) and gigahertz (for Brillouin); in these experiments, the stiffness properties of materials could be examined over a length ranging from several to hundreds of nanometers. An analysis of spectral modifications of the Boson peak and changes of the Brillouin frequency shows that the crosslinking degree and the elastic properties of CD nanosponges can be modulated by varying the amount and the type of the crosslinker, however, the size of CD does not influence the stiffness of nanosponges significantly. The above results are useful for controlling the swelling and inclusion properties of CD nanosponges [53].

2.2. Gelation properties of CD polymers

Noncovalently crosslinked hydrophilic polymer networks or hydrogels are often used currently in smart materials which can respond to external stimuli, such as temperature or pH [54]. In order to investigate the gelation properties of CD polymers, the synthesis of hydrogels from γ-CD and pyrene-terminated poly(ethylene glycol) star polymers was performed [55, 56]. They were obtained by forming inclusion complexes of γ-CD with dimers of the pyrene terminals of PEG star polymers; γ-CD acts as a crosslinker in the process.

It is known that, due to its large cavity, γ-CD is able to encapsulate two guest molecules, *e.g.*, two pyrene molecules. Such inclusion complexes may serve as crosslinks in the formation of supramolecular networks which induce gelation. Pyrene-terminated PEG star polymers were synthesized for the purpose (Fig. 2) [57] and their self-assembly with CDs was investigated (Fig. 3) [57].

Experiments have shown that simple mixing of γ-CD with pyrene-terminated 8-armed PEG star polymers, namely PEG-8A-pyrene (10k) and PEG-8A-pyrene (20k), results in the immediate formation of strong hydrogels. The process runs very rapidly (k denotes molecular weight in Da). Gelation was induced by the formation of inclusion complexes of γ-CD with pyrene moieties of PEG-8A-pyrene (20k). In these inclusion complexes, two pyrene units were encapsulated in the γ-CD cavity and the inclusion complex acted as a physical

crosslink. Many γ-CD inclusion complexes with pyrene units are formed intermolecularly in the process, affording a large, continuous polymer network, inducing the gelation.
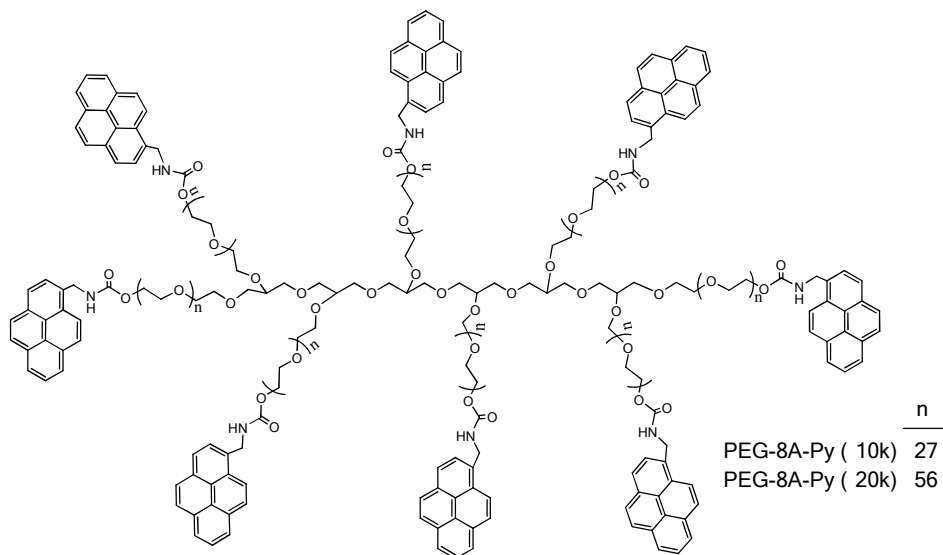

