Recent Advances in Host–Guest Self-Assembled Cyclodextrin Carriers: Implications for Responsive Drug Delivery and Biomedical Engineering

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This Review is an overview of the unique characteristics of cyclodextrin in forming an inclusion complex via host–guest noncovalent interactions. The modification of cyclodextrin advances its application as a pharmaceutical solubilizer, fabrication of functional molecular machines such as polyrotaxane, polypseudorotaxane, and polycatenanes and grafting of cyclodextrin with different linear, branched chain polymers. The different stimuli-based supramolecular assemblies involving cyclodextrin as a key mediator with linked triggering responses on payload release is highlighted. In addition, the applications of cyclodextrin in diagnostic imaging and medical devices is briefly demonstrated. Cyclodextrin is a relatively low cost, biocompatible, biodegradable, and highly explored material with low toxicity for drug formulation, drug delivery, and wide varieties of other biomedical applications such as those in medical devices fabrication, biosensor, tissue engineering, and bio-imaging. The toxicological profile of cyclodextrin is well established and safe for human consumption in food and medicine.

1. Introduction

Cyclodextrin (CyD) is a cyclic polysaccharide obtained from starch by enzymatic hydrolysis with three native forms, αCyD,

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βCyD, and γCyD containing of six, seven, and eight glucopyranose units. Cyclodextrin is the truncated cone with an inner hydrophobic pocket and outer hydrophilic exterior. The inner diameters of hydrophobic cavities are 4.7–5.3, 6.0–6.5, and 7.5–8.3 Å for α, β, and γCyD respectively. It has been an attractive material for various pharmaceutical applications as it has a hydrophobic core to load various hydrophobic drug molecules by forming complexes.[1] Over the past few years wide interest in cyclodextrins has grown and it was explored for its application in the pharmaceutical, food industries, as well as biomedical applications (drug delivery, theranostics, tissue engineering, fabrication/coating of medical devices, biosensors/bio-imaging applications).[2]

Structurally, cyclodextrin is a truncated cone-like structure with an inner hydrophobic environment that usually accommodates the small hydrophobic molecules and even a small portion of the polymeric structure by noncovalent interactions. The exterior portion of the cavity is made from the hydroxyl group which is not only responsible for aqueous solubility but also allows the hydroxyl group to interact with the hydrophilic component and make the hydrophobic drug into a water soluble complex.[3] It has been used from many decades as a pharmaceutical solubilizer to improve the solubility profile of BCS class II drugs (low solubility, high permeability) to improve the pharmacokinetics of the drugs.[1a] Nowadays, there are various derivatives of cyclodextrin which have been investigated for pharmaceutical, biomedical and other applications. Cyclodextrin forms the 2D and 3D supramolecular architecture with linear and branched chain polymeric and inorganic material (hyaluronic acid, chitosan, alginate, hydroxyapatite, calcium phosphate) that facilitate the cell differentiation, improve the biocompatibility of native material, additional crosslinking by covalent bonding and improve viscoelastic properties required for the regeneration of cells and tissues (**Figure 1**).[4]

Cyclodextrin is a highly safe material for animal and human administration as indicated by Food and Drug Administration (FDA) approval. Various reports and the FDA suggest that it does not elicit any immunogenic response and has a low toxicity profile.[1a] The aqueous solubility of native cyclodextrin, α, β, and γ are 13%, 2%, and 26% w/w, respectively. Low

solubility of βCyD (18.8 g L^{-1} or 16.6×10^{-3} M) is due to the strong interaction of inner hydrogen bonding formation among the secondary hydroxyl groups. The modification of βCyD can cause the disorganization of this strong hydrogen bonding that results in improved water solubility such as hydroxypropyl-βCyD which has an aqueous solubility of 60% (w/w) compared to native βCyD at 2% (w/w).[5]

2. Cyclodextrin Chemistry

2.1. Host–Guest Interactions: Inclusion Complex Formation

In the aqueous environment, the cyclodextrin cavity has a slightly nonpolar nature which is not favored by the presence of water molecules around in terms of energy (polar–nonpolar interaction) and this can be spontaneously replaced by suitable guest molecules having less polar than water molecules. The cyclodextrin dissolved in water acts as a host moiety that can accommodate the appropriate guest molecules and this inclusion complex formation is driven by the replacement of the high enthalpy water molecules. In this inclusion complex phenomenon, more than one cyclodextrin moiety can participate by entrapping one or more guest molecules, the most common one being the 1:1 complexation phenomenon. However, sometimes a more complex phenomenon does exist such as 2:1, 1:2, 2:2, or even a higher magnitude of complexation with more stable, crystalline compound. Once, dissolved in an aqueous media, they immediately established the equilibrium among dissociated and associated molecular species that can be expressed by the complex stability constant Ka. The association of CyD molecules and guest molecules, considered as D is governed by the thermodynamic equilibrium as presented in **Figure 2**.[6]

Various factors affect the inclusion of complex formation with CyD. Several instrumental techniques were used by the researcher to understand the thermodynamic of CyD complexation, but due to the inconsistent nature of the complexation phenomenon, there is no standard rule for the inclusion of guest molecules. The hosting of guest molecules in the cavity is mainly influenced by the molecular size of guest molecules, presence of hydroxyl and methylene group on an aliphatic chain, aromatic ring size, hydroxyl group position on the ring, conformational flexibility and chirality of guest molecules.[7] Moreover, the complexation is also affected by the solvent used for the preparation of complex such as water, hydro-alcoholic or pure organic solvent.[8] Hence, it is challenging to classify the guest molecules based on structural origin to predict the inclusion complexation phenomenon. The penetration of guest in CyD cavity is not consistent and reproducible although guest molecules exhibit a structural resemblance or class of compound that belong to same structural family.[7]

Inclusion complex formation at molecular level can be investigated using various spectroscopic techniques. Wankar et al., 2017, examined the inclusion complex formation of guest, ethionamide in β-cyclodextrin polymer as host moiety. Ethionamide is a nonchiral molecule so does not a have an intrinsic circular dichroism signal but, when ethionamide forms the inclusion complex with β-cyclodextrin polymer, it exhibits the induced circular dichroism signal which confirms the inclusion

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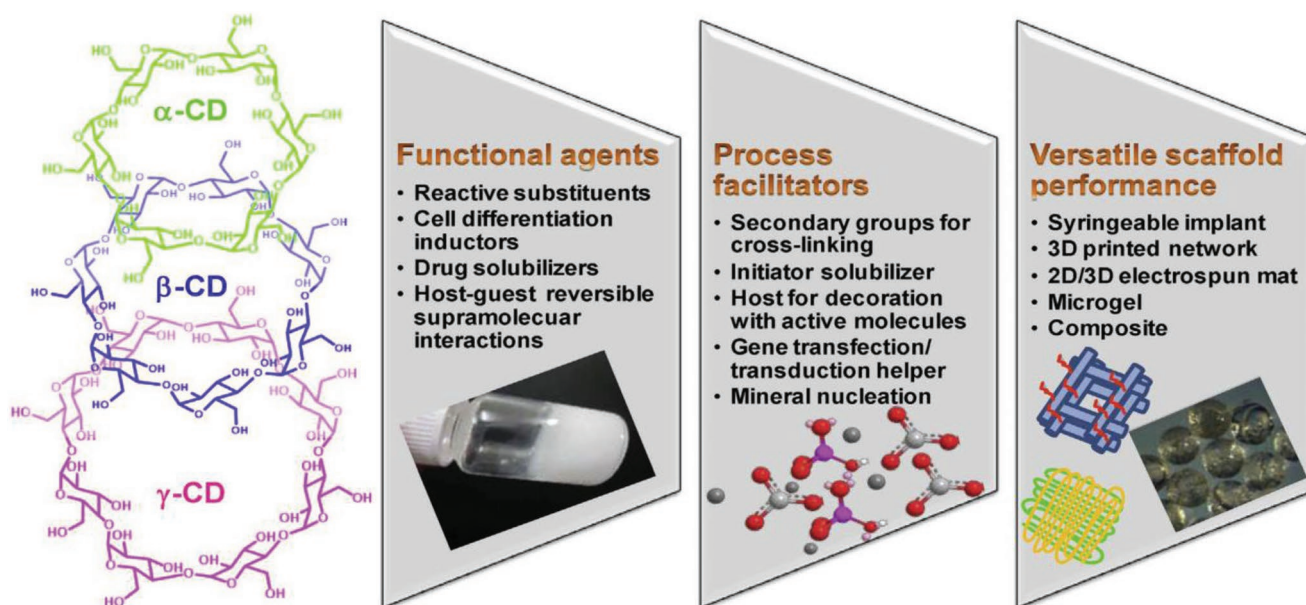
Figure 1. Role of cyclodextrin in regenerative medicine, Reproduced with permission.[4] Copyright 2017, Elsevier B.V.

