Advances of cyclodextrin polymers for the delivery of biotech drugs

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ABSTRACT

Currently, biological drugs such as gene, protein, and monoclonal antibody are widely applied in the clinic due to their excellent effectiveness. However, they still have some problems, including poor solubility, instability, toxicity, and weak capability to cross cell membranes. Owing to the specific structure of cyclodextrins (CDs) and the advantage of polymeric backbones, various cyclodextrin polymers (CDPs) have been designed as delivery systems for biotech drugs. In this review, after a brief introduction on CDPs and discussion of their physicochemical and biological properties, we will focus on recent advances in the use of CDPs for the delivery of biotech drugs. This review highlights the structure-function relationship of CDPs to their performance in biotech drug delivery. Finally, an outlook will be proposed on the developing trends and challenge in this field.

Keywords: Cyclodextrin polymers; Drug Delivery System; Biotech Drugs; Gene; Protein.

1. INTRODUCTION

Biotech drugs, derived from organisms, are widely applied in prevention, treatment, and diagnosis as well as regulating physiological function, promoting physical recovery, and maintaining health. These drugs are active, specific, and unequivocal; thus, they have rapidly expanded to most medical fields. Nonetheless, many of them require special formulation technologies to overcome drug-associated problems. Such potential challenges are: limited chemical stability in vivo after administration; poor permeability, bioavailability, and solubility; and potentially strong side effects requiring drug enrichment at the site of targeted action.\textsuperscript{1} These urgent problems have raised demand for appropriate delivery systems. Thus, plenty of biomaterials have been designed for biotech drug delivery in past decades. Among them, cyclodextrins (CDs) are one of the most suitable materials owing to their high biocompatibility, stability and low immunogenicity.\textsuperscript{2}

CDPs are derived via the enzymolysis of glucose-based biopolymers, such as starch, glycogen, or maltose.\textsuperscript{3} In the family of macrocyclic oligosaccharides, \(\alpha\)-, \(\beta\)-, and \(\gamma\)-CDs are the most common members, which are composed of 6, 7, or 8 glucose units linked by \(\alpha\)-1,4 glycosidic bonds, respectively. CDs presented a hollow, semi-conical tubular structure that is stable; the intramolecular hydrogen bonds are such that the glycosidic bond of glucose units cannot rotate freely in the aqueous phase.\textsuperscript{4} The exterior of CDs is hydrophilic, while the interior consists of hydrophobic cavities resulting from the shielding interaction by C-H. However, due to the limitation of the size of their cavities, CDs could only obtain effective inclusion of drugs with a low molecule weight (below 400). Thus, they are not able to load the macromolecular biotech drugs efficiently.\textsuperscript{5} In addition, parent CDs produce a trace of cytotoxicity and nephrotoxicity, arising from the extraction of cholesterol from the cell membrane.\textsuperscript{6}

To overcome these drawbacks, especially for the purpose of the delivery of biotech drugs, various CDPs are being developed, which appear to be promising due to their merits compared to parent CDs, e.g., they can form supramolecular complexes with a wide range of drugs with multiple sites and conjugate additional functional groups.\textsuperscript{1,7} CDPs can improve the therapeutic effect of biotech drugs by: 1) enhancing the half-life of the drug; 2) improving the selectivity of the drug; 3) reducing the toxicity of drug molecules; 4) overcoming the problem of agent configuration or aggregation during the delivery process; and 5) carrying the drug to the targeted sites. After the release of biotech drugs, the biodegradable CDPs will not accumulate in the body, due to degradation by hydrolysis or enzymolysis. The key point is to design CDPs possessing good biocompatibility with the tissue, blood, and immune system.\textsuperscript{8} Proper polymeric structure and chemical modification in the design of CDPs are of great importance to improve their functionality and to obtain an ideal delivery/release capability for biotech drugs.\textsuperscript{9} Thus, this review focuses on recent advances in the design of such CDP carriers for biotech drugs and provides an overview and discussion on their structure-function relationship.

2. STRUCTURES AND PROPERTIES OF CDPs

Considering the high standards required for biomedical applications from a practical viewpoint, CDPs should be designed and synthesized with well-defined structures in terms of architectures and physicochemical properties. CDs have been conjugated
onto polymers of various architectures to offer materials with unique features and excellent biocompatibility. CDPs have been synthesized to increase interactions of CDs with biotech drugs and biological membranes, and to render self-assembly capacity in aqueous solutions. For example, hydrophobic CDPs have been designed to develop sustained-release carriers. This section will briefly summarize CDPs that have been employed to fabricate functional structures for the delivery of biotech drugs.