	n
PEG-8A-Py (10k)	27
PEG-8A-Py (20k)	56

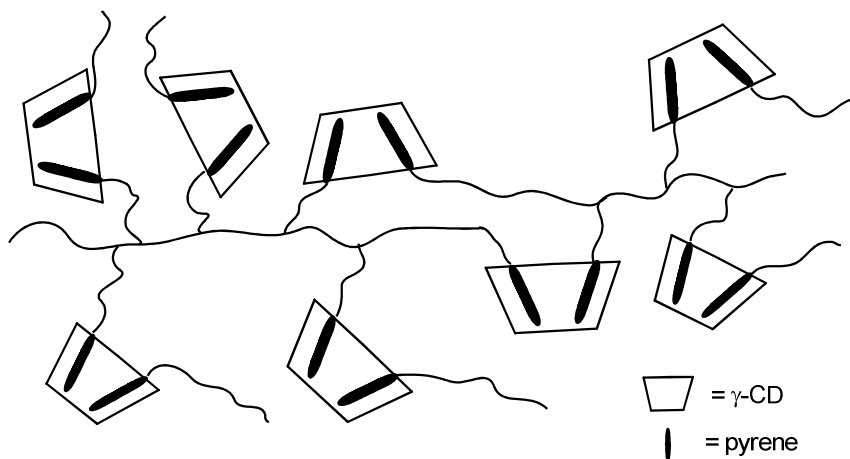Fig. 2. Structures of pyrene-terminated 8-armed PEG star polymers

= γ-CD

= pyrene

Fig. 3. Schematic representation of hydrogel formation from γ-CD and PEG-8A-pyrene (20k)

It should be emphasized that the mechanism is different from that of gelation between α-CD and PEG, where many α-CD rings are threaded onto PEG chains, and the inclusion complexes self-assemble the further formation of crystal domains as physical crosslinks. As a result, such gelation of α-CD/PEG

is slow and the gels are opaque while the gelation of γ-CD/PEG-8A-pyrene (20k) is rapid and the obtained gels are transparent.

It is noteworthy that no gelation occurs in the case of α-CD and PEG-8A pyrene (20k) since a majority of PEG arms are end-capped with pyrene units which are too large to enter the α-CD cavity. Similarly, in the case of β-CD and PEG-8A-pyrene no gelation takes place either because β-CD can include only one pyrene unit, therefore, crosslinking is impossible [57].

The formation of inclusion complexes of γ-CD with pyrene dimers which induces gelation was confirmed by fluorescence measurements.

2.3. Adsorption capacity of CD polymers

For the study of the adsorption capacity (Q_c) of CD polymers toward fuchsin (Fig. 4), the three water insoluble β-CD polymers **H** with nonionic hydroxyl group, **C** with carboxyl group, and **A** with amidogen served as models (Fig. 5) [58, 59]. They were synthesized by the crosslinking of corresponding β-CD derivatives with epichlorohydrin (EP), and their properties for adsorption of water soluble dye fuchsin from aqueous solution were investigated. It was found that **C** was a more effective extractant, compared with **H** and **A** which showed lower Q_c, compared with fuchsin. For **C**, the influence of contact time, pH and temperature and of degree of substitution (DS) on adsorption capacity, Q_c, were examined.
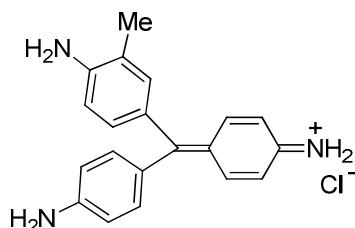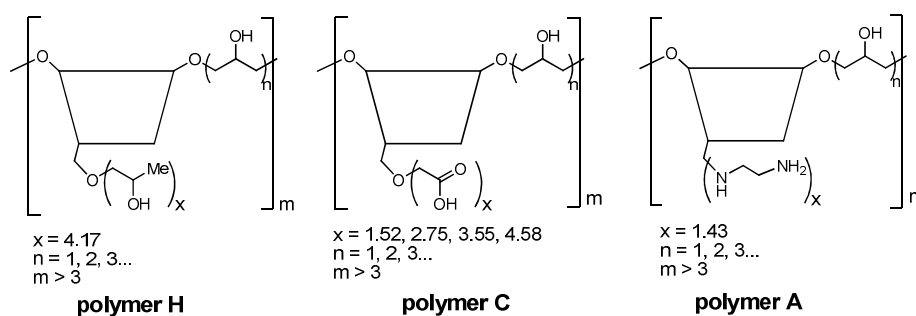

Fig. 4. Structure of fuchsin

Fig. 5. Structures of polymers H, C and A

It is known that β-CD is used in various areas, *e. g.*, in pharmaceuticals, foods, and in analytical methods. Many derivatives of β-CD have been

synthesized in order to improve its inclusion properties, however, the water solubility of β-CD and its derivatives is a drawback in their use for the removal of organic pollutants and heavy metals from aqueous solution. Therefore, to overcome the difficulty the water insoluble CD polymers have been synthesized as adsorbents which are useful for the removal of organic pollutants and heavy metal ions from water [58].