complex formation shown in (**Figure 3**B).[9] Salzano et al., 2017 used fluorescence spectroscopy to study the inclusion complex formation via host (booster BDM43266) guest (β-cyclodextrin) interactions. The decrease in intrinsic fluorescence of

booster BDM43266 with 24 nm blue shift was observed upon complexation. The authors performed global analysis of the fluorescence spectra to calculate the equilibrium binding constant considering 1:1 complexation as shown in (Figure 3B).[10]

Figure 2. Host–Guest interaction of CyD with model drug molecule with magnitude of 1:1, 1:2. Reproduced with permission.[6] Copyright 2004, Springer Nature.

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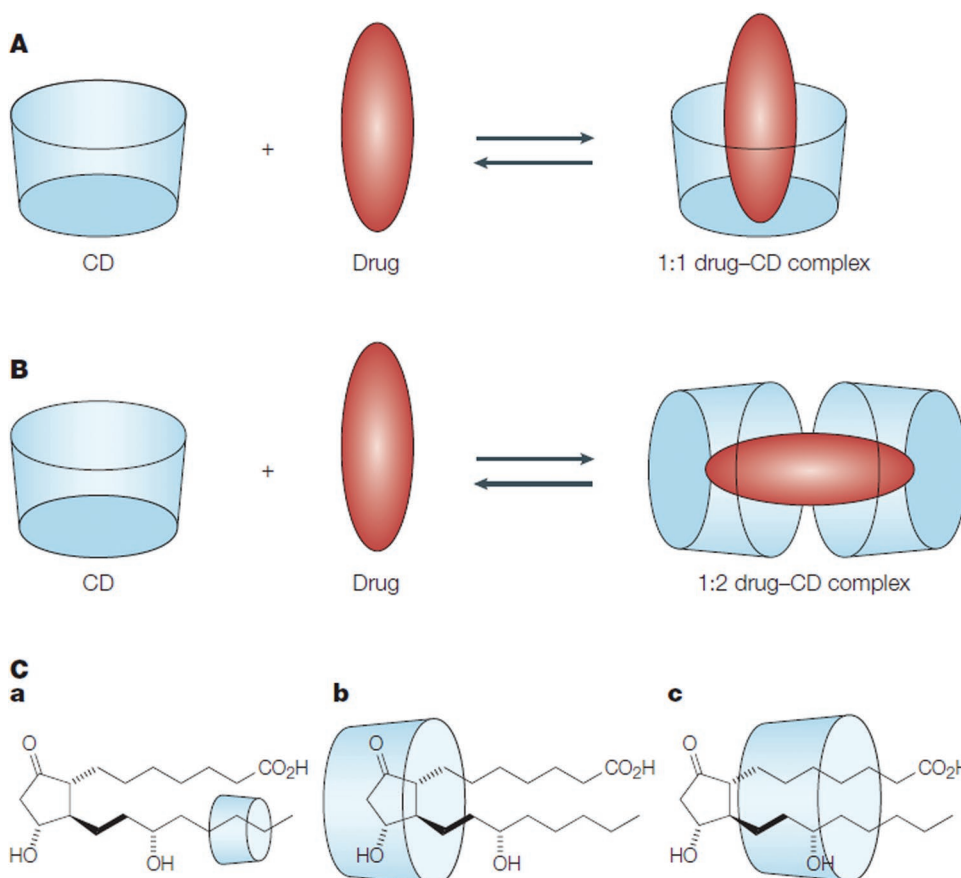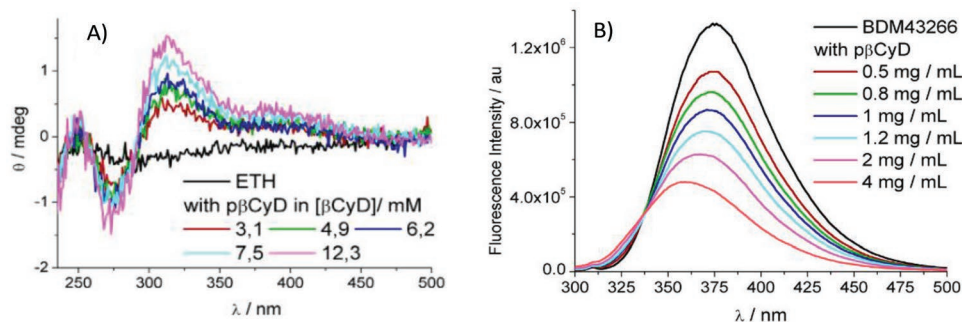
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Figure 3. Spectroscopic technique to study host–guest interaction. A) CD spectra provide information about ethionamide complexation with PβCyD. Reproduced with permission.[9] Copyright 2017, Elsevier B.V. B) Fluorescence spectra provide information about BDM43266 complexation with PβCyD. Reproduced with permission.[10] Copyright 2017, Elsevier B.V.

Hendy and Breslin, 2011 have investigated the complexation of dopamine (guest) and sulfated cyclodextrin (host) using ultraviolet (UV) and nuclear magnetic resonance spectroscopy (NMR) spectroscopy where they confirmed that the aromatic group of dopamine fits into the hydrophobic cavity based on the data obtained from spectroscopic techniques.[11]

Several spectroscopic techniques can be used to investigate the inclusion complex formation. In UV spectroscopy, the change in spectrum increase or decrease in absorption intensity with varying concentrations of host moiety can give information about the complexation of the guest molecules with the host. Similarly, in circular dichroism the induced CD signal will provide the information about the inclusion complex formation between host and guest lacking the intrinsic CD signal. Fluorescence spectroscopy can provide the information about the inclusion complexation by recording the change in fluorescence spectra and intensity. Fluorescence lifetime techniques reveal details about inclusion complexation by measuring the fluorescence lifetime of each species such as host, guest, and complex species. In NMR spectroscopy, the chemical shift of complexed species can be easily distinguished from that of host and guest molecules. There are several other spectroscopic techniques available for the inclusion complex formation that can be utilized based on the characteristic of the host and guest moiety.[12]

The host–guest inclusion complex formation is a dynamic process and assessment of the association and dissociation of guest molecules is difficult. There are no gold standard techniques that can provide complete information about the CyD–guest inclusion complexes. Generally, simultaneous estimation is performed using different analytical techniques to measure the variation outcome to understand the noncovalent interaction involved in the complexation phenomenon at a deeper level. The reliability of the method often depends upon the properties of the guest molecule (chirality, intrinsic fluorescence), CyD inner cavity diameter, and solvent effect. Each method has its pros and cons and the selection of the method requires in-depth knowledge about the chemistry involved in inclusion complex formation. So far, NMR has helped in the understanding the inclusion complex formation in solution. However, other spectroscopic techniques such as UV, CD, and fluorescence spectroscopy in combination with isothermal calorimetry, capillary electrophoresis (CE) and high-performance liquid chromatography (HPLC) can provide in-depth information about the noncovalent interaction and CyD–guest complexation.[13]