One example of the CDP structure is the pendant CDP. The mono-substituted CDs are attached on the side of the polymeric chain; thus, the noncovalent linkage driven by the host-guest interaction leads to sustained drug release. Pendant CD units can be inserted on the remaining hydroxyl groups of the cationic polymer backbone with the aim to improve cell transfection. This modification was thought to affect colloidal stability of carrier systems by imparting positive surface charges. For example, a series of CD-pendant polymer vectors were designed based on the self-assembly of cationic β-CD derivatives comprised of cholesterol modified poly (ethylene glycol) – poly (vinyl alcohol) (PEG-PVA), and the amino-cholesterol derivatives may promote disruption of biological membranes under physiological pH conditions. In addition, the conjugation of pendant CDs, particularly β-CD, improved the transfection efficiency of polyamidoamine (PAMAM) dendrimers due to its stabilizing effects, which in turn led to significant protection against enzymatic digestion. At the same time, the ability of CDs to disrupt membrane suggested that PAMAM-CD derivatives were able to induce early escape from lysosomal vesicles before degradation. Moreover, shielding the surface positive charge on PAMAM structure may reduce its cytotoxic effects. This structure also can be used by polysaccharides as a polymer carbon backbone. When the chitosan-CD conjugates are used as the delivery system, their adhesive properties can prolong the residence time based on the coupling of a mono(6-(2-aminoethyl) amino-6-deoxy)-β-CD derivative with chitosan, which are potential for the delivery system of biological macromolecules.

Meanwhile, the novel superstructure of CDPs has been studied for use in the delivery systems of biotech drugs. For example, the polyrotaxanes (PRXs) are a class of supramolecular structures threaded onto the main-chain or side-chain of polymers. To date, various combinations of cyclic molecules and polymers that can form PRXs have been discovered. A functional molecule could be covalently conjugated to the side chain or terminal of hydrophilic polymers. The conjugates that release drugs via the dissociation of the supramolecular structure could be applied in the delivery system. The self-assembly process of PRXs allows for straightforward control over their structural properties, which can be varied by adjusting the degree of CD threading and the number of CD units. It is likely that terminal moieties of the PRXs are first degraded by hydrolytic enzymes to generate the release of biological drug-immobilized CDs. Practically, the cationic PRXs display cytotoxicity profiles that are lower than the commercial standard polyethyleneimine (PEI). One of the structural characteristics of PRXs is their unique linking system: CDs are mechanically locked with a linear polymeric chain such as PEG, and CD molecules are freely mobile along the polymeric chain capped with bulky end groups. (Figure 1) Thus, it is assumed that the mobility of CD molecules along the chain, including the sliding and rotational motion of CDs, plays a crucial role in binding with biotech drugs.

![Fig. 1](A) The structure of the cytocleavable dimethylaminoethanol (DMAE)-PRX. (B) Schematic illustration of supramolecular polyplex formation between siRNA and DMAE-PRX and the cytoplasmic release of siRNA through the cleavage of terminal disulfide linkages by intracellular glutathione (GSH). (Reprinted from ref. [25], copyright ©2012, with permission from The Elsevier)

Recently, star-shaped CDPs have also attracted much attention because of their adjustable properties such as solubility, topology, and temperature- or pH-sensitivity. These properties could be manipulated by parameters such as the block composition, molecule weight, and arm-numbers. The star-shaped polymer possesses the following characteristics: 1) good solubility and low melt viscosity, 2) attachment of a large number of functional groups. Therefore, star-shaped polymers based on CDs have exhibited excellent physicochemical properties. Some star CDPs could prolong the circulation time in mice, without provoking inflammation in major organ tissues. In addition, star CDPs develop pharmacokinetic advantages at resisting nonspecific protein adsorption compared to linear grafts. Meanwhile, their diameters are relatively stable because their branches are covalently bonded. Furthermore, the size correlation between the polymer chain length and the type of CDs was considered a significant issue in the formation of the inclusion complex with different physicochemical and biological properties.
3. CDPS IN THE DELIVERY OF BIOTECH DRUGS