In order to prepare the water insoluble polymers **H**, **C** and **A** for the synthesis of polymer **H**, its monomer was dissolved in a 30% aqueous NaOH (30% w/w) solution and treated with EP. For the synthesis of polymer **C**, the reaction of β-CD with chloroacetic acid was performed and the obtained monomer **C** was crosslinked with EP [59] as above.

The synthesis of polymer **A** begins with the reaction of β-CD with tosyl chloride releasing TsO-β-CD which yields monomer **A** when treated with diaminoethane. The subsequent reaction of monomer **A** with benzaldehyde leads to the formation of Schiff base **B**, which was crosslinked with EP to give polymer **A** (Fig. 6).
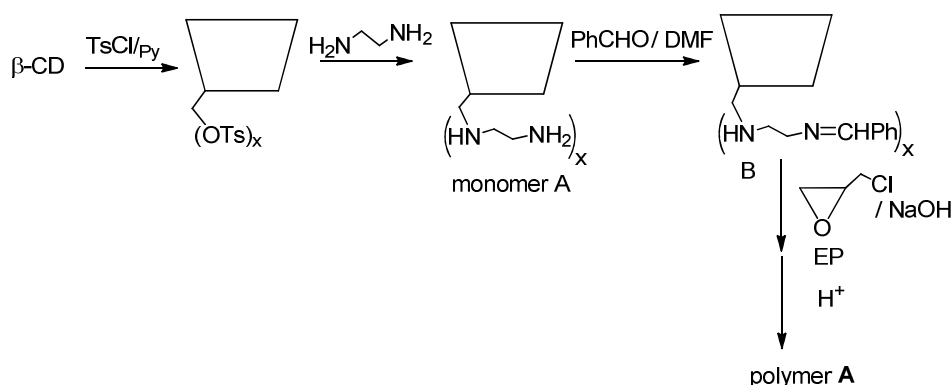

Fig. 6. Synthesis of polymer A

The study of fuchsin adsorption showed that the type of functional groups of the considered polymers greatly influenced their adsorption capacity: polymer **C** showed to be the most effective extractant from among **H**, **C** and **A** and a non-modified β-CD polymer [59].

2.4. Stability of CD polymers

When investigating the stability properties of CD polymers, attention is paid to polymer nanoassemblies in view of their biomedical applications as drug delivery systems. It was established that simple mixing of two polymers in water may yield polymer nanoassemblies [60]. The two polymers selected were the β-CD polymer and a hydrophobically modified dextran which, when mixed under precise concentration conditions, spontaneously associate to give nanoassemblies, which are of interest as drug delivery agents. However, their

sensitivity to ionic strength is a disadvantage: even a small addition of salt leads to their destabilization.

Therefore, a system which is intended to overcome such difficulties was designed; it is based on similar nanostructures but provides a stability required for biomedical uses. For this purpose, the disubstituted dextrans were used, in which one substituent (dodecyl or adamantyl) is hydrophobic and the other substituent (cyclohexanecarboxyl A) combines the pH-dependent affinity for CD cavity with pH-dependent charge density introducing electrostatic interactions into the system [60]. The properties of the β-CD polymer, mixed with disubstituted dextran were studied, and the conditions suitable for the formation of stable nanoassemblies were determined.

It was found that the mixing of polymer β-CD solutions with disubstituted dextran releases assemblies showing an interesting dependence on pH: at a pH=7 (the groups A are fully charged), the polymer mixture provides a clear monophasic solution, while at pH=2 (the groups A are fully protonated) the associative phase separation occurs with precipitation. Between these two cases, at pH 4, the associative phase separation still occurs, but metastable nanoassemblies are formed [60].

The above experiments have shown that mixing, in aqueous solution, of the β-CD polymer with amphiphilic disubstituted dextran leads to pH-dependent associative phase separations with colloidal nanoassemblies being formed in a well defined pH range [60]. The obtained stimuli-responsive systems are promising for biomedical applications.