3. Modification of Cyclodextrin

The cyclodextrin consisting of the glucopyranose unit has a primary hydroxyl group at sixth position and secondary hydroxyl groups at second and third positions. The intramolecular hydrogen bonding of secondary hydroxyl groups (2- and 3-position) with an adjacent glucopyranose unit imparts the rigidity to cyclodextrin which ultimately creates the rotational hindrance of secondary hydroxyl groups whereas primary hydroxyl groups are freely movable. This factor causes the reduction of inner diameter cavities at the primary sides of CyD. The chemical modification of CyD was influenced by two important factors; the nucleophilic nature of hydroxyl group; and the complex formation behavior with a chemical reagent used. The three types of hydroxyl groups present on CyD, the 6-position hydroxyl group is basic in nature; the 2-position hydroxyl group is acidic in nature; while the 3-position hydroxyl group is inaccessible for chemical modification. Hence, in the normal reaction condition, the 6-position hydroxyl group is the favored one and is easily involved in a reaction where electrophile can attack. To a certain extent, electrophile can also attack at any other position, hydroxyl groups (2- and 3-) which are less favored.[14] More than 40% percent of compounds in drug discovery suffer from drug development issues due to the low aqueous solubility; some compounds suffer from photostability and some have a bad taste problem. Cyclodextrin has become a material of choice to solve the solubility, photostability, and bad taste problems. The native βCyD has limited pharmaceutical application due to its low water solubility although it has an effective inner diameter for the inclusion complex formation with small molecules. In the cyclodextrin development, creating water-soluble cyclodextrin was a major point of interest. Hence, various CyD derivatives were developed with an enhanced water solubility profile of native cyclodextrins. The first commercial pharmaceutical product based on cyclodextrin complexation was introduced in Japan in 1976; prostaglandin E2/βCyD (Prostarmon E sublingual tablets). After a decade, in 1997 the European Union marketed Piroxicam/βCyD product (Brexin tablets) and the first USA approved product is Itraconazole/Hydroxypropyl βCyD oral solution (sporanox). Currently, worldwide, 35 different cyclodextrin-based drug formulation are available in solid and solution forms for human use.[15]

4. Role and Importance of Cyclodextrin-Based Functional Polymers

Cyclodextrin-based functional polymer has been developed to enhance drug encapsulation, biodegradability, and host–guest interaction. Soluble CyD has gained huge attention in drug delivery and biomedical engineering due to the availability of a greater number of cyclodextrin units for the complexation with guest molecules.[16] As stated before, βCyD has a favorable cavity size for the encapsulation of large number of drug molecules; however, its low aqueous solubility hinders drug delivery applications. To resolve this issue, associated with βCyD, modified form, HP-βCyD was introduced to improve the solubility, encapsulation efficacy profile of βCyD. Renard et al., 1997 have demonstrated the fabrication of βCyD polymer by polycondensation of the CyD unit using the bifunctional crosslinking agent, epichlorohydrin, which has been widely explored for the drug delivery applications.

Epichlorohydrin crosslinked cyclodextrin create the polymer a having molecular weight of around less than 100 kDa. Each cyclodextrin unit has more than 18 hydroxyl group which participate in the formation of hydrogen bonding with guest molecules. The guest containing electrophilic group donates its electron to the nucleophilic hydroxyl that group results in formation of a hydrogen bond association between host CyD and guest molecules.[8,17] Certainly, this polymer shows the synergic action and behaves better in dissolving the hydrophobic drug than the native CyD form.[18] Cyclodextrins has molecular cavity sizes ranging from 4.7 to 8.5 nm with cavity

volume of 0.10–0.20 mL g^{-1}. It was assumed that mostly small molecules of aliphatic and aromatic structures interact very well with CyD inner cavity and outer rim of hydroxyl groups.[19] As per BCS classification, the drug that belong to BCS-II and IV classes suitable candidates for the molecular encapsulation in CyD.[20] The large molecules such as protein drugs faced the huge challenges of accommodating to the very small cavity of CyD. The Functional group and presence of electric charge on CyDs plays an important role in modifying the physicochemical properties of guest molecules (solubility, stability, taste masking). Cationic CyD interact with anionic drug molecules and vice-a-versa which provide the ionic interaction results in the formation of stable inclusion complex; example, clofazimine has net positive charge at certain pH which interact with negatively charged, SBE-βCyD polymer and form the well compact nanosized complex compared to the SBE-βCyD monomer.[18] The modification of cyclodextrin are explained to improve the solubility of native cyclodextrin and functional modification of CyD are covered in grafting Section 5.4 of CyD which improves the CyD ability to form the inclusion complex by accommodating large payload and the functionalities will provide the additional groups which will interact with guest molecules. Specifically, βCyD polymer is produced by a controlled polycondensation reaction between the βCyD unit and epichlorohydrin. The polycondensation reaction is performed in the sodium hydroxide (NaOH) solution to activate the hydroxyl groups of CyD and epichlorohydrin. The epichlorohydrin reacts with alkoxide groups of βCyD and forms βCyD polymer shown in (**Figure 4**). The reaction should be
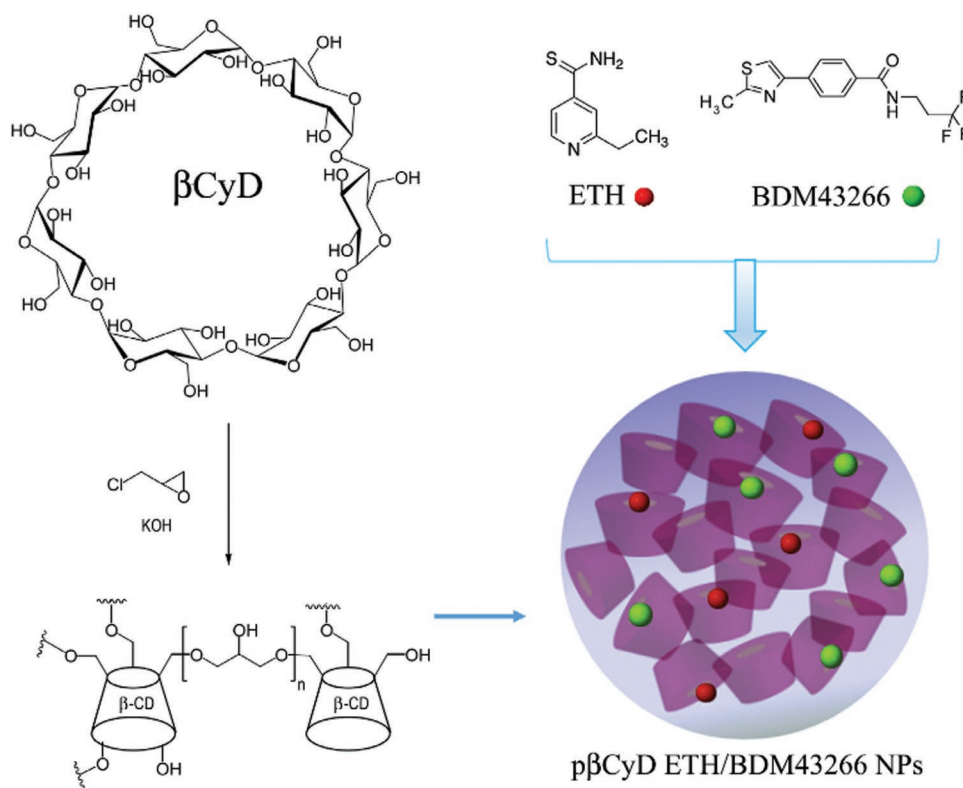

Figure 4. Drug encapsulation in epichlorohydrin crosslinked βCyD Polymer. Reproduced with permission.[10] Copyright 2017, Elsevier B.V.