3.1 Gene Delivery

Gene therapy is a very promising field of research. However, if the therapeutic injections were applied directly, the naked gene (siRNA or DNA) would be cleared quickly by the body. Thus, many gene vectors, including polymers, have been designed for the delivery of genes. For example, after the breaking discovery of RNA interference, an endogenous mechanism for sequence specific regulation of gene expression via short interfering RNA (siRNA) was explored for a period. Researchers have pursued the design of nanocarriers that can mediate safe and effective gene delivery. Among them, CDPs used for gene delivery showed great progress in cancer and other fatal disease therapy. M.E. Davis performed pioneer work using CDPS for gene delivery. The synthetic strategy was based on the polycondensation of difunctionalized CD monomers in which two hydroxyls have been replaced by segments and cationic difunctionalized co-monomers, to form a linear polymeric chain with alternating CDs and cationic units. Apart from the inherent properties of CDs as nanometric vectors, the capability to improve drug bioavailability has been suggested to benefit from two additional features: 1) capability for cell membrane endocytosis and 2) ability to stabilize biomolecules in physiological media. CD interaction with biological membranes gives the desirable properties, because the lipophilic CD derivatives can alter lipid distribution in vivo and affect cell signaling through the alteration of lipid raft systems.

Other CDPs were also investigated by synthesizing repeated CDs based on six methylene units, which could reduce toxicity, serve as sites for further modification, and provide the positive charge needed to condense anionic nucleic acids. The polymer protected the nucleic acid from nuclelease degradation and disassembly at physiological physiological salt concentrations. Meanwhile, the polymer caused minimal erythrocyte aggregation and typically was used in vivo. Polymer-based nucleic acid nanoparticles are primarily assembled via entropically driven polyionic condensation. They are relatively easy to formulate with siRNAs. Much effort has been devoted to manipulate the properties of pre-existing gene transfecting polymers by attaching CDs. Since many early gene delivery formulations used commercially available cationic polymers, the effective ones could be chemically manipulated to enhance their delivery efficiency, reduce their toxicity, or to furnish them with additional capabilities. One widely studied cationic polymer for siRNA delivery is PEI. However, the high molecular weight PEI has failed to progress clinically due to its cytotoxicity and in vivo instability, especially during physiologic systemic administration. In this regard, it is not surprising that its properties are sub-optimal for gene delivery. Finally, oligoethylenimine (OEI) caught the attention of researchers, and a type of OEI-CDP was developed. It not only retains the high gene-delivery efficiency of PEI, but also the CD subunits allow targeting molecules to be attached via non-covalent bonds with strong inclusion of hydrophobic alkyl chains linked to the ligands, further enhancing the transfection. It has been verified that OEI-CDPs are essentially nontoxic to cells at concentrations optimal for gene delivery and mediate higher gene expression than unmodified PEI. The OEI-CD transfected DNA is internalized by binding membrane-associated proteoglycans. The endocytic pathway of the OEI-CD particles is caveolae- and clathrin-dependent with both pathways converging to the lysosome. The intracellular fate of the OEI-CD provides visual evidence that it can escape from the lysosome.

The OEI is also used to synthesize star-shaped cationic polymers containing a β-CD core and multiple branched OEI arms with conjugated hyaluronic acid (HA). HA specifically binds to its cell surface receptors to regulate cell proliferation and movement. The polymer could fully inhibit the migration of pDNA on agarose gel through formation of complexes with pDNA. In particular, CD-containing polymeric carriers have the advantage of being able to deliver hydrophobic drugs and genes simultaneously through inclusion complexes between hydrophobic moieties of the drugs and CD moieties. It is now well documented that both hydrophobic benzyl groups and the CD moieties contribute to the nano-assembly of PEI-grafted β-CDs and poly(β-benzyl-L-aspartate) (PBLA). (Figure 2) The β-CDs–PEI/PBLA assemblies delivered dexamethasone (DMS) as a hydrophobic drug and DNA in an osteoblast cell line. It was found that a slight increase in transfection efficiency was obtained for the delivery system compared to the counterpart without DMS due to the increased nuclear translocation. In addition, the CDs provide multiple sites to form the reticulate structure, as there are many radical hydroxides. For example, the
complex self-assembled with (2-hydroxypropyl)-b-CDs and (2-hydroxypropyl)-c-CDs cross-linked by the cationic OEI polymer via a facile synthetic route. Both complexes showed lower cytotoxicity and higher transfection efficiency. Meanwhile, OEI-β-CDs with N-succinimidyl-3-(2-pyridyldithio) propionate as a linker were coupled to CY11 peptides, which had been proven to combine especially with fibroblast growth factor receptors on cell membranes. It was shown that the polymer possessed less cytotoxicity and more efficient gene delivery capabilities than PEI-CDs.