3. APPLICATIONS OF CD POLYMERS

Four examples of CD polymers applications are described below, including two examples of industrial applications, and two examples of their applications in the medicinal field. The first two examples deal with the application of CD polymers in the preparation of flame retardants and in enhancing oil recovery, and the latter two examples concern the application of CD polymers in siRNA compaction and in the preparation of magnetic nanoparticles.

3.1. Industrial applications of CD polymers

Example 1. Application of CD polymers in preparation of flame retardants

Among the properties of CD polymer, their usefulness in the preparation of flame retardants should be pointed out. When an intumescent material is subjected to a heat flow, a carbonaceous shield, *i.e.,* char, will form on its surface. It is a protection acting as a physical barrier, able to limit the transfer of heat, fuel and oxygen between the polymer and the flame.

Intumescent materials usually consist of three components, namely: 1) an acid source (ammonium phosphates or polyphosphates) releasing phosphoric acid at ca 150^0C; 2) a carbon source (pentaerythritol, sorbitol, arabitol,

saccharides, polysaccharides); and 3) a blowing agent (guanidine, melamine), releasing large amounts of expandable or non-combustible gases (ammonia or carbon dioxide) upon heating.

The char originates from reactions occurring between the above three components of the intumescent formulation. Some compounds, *e.g.,* ammonium phosphates or polyphosphates are advantageous since they act simultaneously as the acid source and the blowing agent, releasing ammonia.

A number of methods were designed for improving the efficiency of intumescent systems or for reducing the flame retardant content without significantly affecting their fire protection properties; among them, the use of CDs [61, 62] and of CD nanosponges [63] was reported. The CD nanosponges have a porous structure and an outstanding stability (up to ca $300^{0}C$ in air); it is noteworthy that they can include, transport and selectively deliver a variety of substances because of their structure, containing cavities.

Green flame retardants are based on a complex of CD nanosponges with phosphorus derivatives, namely triethylphosphate (TEP) and ammonium polyphosphate (APP). The CD nanosponges, *i.e.,* β-CD polymer crosslinked by organic carbonate were synthesized by treatment of β-CD with diphenylcarbonate in DMSO (Fig. 7) [64]. The mechanical grinding of the obtained CD nanosponges with TEP or APP provided nanosponge complexes with TEP or APP. They were melted with polypropylene (PP), linear low-density polyethylene (LLDPE), or polyamide 6 (PA6) in order to improve their thermal stability and flame retardancy properties [65]. The presence of the above polymers allows to reduce the content of phosphorus derivatives, as in recent industrial flame retardant formulations.
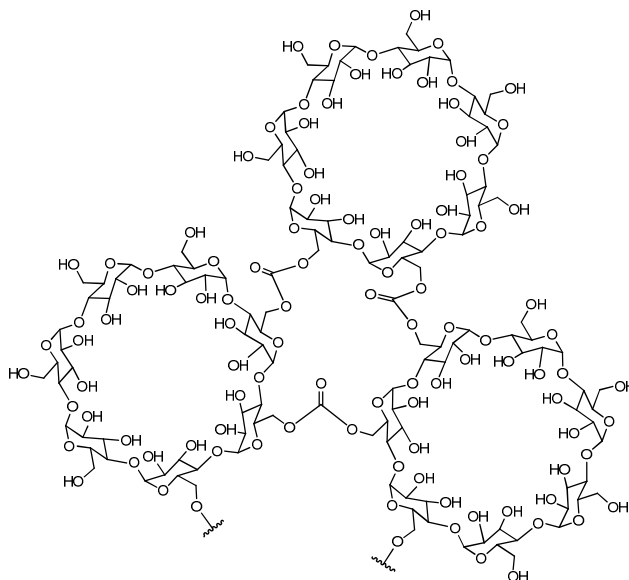

Fig. 7. A fragment of β-CD nanosponge structure

The flame retardancy properties of the prepared samples were measured by two following tests: i) flammability test, *i.e.,* the ignitability of the sample in the presence of a flame spread was tested by applying a methane flame; ii) combustion behavior of the sample under the irradiative heat flow, developed as a result of exposure to the flame, was determined by cone calorimetry.