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performed in controlled conditions to avoid the generation of another polymeric residue. Using this method, several derivatives of CyD such as α, γCyD and sulfobutylether CyD have been explored for the synthesis of their counter polymeric material.[21] Salzano et al., in 2017 studied the co-encapsulation of two therapeutic molecules; ethionamide, and booster molecule in the epichlorohydrin crosslinked βCyD polymeric nanoparticle, and spectroscopic data shows that these two molecules do not compete with each other for binding in the single cavity of cyclodextrin.[10]

The coupling of cyclodextrins with other polymers forms the self-assembled nanoparticle systems by the various methods enumerated in **Table 1**.

5. Cyclodextrin—Polymer Hydrogel/Biomaterials

5.1. Polyrotaxane

Rotaxanes are the mechanically interlocked molecular structures where the ring-like molecules thread into a chain-like structure and dissociation of ring-like molecules can be prevented by attaching a bulky group as a stopper at the end of chain axes. There can be more than one ring- like and chain-like structures present in rotaxane. The most common examples of this interlocked molecular structure are catenanes, rotaxanes, and knots.[39] Over the last two decades there has been high interest in functional material structures because these allow the fabrication of highly sophisticated molecular machine/devices.[40] The ring-like structure and chain-like axes in rotaxane are a ring-slide structure around the axis and not a covalently attached and highly stable structure shown in (**Figure 5**A). The rotaxane is single unit like other monomeric structures and can be polymerized by covalent linking to obtain the polyrotaxane. Several strategies have been explored for the covalent linking of ring to ring, ring to chain, or chain to chain of rotaxane, in which threading of the chain axis is an essential step in the formation of rotaxane. The yield of rotaxane is often low due to the absence of any specific interaction between chain and ring-like structure molecules.[41] Here, CyD performs an essential role in the fabrication of rotaxane due to its intrinsic ability of the host–guest inclusion complex formation via noncovalent molecular interaction with a large variety of the guest molecules. Moreover, cyclodextrins are readily available and easy to functionalize to obtain the rotaxane that has the desired properties. Henceforward, CyD-based rotaxane will have acquired high scientific interest in developing novel material structures for drug delivery and biomedical applications.[42] Li et al., 2006 have shown the fabrication of polyrotaxane based on a cationic PEI-based supramolecular structure for effective gene delivery, where β-CyD grafted oligoethylenimine was used as a ring-like structure. The Pluronic triblock copolymer (MW-2900) and polyethylene oxide were used as a threading polymer for the cyclodextrin ring. The dissociation of βCyD from the polymer chain was prevented using the bulky stopper end, 2,4,6-trinitrobenzene sulfonate (TNBS) which is large enough to entrap the threaded βCyD on the polymeric chain.[43]

5.2. Polypseudorotaxane

Pseudopolyrotaxane is very similar to rotaxanes, in which the system is governed by the noncovalent interactions between cyclic host (mostly cyclodextrin) and linear guest polymer. The pseudopolyrotaxane involved both the noncovalent interactions and the covalent linking that govern its formation.[44] The covalent crosslinking of many axes to different polymers gives the great varieties of supramolecular constructions with CyDs shown in (Figure 5C). Both linear and branched polymers can be used for inclusion complex formation with CyDs.[42] Liao et al., 2010 have used the α-cyclodextrin as a ring molecule and PEG10K as a threading polymer for the fabrication of the photoresponsive pseudopolyrotaxane-based hydrogel that encapsulates the dye, azobenzene. The pseudopolyrotaxane formed shows light responsive behavior upon UV/light irradiation.[45] Wang et al., 2013 have developed pseudopolyrotaxane prodrug micelles using modified αCyD conjugated with doxorubicin and poly (ethylene glycol)-b-poly (2-methacryloyloxyethyl phosphorylcholine) block copolymers intracellular drug delivery of anticancer drug.[46] Adeli et al., 2011 have prepared the pseudopolyrotaxanes using a CyD ring molecule that threads into the polyethylene glycol axes. The dethreading of the αCyD ring molecules from the polyethylene glycol axes was prevented by host–guest inclusion complex formation of end group (PEG) with the bully moiety of β-CyDs modified quantum dots (βCyD-graft-QDs) shown in (Figure 5C). The formed supramolecular assembly was used for targeted delivery of cisplatin tagged with folic acid as a targeting moiety for cancer-targeted cancer therapy.[47] Tong et al., 2016 have utilized hydrazide modified αCyD conjugated with 5-aminolevulinic acid (ALA) and hydrophilic PEG polymer conjugated with a cell-penetrating peptide (R6H4) for the fabrication of pseudopolyrotaxane prodrug micelles with dual pH-responsive properties having efficient photodynamic activity against cancer.[48]

5.3. Polycatenanes

Unlike rotaxane, catenanes are also mechanically interlocked molecular structures in which one or more macrocyclic moieties are interlocked.[49] Catenanes are classified as main-chain, sidechain, connected, radial, and network types shown in (Figure 5B).[50] Higashi et al., 2019 have fabricated the polycatenanes using βCyD and Pluronic P123, in which carbonyldiimidazole and cystamine were used to modify the Pluronic P123 activated PEG–PPG–PEG dithiol. In the formation process, oxidizing agent, H_2O_2 was used to oxidize the thiol groups of PEG–PPG–PEG dithiol that cyclize disulfide bond formation results in the creation of polypseudorotaxane (polycatenanes). The polycatenanes obtained can be an advanced material for drug delivery and biomedical applications.[51]

5.4. Cyclodextrin Grafting Based Systems

Cyclodextrins have been explored for enormous grafting systems because of the unique ability of host–guest inclusion complex formation. CyDs are used for the grafting with

Table 1. cyclodextrin-based nanoparticulate system for drug delivery.