The co-delivery of medicine and genes has become a valid strategy in cancer and other disease therapy in recent years, because cytotoxic chemotherapeutic agents primarily affect the dividing cells and cause apoptosis, and genes further induce additive cell apoptotic effect and/or increase the sensitivity of cancer cells to chemotherapeutic agents, thus synergistically increasing therapeutic efficacy. A multifunctional, bioreducible and synergistic co-delivery system for the p53 gene was developed for cancer therapy. This was accomplished by preparing a supramolecular self-assembled inclusion complex from a star-shaped cationic polymer with γ-CD core, multiple OEI arms, and folic acid conjugated via a disulfide linker. The inclusion complex was formed by the hydrophobic cavity of the γ-CD core. Folic acid was readily released under reductive conditions. The results showed that the folate-targeted function induced higher gene transfection efficiency in the folate receptor-positive human oral squamous carcinoma cells. The redox-sensitive disulfide linker in the self-assembly system led to the detachment of the folate groups from the carrier after the folate receptor-mediated endocytosis (Figure 3).

It is essential for CDPs to efficiently assemble through host-guest interactions in supramolecular nanotechnology. Supramolecular approaches utilizing CDs can expand the design and applications of functional biological delivery systems. Owing to good inclusion ability, they are commonly used in the construction of supramolecular structures. The interaction between CDs and the guest moiety imparts new attributes to the nanosystems from the functional groups of the guest molecule, such as adamantyl (Ada)-PEG for coating protection and Ada-prodrugs for gene delivery. Controlled release by application of responsive structures can be triggered by the host-guest interaction. Along with the binding selectivity and controlled release, the host-guest nanoparticles show enhanced efficacy in gene delivery systems.

The advantage of the Ada-PEG guest is exploited by various nanocarriers in the delivery of biotech drugs. For example, Ada-PEG was imported to a star shaped cationic polymer consisting of functionalized polymeric component grafted β-CDs to obtain a supramolecular pseudoblock polycation. A nanoparticle is formed by conjugation of p53 plasmid DNA to the polycation and then coated with PEG for serum stability. The Ada-PEG coating reduces the polymer toxicity and improves the gene transfection efficacy. The different cationic β-CD derivatives to Ada-coated dendrimers or different cationic Ada-end derivatives to β-CDs-containing polymers can modulate the surface charge. To stabilize the CDP-siRNA nanoparticles and prevent protein-induced aggregation in serum, a steric stabilizing Ada-PEG component was added by non-covalent interaction with surface accessible CDs on the CDP-siRNA nanoparticle. It was demonstrated that these two groups stabilize the CDP-siRNA nanoparticles in serum and keeps the particle size constrained to 60-80 nm irrespective of siRNA concentration. The poly β-CDs/Ada5/DNA polyplex added to an adamantane derivative presenting an imidazole group showed an efficient transfection system. This compound improved the transfection most likely by increasing the endosomal escape of DNA. This is supported by the fact that Ada5 successfully replaced the fusogenic peptide JTS-1 in the delivery system. Burckbuchler et al. used the characteristic technique of surface enhanced Raman spectroscopy to verify the interaction among the CDs/Ada/DNA. This method provides an alternative and accurate way to study the DNA compaction by probing the external accessibility of the nucleic acid residues inside the structures.
poly(2-(dimethylamino)ethyl methacrylate) (pDMAEMA) (Figure 4), which can be linked to a β-CD core with bio-reducible disulfide bonds (β-CDs-SS-pDMAEMA). The guest polymer is an adamantyl-end-capped adamantyl-poly(2-methacryloyloxyethyl phosphorylcholine) (Ada-pMPC). Therefore, CDPs and Ada-pMPC could self-assemble to form a supramolecular copolymer, providing the polyplex nanoparticles with high extracellular stability and protein resistance due to the shielding effect of pMPC, as well as high efficiency of cellular internalization due to the membrane-mimic structure of pMPC. Once internalized into the cytoplasm, the payload gene can be readily released because the disulfide bonds are broken by the intracellular reductive environment. The octa-arginine (CDR) modified dextran gene vector with pH-sensitivity was developed via host-guest interactions. The α-CD was modified with CDR, which had excellent cell-penetrating ability. Dextran was selected as a backbone and modified with azobenzene as guest units by acid-labile imine bonds (Az-I-Dex). The dextran shell of CDR/Az-I-Dex/DNA polyplexes improved the stability under physiological conditions. They had higher cellular uptake efficiency than PEI/DNA polyplexes, which was confirmed by an endosomal escape agent could not improve the transfection of CDR/Az-I-Dex/DNA polyplexes. Thus, the polyplexes coated with polysaccharide have good endosomal escape ability for non-viral gene delivery carriers.