The role of CD nanosponges both as a carbon source and a foaming agent in such intumescent formulations was shown: the nanosponge structure includes and protects the phosphorus derivatives TEP and APP and, therefore, they are able to generate phosphoric acid directly *in situ* at high temperatures. Phosphoric acid facilitates nanosponge dehydration giving rise to water vapor and inducing char formation. As a result, CD nanosponges undergo dehydration in the presence of the acid source, releasing water vapor; this favors char formation and the polymer resistance toward combustion is strongly enhanced. It is noteworthy that the intumescent technology may efficiently improve the flame retardant properties of polymers in a safer way, compared with the use of halogens and halogen derivatives.

The CD nanosponges, employed for the preparation of flame retardants, have networks with both internal and external cavities, where phosphorus compounds can be easily included. Therefore, due to their structure, CD nanosponges may finetune the flame retardant release upon heating, in this way enhancing its fire resistance. Moreover, they induce char formation and act as foaming agents.

Example 2. Application of CD polymers for enhancing oil recovery

It was found that β-CD anionic and cationic acrylamide polymers may be used for enhancing oil recovery. One should point out that β-CD, although widely applied in a variety of areas such as medicine, pharmacy, environmental protection, etc. [66], has never been used before for the preparation of chemical flooding in tertiary oil recovery.

It is known that polyacrylamide (PAM) is valuable for its rheological behavior, thickening and flocculation, is largely employed in the oil industry, papermaking, and water treatment [67].

However, PAM has the drawbacks of only weakly improving the oil-water-rock interfacial tension and having low salt resistance [68]. To overcome the difficulty, intensive investigations concerning modification of PAM structure are carried out; in this aspect, anionic and cationic β-CD acrylamide polymers A and B have been synthesized. To this end, acrylamide and allyl-β-CD were submitted to redox free-radical aqueous copolymerization with acrylic acid to give the anionic polymer A, and with dimethyl diallyl ammonium chloride to give the cationic polymer B (Fig. 8) [69].
The β-CD molecules, due to their cavity-like structure may combine with a surfactant to form inclusion complexes; they can selectively assemble and release guest species [70]. Therefore, the surfactant can easily be recognized by the oil phase on the interface between the displacing fluid and the oil phase. It is

noteworthy that, due to the rigid structure of β-CD molecules, polymers A and B can resist the high temperature of the strata and the shearing effect of clay, and are important for enhancing oil recovery. It should be pointed out that the incorporation of β-CD molecules into the acrylamide polymers, due to their hydrophobic cavities and hydrophilic outer cores, improves the polymer stability under high-temperature, high mineralization, and high shear oilfield conditions for enhanced oil recovery.
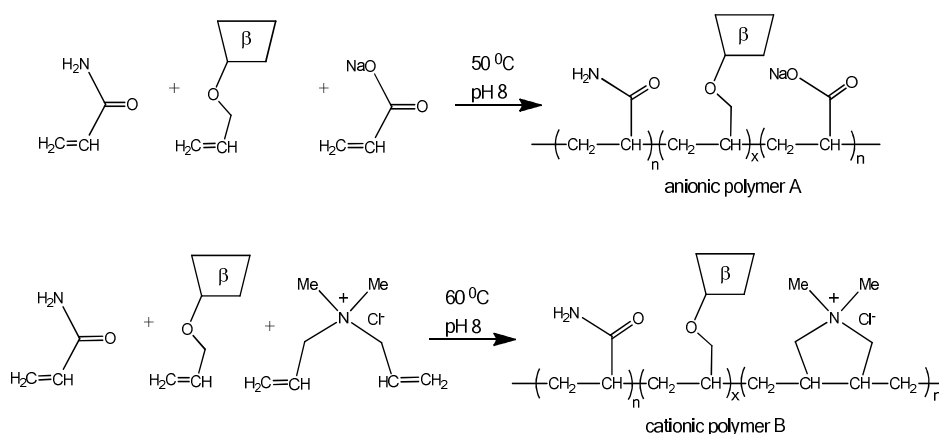

Fig. 8. Synthesis of β-CD acrylamide polymers A and B

It was observed that polymers A and B show a better performance in terms of interfacial tension, salt resistance, temperature tolerance and shear resistance, compared with polyacrylamide. This comparison indicates that the polymer A more efficiently decreases interfacial tension for the tertiary recovery process, while the polymer B is more suitable for enhancing oil recovery in high-temperature and high-mineralization oilfields.