Preparation techniques	Guest	Host	Purpose	In vitro and in vivo studies reported	Major findings	Ref
Co-lyophilization and nanoprecipitation	Camptothecin	6-O-Capro-βCyD and βCyDC6.	To compare the CyD and polymeric nanoparticles poly lactic-co-glycolic acid (PLGA) and polycaprolactone (PCL) NPs for Camptothecin delivery for cancer	Effect on L-929, mouse fibroblast and MCF-7 human breast adenocarcinoma cell lines	Increased stability, drug-loading with that offer the control release up to twelve days and promising anticancer efficacy compared to PLGA and PCL nanoparticles	[22]
Epichlorohydrin cross-linked SBE-βCyD polymers form self-assembled nanoparticle in water	Clofazimine (CLZ)	SBE-βCyD and 6-deoxy-6-[(5/6) rhodaminyl-thioureido]- β-cyclodextrin (Rho-βCyD), and rhodamine-labeled sulfobutylether β-cyclodextrin oligomer (Rho-SBE-pβCyD)	To improve the efficacy of clofazimine using SBE-βCyD nanocarrier to treat infection caused by Gram-positive bacteria such as *Staphylococcus epidermidis*, etc.	SBE-βCyD carrier both with and without CLZ does not exhibit cytotoxicity up to 1×10^{-6} M , whereas pure CLZ is cytotoxic at identical concentrations.	SBE-βCyD polymer has molecular weight of 53 kDa with particle size of 20–60 nm. 25 mg mL^{-1} SBE-βCyD polymer dissolve around 0.5 mg mL^{-1} CLZ. Circular dichroism confirms CLZ encapsulation in carrier system. CLZ has IC50 inhibition values less than 100×10^{-9} M against staphylococcus epidermidis and clinical isolates of MDR strains of S. epidermidis	[18]
Oil-in-water (o/w) emulsion solvent evaporation	Paclitaxel	Acetonation of αCyD	pH responsive biomaterial and comparison to PLGA NPs, and PTX	B16F10, Hela, HepG2, MCF-7 and MDA-MB-231, intracellular uptake and immunofluorescence, flow cytometric apoptosis study, acute toxicity and in vivo anticancer investigation.	pH-controlled hydrolysis, increased antitumor activity, biocompatibility, effective drug loading, lower side effects and reversal of the MDR resistant cancer cells	[23]
Nanoprecipitation method	Paclitaxel	Novel amphiphilic CyDs (FCyD-1 and FCyD-2) prepared from TBDMSβCyD	CyD-based targeted delivery against folate positive breast tumors	L929 cells, T-47D, and ZR-75-1 human breast cancer cells	Folate conjugation stability, high loading and higher anticancer efficacy	[24]
Solvent injection technique	Acyclovir	βCyD-poly(4-acryloylmorpholine) mono-conjugate (β-CyD-PACM)	Antiviral activity	HSV-1 (HSV-1 BGM, HSV-1 MRC), cellular uptake study by confocal laser microscopy	Particle size, 150 nm that enhance the antiviral activity and perinuclear accumulation	[25]
Nanoprecipitation technique	Casein Kinase 2 CK2 inhibitor 1-amino-5-isopropyl-5,6,7,8-tetrahydroindeno[1,2-b]indole- 9,10-dione (CM1)	Fluorinated or hydrocarbonated amphiphilic CyDs hexakis[6-deoxy-6-(3 perfluorohexylpropanethio)-2,3-di-O-methyl] αCyD	Controlled delivery of CK2 inhibitors in cancer	Particle size encapsulation and controlled release study	Around 65% drug encapsulation efficiency with prolonged release of the drug over 3 h	[26]
Formed from Tf-PEG-AD conjugate	Adamantane	Transferrin modified CyD	Nucleic acid therapeutics for Cancer	PC-3 (human prostate carcinoma) and K562 (chronic myelogenous leukemia) cells	High receptor binding and effective transferrin receptor-targeted drug delivery	[27]
Emulsion solvent evaporation	Docetaxel	Amphiphilic CyD heptakis (2 Ooligo(ethyleneoxide)-6-hexadecylthio-)-βCyD (SC16OH)	Tumor therapy	Size, zeta potential, drug entrapment, release rate, and degradation rate. hemolysis, cell viability and immunofluorescence Human Caucasian larynx carcinoma epidermoid cells (HEp-2)	Particle size of 95 nm with very small burst effect (7%) and drug release up to 8 weeks. No considerable mortality in cell lines and enhanced docetaxel intracellular activity on solid tumor	[28]
Atom transfer radical polymerization (ATRP) for modified CyD Star copolymer micellar nanoparticles	Doxorubicin	βCyD-based star copolymers covalently conjugated with doxorubicin (DOX), folic acid (FA), and DOTA-Gd moieties (DOTA-Gd)7-CyD-(PHPMA15)14-star copolymer	Image guarded tumor therapy	HeLa cells, in vitro cytotoxicity, characterization and MR imaging experiments, in vivo magnetic resonance imaging (MR) study in rat model	Multifunctional pH-disintegrable micellar nanoparticles, 10%, 53%, and 89% conjugation of DOX at pH 7.4, 5.0, and 4.0, T1 relaxivity (r1 ¼ 11.4 s1 mM1) with localization of micellar nanoparticles in the liver and kidney of rats and significant positive contrast enhancement.	[29]

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Table 1. Continued.

Preparation techniques	Guest	Host	Purpose	In vitro and in vivo studies reported	Major findings	Ref
Ionic gelation mechanism	Epigallocatechin gallate (EGCG)	CSH-SBE-βCyD nanoparticles (CSNs)	Encapsulation of tea phenol	Complex characterization by Job method, fluorescence spectroscopy and NMR Particle size, encapsulation and atomic force microscopy (AFM), Fourier-transform infrared spectroscopy (FTIR)	CSH/ SBE-βCyD mass ratio, CSH and TP concentration can affect physicochemical effect on nanoparticles.	[30]
Ionotropic gelation method	Interleukin-12 (IL-12) pUMVC3-hIL12	chitosan/βCyD (LMW CS/CyD)	Cytokine for antitumor therapy	CT-26 colon carcinoma cell line	Average particle size(171.3 nm), PDI (0.231), Positive zeta potential (34.3), good DNA encapsulation (83.315 %), high transfection ability and low cytotoxicity	[31]
Nanoparticles by spray-drying, freeze-drying, kneading, or lyophilization	Captopril (CAP)	CyDs (α-, β-, and HP-βCyDs)	Hypertension as ACE inhibitor delivery	Characterization by NMR, differential scanning calorimetry (DSC), SEM, FTIR, X-ray crystallography (XRD), size and mean arterial pressure in animals	(CAP/α-CyD:KM) highest degree of complexation (superior to 34%) and exhibits the potent and long-lasting inhibition for 22 h	[32]
NH$_2$-βCyD-carboxymethyl dextran forms NPs and mineralization with calcium nitrate and ammonium phosphate via deposition	Carbonic anhydrase B (CAB)	βCyD (protein-binding moiety) and carboxymethyl dextran (substrate for mineralization)	Sustained protein delivery	FT-IR, thermogravimetric analysis (TGA), transmission electron microscopy (TEM) and energy dispersive X-ray photoelectron spectroscopic analysis and enzyme activity by 4-nitrophenyl acetate (NPA) assay	High loading efficiency (80%) sustained manner for 21 days by mineralized CyD, no loss of enzyme activity	[33]
Emulsion solvent evaporation techniques	Puerarin	(HP-βCyD) and PLGA	Brain injury induced by ischemic reperfusion	Characterization by size, morphology, DSC, XRD, FTIR, release kinetics, activity in middle cerebral artery occlusion/ reperfusion, CT scans, Histology studies	Particle size (165 nm), infarct volume significantly improved 110.7 ± 12.62 vs 84.3 ± 10.51 on the day 7, EEG improvement	[34]
Nanoprecipitation method	Paclitaxel	Amphiphilic CyD, 6-O-CAPRO-βCyD	Tumor	Characterization NMR, FTIR, DSC, and SEM	Nanosphere (150–250 nm), nanocapsules (500 nm), Zeta potentials (18–39 mV), 12-month physical stability, higher drug encapsulation with three-fold increase in loading, prolonged drug release profile for nanospheres (12 h) and nanocapsules (24 h)	[35]
Water-in oil-in-water (W/O/W) double-emulsion	Oxaprozin	Methyl-CyD (RAMEB), βCyD OXA-CyD complexes in PLGA NPs	Inflammation and prolonged release	FTIR, XRD, DSC, TGA, and drug release studies	Percentage drug released at 24 h is 16% (alone drug-loaded NPs), 50% (drug-CyD-loaded NPs) and 100% (drug-methyl CyD-loaded NPs); majorly influenced by presence and types of CyD	[36]
Ionic cross-linking of the polycation by sodium tripolyphosphate	Dye, 6-coumarin	Heptakis (2,6-di-O-methyl) βCyD	To increases the solubility profile of the poorly soluble drug	Caco2 cell lines, fluorescence properties by confocal laser scanning microphotographs, drug release and uptake studies	Particle size influenced by preparative technique, changes from 200 to 300 nm, increased solubility of 1.4×10^{-4} M, modulation of drug encapsulation by CyD and increased internalization	[37]
Solvent displacement technique	Flurbiprofen	(HP-βCyD)	To increase solubility, stability and drug release in the presence of CyD	CLSM studies, cornea hydration tests, in vitro release and ex vivo corneal permeation study of the drug-NSs, ocular tolerance, stability, in vivo Draize test	Reduced burst effect, offering a sustained release profile, transcellular pathway stable at 4 °C. and decreased FB transcorneal permeation by CyD	[38]