Fig. 4 Schematic drawing of polymer grafts that rupture the endosomal membrane and release the loaded siRNA cargo into the cytoplasm. (Reprinted from ref. [76], copyright ©2015, with permission from The American Chemical Society)

We have also synthesized a type of cationic star polymer with 21 arms (21ACSPs) through atom transfer radical polymerization (ATRP) using a β-CD initiator with 21 initiation sites. It was found that a co-solvent of 1-methyl-2-pyrrolidione and water (1:1) could facilitate the reaction, resulting in a well-controlled living polymerization. It showed that 21ACSPs have the ability to condense the plasmid DNA to 80–180 nm. 21ACSPs with tertiary amino groups exhibited higher cell transfection efficiency than 21ACSPs with quaternary ammonium groups. The influence of arm number and length on gene delivery was further demonstrated by in vitro cell experiments.

3.2 Protein delivery

Peptide/protein drugs have macromolecular size and high bioactivity. However, the stability, denaturation, and stereostructure deformation of these drugs are issues that still need to be addressed. As the human body is a huge physiological chemical system, the enzymatic and physiochemical function will damage the amino acid sequence of peptide bonds as well as influence the secondary structure. Thus, although peptide/protein drugs have high activity, the short biological half-life in vivo is still a severe problem.

Peptide and protein drugs need to maintain their integrity when passing though the gastrointestinal tract. The oral route exposes protein and peptide drugs to highly active enzymatic conditions, often preventing them from reaching the target site to cure or eliminate pathologic tissues. Meanwhile, their absorption is also hampered by enterocytes via the aqueous phase because of the large molecular size. In addition, with the exception of intravenous delivery, systemic deliveries often cannot permeate the cell layer, preventing absorption. Proteins are charged, large, and hydrophilic, making their bioavailability exceptionally poor. Therefore, it is often necessary to add enhancers to the protein formulation. In developing protein and peptide drugs, an intelligent selection of additives, which can enhance their absorption across membranes and their stability, is essential.

CDs have the potential to enhance the absorption of proteins because of their ability to reduce physical or metabolic barriers to the proteins. Proteins exhibit special activity due to their three dimensional structure and conformation. Therefore, CDs with protein nanoparticles seem to be a promising system for improving oral biotech drug delivery. The research demonstrated that the inclusion of CDs could improve the thermal stability of bovine insulin by decreasing unfolding in solution. It also showed that CDs increase the encapsulation efficiency of insulin and improve uniformity of the microcapsule formation. Thus, the drug molecule combined with appropriate CDPs will improve the drug solubility and dissolution rates and protect them from degradation, allowing release at the target site. On the other hand, CDs are also used to correct the protein folding problems during carrier development. In fact, various approaches have been investigated to promote oral peptide delivery, such as chemically modified peptide drugs, an absorption enhancer, and a protease inhibitor to protect drugs against enzyme degradation and liposomes.
Thus, the CD inclusion compounds improve the bioavailability by allowing more efficient permeability of the biological membrane and increased proportion of macromolecular drugs that pass through biological barriers. Poly(D.L-lactide-co-glycolide) (PLGA) and poly(lactic acid) (PLA) are approved biocompatible and biodegradable polymers that have been extensively studied. The vectors of optimal hydrophobic-hydrophilic balance must be considered for the controlled delivery of drugs. Thus, the modifications of the polymers have been proposed in which star-branched PLGA-β-CD nanoparticles resulted in maximum loading efficiency (95%) with minimal particle size (e.g., 120-350 nm) that also displayed the slowest drug release profile. Additionally, biodegradable nanoparticles were prepared from PEG-PLGA and PLGA by both solvent evaporation and solvent diffusion methods with inclusion of ionic additives of negative charge sulfobutyl ether-β-CDs (SB-CDs). The inclusion has also led to the formation of smaller sized nanoparticles. Isothermal titration microcalorimetry verified the interaction between dalargin and SB-CDs. Polylactide is another biodegradable copolymer used as a protein delivery carrier, which was coupled onto mono[6-(2-aminoethyl) amino-6-deoxy]-β-CDs to obtain the amphiphilic polymer. They connected with two CD units so that their cooperative binding effect toward guest molecules showed the desired effect. The complex stability study indicated that CD dimers bind to bovine serum albumin better than CDs because of the cooperative binding effect of two adjacent hydrophobic cavities.