3.2. Medicinal applications of CD polymers

In both examples below, it is established that the disadvantages of conventional chemotherapeutics can be decreased by means for controlled drug release and drug targeting technologies.

Example 3. Application of polymer Chol/PVA/PEG/amino-β-CD for siRNa compaction

In the study of vectors for gene silencing recently a novel siRNA (small interfering RNA) delivery vector was designed. It is based on the self-assembly of monosubstituted cationic β-CD derivatives **1-3** with polymer Chol/PVA/PEG, consisting of cholesterol, poly(vinyl alcohol) PVA and poly(ethylene glycol) PEG (Fig. 9).
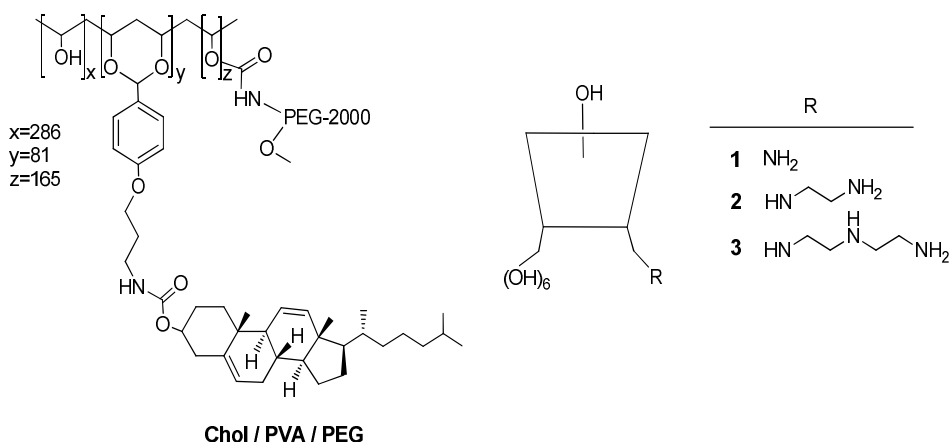
Fig. 9. Polymer Chol / PVA /PEG and β-CD derivatives 1-3

RNA interference (RNAi) is a post-transcriptional gene-silencing mechanism which arises from degradation or translation arrest of target RNA. It is known that the ability of 21-23 nucleotide RNA (siRNA) to mediate RNAi in mammalian cells is of a great therapeutic potential for the treatment of viral infections, cancer, and neurological diseases.

The use of siRNA is more advantageous, compared with the treatment based on conventional chemotherapy, however the efficient and safe delivery of siRNA, specifically to target cells, is now a great challenge [71]. Various viral and nonviral vectors have been designed for the purpose, among them, the nonviral vectors are widely studied due to their modest host immunogenicity and manufacturability [72-74].

Many methods concern the elucidation of the mechanism of nucleic acid complex disassembly and escape from the endosome of the cells that have internalized them [75, 76]. It was reported that the presence of aminocholesterol derivatives may promote disruption of biological membranes to facilitate intracellular siRNA delivery [75]. Therefore, a delivery vector for siRNA was prepared based on the self-assembly of cationic β-CD derivatives with polymer Chol/ PVA/PEG [77]. In that delivery vector, the cholesterol units are connected *via* an acid-sensitive acetal linkage. For the synthesis of Chol/PVA/PEG/amino-β-CD, the cationic β-CDs **1-3** were used.

It was assumed that siRNA compaction would occur *via* complexation with the self-assembled polymer Chol/PVA/PEG/amino-β-CD. The approach enables the compaction of the siRNA cargo into stable nanometer-size particles, which can be internalized by target cells into acidic endosomes. The endosomal degradation of the acetal linkage of the polymer should promote the release of pendant cholesterol groups and decondensation of the cationic CDs and siRNA cargo, thereby facilitating endosomal escape of the siRNA cargo.

For evaluation of the ability of the Chol/PVA/PEG/amino-β-CD polymer to condense siRNA, two complexation methods, denoted a and b, were applied:

- in Method a) Chol/PVA/PEG was preassociated with amino-β-CD before addition to the siRNA solution,
- in Method b) the siRNA was first complexed with amino-β-CD and then Chol/PVA/PEG was added.