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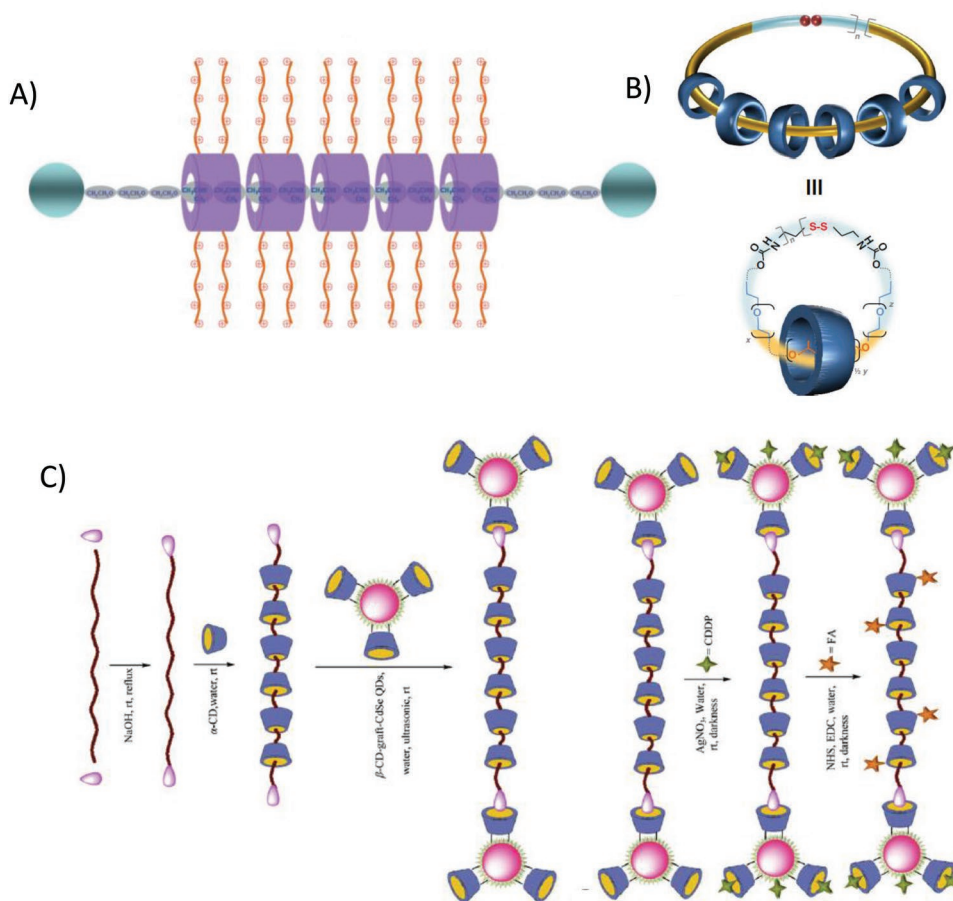MATERIALS**
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Figure 5. Supramolecular constructions of A) polyrotaxane, B) polycatenanes, C) polypseudorotaxane. A) Reproduced with permission.[43] Copyright 2006, Wiley-VCH Verlag GmbH & Co. KgaAl. B) Reproduced with permission.[51] Copyright 2019, Springer Nature. C) Reproduced with permission.[47] Copyright 2011, Elsevier Ltd.

various linear, branched, cationic, anionic, copolymer, co-block polymers, in which CyDs have the ability to forms the self-assembled nanoassembly with grafted polymers.[52]

CyD has hydroxyl groups aligned on the surface of a truncated cone which is fundamental for the CyD grafting with other polymeric materials. Different chemical reactions were implemented to modify the CyDs (such as amination, esterification, and sulfonation) to introduce the amine group, alkoxy group and sulfite group that can be further conjugated with a suitable carrier system to impart the cyclodextrin's intrinsic ability of host–guest formation via noncovalent interactions to synthesize different self-assembled supramolecular structures or organizations.[53] The most commonly used cyclodextrin intermediates and click chemistry agents for the grafting are

1) Mono-6-deoxy-6-(*p*-toluenesulfonyl)-βCyD (6-OTs-βCyD)
2) βCyD dimer synthesized by using ethylenediamine, terephthalic acid
3) Introduction of azido group on cyclodextrin
4) 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)/*N*-hydroxysuccinimide (NHS) chemistry to joined amino-CyD with carboxylic group containing polymeric material
5) Carbodiimide crosslinker

5.4.1. Chitosan: CyD-Modified Chitosan Polymers

Chitosan has gained wide importance in the field of drug delivery and tissue engineering because of its biocompatibility and high reactivity of amine groups which impart the cationic functionalities to the polymer.[54] This can be easily modified into the desired material for drug delivery with biological functionalities. Chitosan is known to interact with the mucin layer of the gastrointestinal tract as it has a cationic, mucoadhesive nature which is exploited in drug delivery applications.[55] Several modifications of chitosan were performed with CyD to form the supramolecular assembly for the drug delivery and tissue engineering. Additional properties such as inclusion complex formation and noncovalent interactions that are provided by CyD improve the chitosan's ease of application for developing nanoassembly structures.[56] The introduction of reactive groups (carboxylic or aldehyde) on CyDs is needed for grafting applications. Several methods have been developed to simplify the cyclodextrin grafting such as multiple step or facile single step.[37] Izawa et al., 2016 have developed the facile method for modification of α β and γCyD. The chitosan polymer was grafted with cyclodextrin using a carboxymethylation reaction that forms the carboxymethylated CyD which further reacts

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with chitosan by EDC/NHS crosslinking-based dehydration and condensation to form the βCyD-chitosan grafted polymer. This polymer-based nanoparticle was synthesized by ionic gelation using sodium tripolyphosphate for the encapsulation of anti-cancer drug, doxorubicin.[56] Yuan et al., 2013 have synthesized the chitosan grafted βCyD nanoparticle using a similar method with slight modification. Specifically, they synthesized Mono-6-Deoxy-6-(p-toluenesulfonyl)-βCyD (6-OTs-βCyD) that further reacts with chitosan to obtain chitosan grafted-βCyD polymer. The nanoparticle was fabricated using ion gelating crosslinking between the positively charged amino group of CyD-g-CS and the negatively charged tripolyphosphate (TPP) for delivery of hydrophobic drugs, Ketoprofen.[57]