Accordingly, hydrogels are three-dimensional hydrophilic networks that have a wide variety of pharmaceutical and biomedical applications. In particular, hydrogels provide an excellent opportunity for use as a protein releasing system in most vectors, due to their high water content, appropriate biological compatibility with proteins, and controlled release kinetics. The CDP hydrogels possess some functional groups or structures for controlled release of the protein. For example, a self-assembling hydrogel inclusion complex with 8-arm star shaped PEG was modified with β-CDs functionalities via a hydrolytically cleavable succinyl linker. Moreover, the mechanical properties of this gel system are easily controlled by various parameters, such as temperature, polymer concentration, β-CDs stoichiometry, or the use of different architectures of polymer. Therefore, star-shaped poly(e-caprolactone) using a tetrahydroxyethyl-terminated porphyrin as a core initiator was designed. The α-CDs played a role in adjusting the hydrophobicity-hydrophilicity balance and the crystallinity of the PCL backbone. It was shown that PEO/PPO star copolymers as α-CD core with different architectures showed outstanding properties for bovine serum albumin delivery. This indicated that the release of substances from these gels was dominated by the erosion of the gel matrix. Despite being dependent on the hydrogel composition, the hydrogel surface dissolution also substantially controls the release of proteins from the gels, which results in continuous, nearly zero-order release patterns of entrapped proteins. In addition, carrying out the in vitro release with smaller diameter leads to a prolonged release profile and decreased the rate of release. The variation of protein concentration does not produce observable difference in the rate of release, leading to the conclusion that erosion of the gel surface seemed to be the dominant factor for release of the proteins into the buffer solution via enzymolysis. The PEGylated insulin/γ-CDs PRX displayed a significantly higher resistance to proteolysis. This indicated that the PRXs could be formed with randomly PEGylated insulin and work not only as a sustained release system, but also as a stabilizing agent to enzymatic degradations of PEGylated insulin.

Moreover, the light-controlled release of proteins could build blocks of a supramolecularly cross-linked hydrogel. The inclusion complexes dissociate upon trans–cis isomerization of the azobenzene (AB) after irradiation with UV light (365 nm), resulting in dissolution of the hydrogel (Figure 5). Furthermore, proteins can be physically entrapped in this supramolecular gel matrix simply by dissolving it into the polymer solutions before the gel preparation. Using green fluorescent protein (GFP) as a model protein, the light-controlled in vitro release was demonstrated.

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**Fig. 5** (a) Preparation of azobenzene modified dextran (AB–Dex) and CD modified dextran (CD–Dex) through the thiol–maleimide reaction. (b) Schematic representation of photoresponsive protein release from the gel composed of trans AB–Dex and CD–Dex. (Reprinted from ref. [102], copyright ©2010, with permission from The Royal Society of Chemistry)
glycidyl methacrylate monomer (GMA) onto gelatin in the presence of ammonium ceric nitrate as an initiator. Immobilization of β-CDs onto the hydrogel was then carried out. The polymer release profiles were established separately in both enzyme-free simulated gastric and intestinal fluids showing the desired result. Another structure of triblock copolymers is also used for the protein delivery. A supramolecular hydrogel based on biodegradable PCL-PEG-PCL triblock copolymers and γ-CDs was prepared through inclusion complexation as an injectable, sustained release vehicle for insulin. The unique advantage of preparing a drug-loaded gel is that the drug can be easily encapsulated during sol-to-gel transformation and it is a suitable system for providing sustained release of therapeutic proteins, with desirable flow behavior.

4. CONCLUSIONS AND PERSPECTIVES

Multifunctional CDPs have been developed for the delivery of biotech drugs such as gene and protein. With their delicate design and well-controlled manipulation, the CDP-based systems have exhibited unique characteristics and excellent properties such as good protection against degradation, prolonged in vivo circulation time, and targeted delivery. Introducing CDs into supramolecular polymeric platforms can also enhance the biocompatibility, functionality, flexibility, and recognition capability for both the biotech drugs and the therapeutic targets. Recent advances in this field take full advantage of host-guest interactions and other noncovalent forces by utilizing CDPs. Nevertheless, most of these novel studies are still in the concept stage, and only a few of them have been comprehensively applied. The successful translation of these laboratory innovations to clinical reality remains challenging. For future practical biomedical applications, more intelligent designs of CDPs with more biological functionalities, as well as more detailed investigation are needed.

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