Zeta potentials for both types of complexes were measured to determine the surface charge of the resulting transfection particles. The complexes formed by both methods had slightly negative zeta potentials. The absence of the positive charge on the surface is due to the high loading of PEG on the polymer backbone, which effectively shields the positive charges arising from the cationic CDs. It should be pointed out that the absence of a positive charge is advantageous, since the positive surface charge would lead to nanoparticle opsonization or macrophage uptake.

The dynamic light scattering results as well as AFM images confirm the preparation of the Chol/PVA/PEG/amino-β-CD polymer as a noncovalent assembly, capable of condensing siRNA into compact, unimodal particles. It the process, the PVA connected with Chol *via* a pH-sensitive acetal linkage forms a scaffold for binding cationic amino-CD that condense siRNA into particles of a size < 200 nm, which are an effective, low-toxicity vehicle for delivering siRNA cargo to target cells [78].

Example 4. Application of β-CD polymer in the preparation
of magnetic nanoparticles

Numerous investigations have been conducted recently to develop targeted therapeutic systems by using external forces such as magnetic or electric fields, ultrasound, temperature etc., for concentrating drugs within tumor sites [79, 80]. In the reported system described below, the drug is localized at a targeted area by external magnetic forces. The magnetic particles tagged with drug molecules are targeted to specific sites of the body by external magnetic fields; in those sites the drugs are gradually released. As a result, the therapeutic efficiency of drugs is improved by lowering the collateral toxic side effects on the neighboring healthy cells [80].

Curcumin, a traditional Indian and Chinese medicine [79], is a polyphenolic pigment of the turmeric root (*Curcuma longa* L.), which has antitumor, antioxidant and antiamyloid activities. In its clinical applications, curcumin has shown its efficiency in humans, though its poor water solubility is a disadvantage (Fig. 10).

It was found that the solubility of curcumin could be improved by the formation of inclusion complexes with β-CD. Moreover, drug release was extended by the use of the hydrophobically modified dextran, and targeting was facilitated by functionalization of the complex with the magnetic material. For this purpose, the CD polymer was obtained by crosslinking β-CD with EP, and the hydrophobically modified dextran was prepared by reacting dextran with

oleoyl chloride [80]. Dextran, *i.e.*, mainly α-1,6-polyglucose with some α-1,4-branching, is clinically used as a plasma expander.
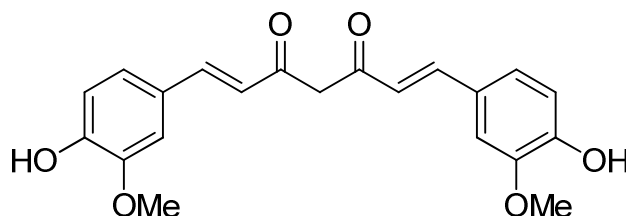

Fig. 10. The structure of curcumin

In order to prepare a formulation of magnetic nanoparticles, the β-CD polymer and oleoyldextran were mixed in water with curcumin, then $FeCl_3 \cdot 6H_2O$ and $FeCl_2 \cdot H_2O$ were added, followed by ammonia solution [80]. It is noteworthy that both polymers: β-CD polymer and oleoyldextran are biodegradable. The obtained spherical curcumin-loaded nanoparticles are superparamagnetic.

It was observed that the encapsulation efficiency of curcumin was increased for higher concentrations of β-CD polymer in the formulation. The drug release was lower when the concentration of oleoyldextran was higher, due to the gelling of oleoyldextran. The reported experiments have shown that the curcumin-loaded magnetic nanoparticles are successful in targeting the drug and in its controlling release.

CONCLUSION

Selected properties of CD polymers, along with examples of their applications in industry and medicine have been described in this survey. In the aspect of a rapid progress in CD polymer investigation, it was impossible to describe all previously published reports on the above subject, however, there are good reasons to hope that the present survey, albeit non exhaustive, would be useful as some enlargement of the knowledge of this interesting area of chemistry and related sciences.

The recently observed intensive study on applications of CD polymers in the medicinal area is promising for the future development of this very important and useful field of scientific research.

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