5.4.2. Alginates: CyD-Modified Alginate Polymers

Alginate is an anionic polymer of natural origin obtained from seaweed and has been extensively studied for drug delivery and biomedical application because of its biocompatibility, biodegradability, low toxicity, lack of expense, and gelation properties when interacting with divalent cation, Ca^{2+}. Alginate hydrogel particularly was explored as a scaffold and carrier for the delivery of cells, growth factor, protein, and small molecules.[58] Cyclodextrin was grafted with alginate to create the supramolecular functional material to improve the ease of application of these two materials synergistically. Pluemsab et al., 2005 fabricated the cyclodextrin-alginate hydrogel using a-cyclodextrin (α-CyD). Mono-tosyl-α-CyD was used as an intermediate to synthesize the 6-amino-a-cyclodextrin. This modified cyclodextrin with amino groups reacts with the secondary hydroxyl group of alginates activated by cyanogen bromide. A spectroscopic study was performed to show the ability of this modified CyD-alginate grafted system to form a host–guest complex with model compound, p-nitrophenol. CyD-Alginate spherical bead hydrogel was prepared using calcium chloride that crosslinked the alginate.[59] Hosseinifar et al.,2018 have used mono-Ts-βCyD as an intermediate for the synthesis of (Tris-deoxy aminoethyl amino) β-cyclodextrin which acts as a cyclodextrin crosslinker. β-Cyclodextrin-alginate hydrogel was synthesized using EDC/NHS chemistry where β-cyclodextrin linked to alginate using the amino group of cyclodextrin which reacts with the carboxylic group of the alginate activated through EDC/NHS chemistry. The prepared hydrogel was used for the encapsulation of the anticancer drug, 5-flourouracil. The author demonstrated that the modified cyclodextrin provide the biocompatibility, pressure sensitivity and controlled release of the 5-flourouracil from CyD-alginate hydrogel. βCyD in the alginate hydrogels plays a dual role of crosslinker and binding site for 5-flourouracil that results in controlled release of the drug with promising encapsulation efficiency in the alginate hydrogels.[60]

5.4.3. Polyethylenimine (PEI): CyD-Modified Polyethylenimine Polymers

Cationic polymer-based systems have attained popularity for being nonviral gene delivery carrier. PEI forms self-assembled structures with the nucleic acids (deoxyribonucleic acid (DNA)/ribonucleic acid (RNA)) through an electrostatic interaction

having sub-micrometer-sized particles which can easily enter the cell by endocytosis.[61] These cationic polymeric vehicles have great advantages over those of viral vectors such as easy synthesis, adaptability and non-immunogenicity but they have certain disadvantages as well which make them unsuitable for systemic delivery. These include high toxicity and aggregation tendency under the physiological conditions.[62] Cyclodextrin grafting with a cationic polymer confers a huge advantage in terms of biocompatibility, inclusion complexation ability with a variety of DNA structures, reduced systemic toxicity.[63] Pun et al., 2004 reported on the synthesis of cyclodextrin-Grafted Branched PEI (CyD-βPEI) and Cyclodextrin Grafted Linear PEI (CyDlPEI) by reacting monotosylated cyclodextrin with amine group of PEI which imparts the useful properties of cyclodextrins such as low toxicity, inclusion complex formation ability and high water solubility to PEI. The authors also studied amount of grafted mass that can be controlled and found that high grafted mass was achieved. The activated CyD reacts with primary and secondary amine group of the PEI, which results in the formation of CyD-grafted linear PEI (CyDlPEI). This conjugation method gives the cyclodextrin that is intact and readily available for inclusion complex formation.[63] Zhang et al., 2008 fabricated the novel hydrogel formulation of temperature responsive semi-interpenetrating polymer networks consist of radically polymerized poly(N-isopropylacrylamide) using βCyD-coupled polyethylenimine. This has a high swelling index at normal temperature and shows the rapid shrinking behavior at temperature above lower critical solution temperature (LCST). The propranolol was encapsulated in a prepared semi-interpenetrating polymeric network hydrogel and the drug release was compared with normal poly(N-isopropylacrylamide) (PNIPAAm) hydrogel. The drug release kinetics was prolonged in cyclodextrin containing a semi-interpenetrating polymeric network hydrogel. Cyclodextrin inclusion complex formation with propranolol provides the improved drug release.[64]

5.4.4. Poly(N-isopropylacrylamide): CyD-Modified poly-(N-isopropylacrylamide) Polymers

The poly-(N-isopropylacrylamide) shows a unique behavior of reversible sol–gel transition around its LCST and this property has been widely explored for the stimulus responsive drug delivery.[65] This polymer has been modified with several small linear chain or branch chain polymers to obtain the desired self-assembled structure that can respond using various types of stimulus. The unique properties of cyclodextrin to form inclusion complexation and thermoresponsive behavior of poly-(N-isopropylacrylamide) can create the versatile material of interest.[66] Wang et al., 2007 developed the βCyD containing poly(N-isopropylacrylamide) hydrogels using the copolymer of N-isopropylacrylamide and mono-(6-N-allylamino-6-deoxy)-βCyD. The guest molecules, 8-anilino-1-naphthalenesulfonic acid ammonium salt (ANS) was used for the encapsulation in hydrogel and to investigate the temperature dependence affinity behavior of copolymerized P(NIPAM-co-CyD) hydrogel and native poly(N-isopropylacrylamide) hydrogels by varying the temperatures (21–60 °C). The enhanced association constant for ANS was observed for the both copolymerized

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P(NIPAM-*co*-CyD) and native PNIPAM gels when temperature rose across the LCST. Additionally, copolymerized P(NIPAM-*co*-CyD) hydrogel containing βCyD as a host component provide the binding site for the guest molecules and thus, exhibit the high affinity for ANS than those of native PNIPAM hydrogel. In addition, copolymerized P(NIPAM-*co*-CyD) hydrogel shows the improved LCST in water system and decreased in in dil. solution of the drug, ANS when compared the native PNIPAM hydrogel. This copolymerized P(NIPAM-*co*-CyD) hydrogel system has proven the potential role in temperature-controlled affinity separation of the guest molecule.[66] Kretschmann, et al., 2006 fabricated the supramolecular hydrogel using a cyclodextrin dimer that was prepared using mono-6-amino-β-CyD via reaction with terephthalic acid forming the bridge between the two cyclodextrin moieties. The adamantyl groups formed the very tight inclusion complex with βCyD by noncovalent interactions. The adamantyl-containing guest polymer was fabricated using free-radical copolymerization of adamantyl conjugated acrylamide derivatives (1-adamantylacrylamide and 6-acryloylaminohexanoic acid 1-adamantylamide) with *N*-isopropylacrylamide and or *N,N*-dimethylacrylamide (DMAA) monomer. The host–guest interaction of these adamantyl-containing copolymer and cyclodextrin dimer forms the supramolecular hydrogel. The authors studied the thermoresponsive behavior around LCST of the copolymer and found it to be lower than that of normal pure NIPAAM copolymers. The prepared hydrogel exhibits the temperature-dependent switchable transparency behavior and has potential application in biomedical sciences.[67]

5.4.5. Hyaluronic Acid: CyD-Modified Hyaluronic Acid Polymers

Hyaluronic acid (HA) is one of most explored biomaterials for tissue regeneration, drug carrier, and tissue engineering applications as it has attractive viscoelastic properties and is abundant in the human body.[68] Moreover, HA has biological functions because of its ability to bind with receptors like CD44, RHAMM at the site of inflammation, cancer and arthritis etc.[69] It is also employed as a building block for the fabrication of new drug carrier and biomaterials for biomedical applications. Additionally, CyD grafted to HA to form a supramolecular assembly for the various applications. Grafted CyD provides the site for inclusion complex formation with drug molecules through the noncovalent molecular interactions that are responsible for the formation of a supramolecular hydrogel system.[70] Charlot et al., 2006 have fabricated the CyD grafted hyaluronic acid system. βCyD monocarboxylic acid was prepared by *O*-(carboxymethyl)-hydroxylamine hemihydrochloride which further reacts with adipic dihydrazide modified hyaluronic acid. CyD derivatives have an aldehyde group that coupled with adipic dihydrazide by reductive amination reaction and results in the formation of hydrogel. The hydrogel-containing CyD was studied for inclusion complexation with adamantane (AD) acetate and Ibuprofen as a model drug for drug delivery applications.[71] Rodell et al.,2013 have fabricated shear-thinning hydrogel using CyD and hyaluronic acid. β-cyclodextrin is converted into tosylated βCyD that further coupled with HA intermediate, hyaluronic acid-tetrabutylammonium hydroxide via amidation to synthesize cyclodextrin–HA structures, these

can interact with adamantane–hyaluronic acid conjugate leads to the formation of hydrogel through the inclusion complexation of adamantane with CyD. Hydrogel shows the shear thinning behavior that can be utilized as an injectable vehicle.[72]

5.4.6. Cyclodextrin-Metal-Organic Frameworks (CyD-MOFs) Materials

MOFs are porous coordination compound-based materials that consist of the joints (metal ions/clusters) and linkers (organic ligands) that have versatile surface features (high surface/porosity) and a well-ordered structure which can allow high payload capacity (drug/imaging agent/gases). The metal ion/cluster, for example, transition, alkali and alkaline earth metals, p-block elements, actinides and lanthanides form the bridge with an organic ligand such as carboxylate, sulfonate, phosphonate, pyridyl, imidazolate, azolate functional groups to obtain the metal-organic frameworks. The MOF was synthesized by solvothermal methods, microwave-assisted, electro-chemical, mechanochemical, and sonochemical synthesis processes.[73]

Cyclodextrin has been successfully explored as an organic ligand to fabricate the MOF-cyclodextrin material where cyclodextrin forms the bridge with the metal ion/cluster. The conventional MOF is made from the metal ion and organic linker that are not safe for in vivo administration in pharmaceutical application. To avoid or minimize the associated toxicity with conventional metal ion and organic ligand, the biocompatible and biodegradable metallic ions such as calcium (Ca), potassium(K), and titanium (Ti) and organic linkers (peptides, carbohydrates, amino acids, and CyD) will be useful. Cyclodextrin is a safely accepted material that has been studied for the fabrication of the MOF-CyD.[74] The γCyD has a bigger inner cavity which makes it a more favorable cyclodextrin than α and βCyD to obtain the MOF-CyD due to the occurrence of the −OCCO− functionality in the primary and secondary sites of γCyD which interact with metal ions and form the complex.[75] Hartlieb et al., 2017, have fabricated the γCyD-MOF for the encapsulation of the Ibuprofen where γCyD was used to prepare the porous network that coordinated with the alkali metal (K^+) on primary and secondary sites of the γCyD. The Ibuprofen was encapsulated in γCyD-MOF by two processes: 1) crystallization of potassium salt of Ibuprofen as a source of alkali metal (K^+) and 2) adsorption and deprotonation results in average 24.5 wt% loading of the Ibuprofen. Ibuprofen-γCyD-MOF does not show cytotoxicity up to the IC_{50} value of 100×10^{-6} M. Animal studies in a mice model provides evidence that pharmacokinetics of Ibuprofen-γCyD-MOF exhibits a similar rapid uptake with peak plasma concentration within 20 min when compared to standard (potassium salt of ibuprofen). The γCyD-MOF formulation of ibuprofen co-crystal confers the additional benefit of showing 100% long plasm half-life and provides stability against the hygroscopic environment compared to pure salt of ibuprofen.[76]

Li et al., 2017 synthesized the γCyD-MOF to improve the efficacy of lansoprazole which is a well-established antacid shows an additional promising antitubercular activity. γCyD-MOF was fabricated using alkali metal (K^+) by the co-crystallization method to encapsulate the lansoprazole. The particle size and surface morphological characterization show the cubical architecture of the lansoprazole-γCyD-MOF system with 6 µm size

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and encapsulation efficiency of 23 wt% considering the 1:1 molar ratio of lansoprazole to γCyD. The spectroscopic study using absorption and fluorescence shows strong evidence that lansoprazole-loaded γCyD-MOF retains the native form even two years after the stability studies. Raman spectra exhibit the peak which confirms the uniform distribution of lansoprazole in an individual particle and inclusion complexation of lansoprazole with γCyD-MOF.[77] The current studies provide evidence that CyD-MOF is a promising carrier system for drug delivery.

6. Cyclodextrin-Based Stimuli Responsive Biomaterial Systems

Conventional drug delivery techniques lead to unpredicted plasma concentration at the targeted site with fluctuations and therefore, they suffer from toxicity and associated side effects after drug administration. An ideal drug delivery system maintains the desired therapeutic concentration at the targeted tissue with either minimal or no systemic exposure or nontargeted tissues avoiding side effects.[78] The smart polymers with intelligent responsive drug carrier systems are developed to trigger the drug release in response to changes in environmental factors. These include physical stimuli (temperature, light, electrical, magnetic or ultrasonic), chemical stimuli (pH, ionic, and redox) and biological stimuli (enzymes, inflammation or biomarkers).[79] The use of stimuli-responsive biomaterial proposes an appealing quality for drug and gene delivery, where the biomaterial turn into an active contributor of the therapeutic agents, rather than a passive carrier in the fabrication of the such intelligent system. The many class of the materials are utilized for the fabrication of stimuli-responsive drug carriers for both, active and passive drug targeting.[80] Inclusion chemistry of CyDs and supramolecular assemblies formed are essentially used to enhance the solubility and bioavailability of the drug. This acts as a carrier to improve the therapeutic profile of the drug by virtue of the hydrophobic cavity through its capacity to form inclusion complexes with guest molecules. Supramolecular assemblies of cyclodextrin and polymers responding to external stimuli lead to interesting smart and intelligent systems shown in **Figure 6**. In this context, the host–guest interaction for drug delivery can be initiated through externally controlled triggers which provide the advantages of drug encapsulation, controlled and targeted delivery with enhanced physiochemical and biopharmaceutical profile. This review provides insight into an approach from material design, chemistry, pharmaceutical, and biomedical applications.

6.1. pH Responsive CyD Systems

6.1.1. pH Responsive Molecular Switches

pH plays an essential role in controlling drug absorption and transport in the gastrointestinal tract. The parameter varies greatly in different organs and is altered in different disease states like inflammation, tumors, and infections or decreased blood perfusion. At the tumor site, the increased anaerobic metabolism and a high rate of glycolysis leads to acidosis resulting in low pH values at the tumor site as compared to healthy cells. The pH gradient can control the endocytosis of drug and events inside the cellular uptake in the lysosomal compartment (pH 4.5–5.5) which reaffirms the importance of pH as a major factor for controlling drug release at the tumor site.[81] With the advent of nanoscale operations in the healthcare industry, developing the nanomachines for controlled drug delivery vehicle through the use of molecular and supramolecular chemistry is a formidable challenge for the chemists, engineers and scientists. One such example of nano machinery operative on molecular level is the nanovalve. This is a device which can entrap and release the drug molecules (guest) through the nanopores by stimuli-induced specific motion. The three categories of external stimuli (chemical, photochemical and electrochemical) can be used to produce mechanical motion in these molecular switches.[82]

6.1.2. pH Controlled Nanomachinery for Tumor

The nanomachines contain movable valve components for controlling drug release and can be grafted on mesoporous silica (MSN) in such a manner that the synced activity of the components is guided by stimuli like pH, photochemical and electrochemical changes.[83] Mesoporous silica provides a nontoxic solid support and the valves can release the cargo molecules under controlled pH conditions via nano pores. Nanopores are big enough to entrap the drug molecules or dye but small enough to be blocked by organic macro cyclic molecules like cyclodextrins. The machines powered by pH change based on MSN system use supramolecular host–guest interaction to control the drug release in the acidic endosomal environment by controlling the nanovalve opening while they remain closed in neutral pH (7.4) and they thereby control the entrance and exit of molecules in and out of valve. Nanopore entrances can be guarded by gatekeepers. Cyclodextrins can act as the gatekeeper, allowing the precise release through valves, as complexing agent or by a modified targeted system using the ligand in native or modified form. The commonly used gatekeepers are supramolecules, nanoimpeller-modified cyclodextrins molecules, pseudorotaxanes, and rotaxanes. Nanovalve assembly constitutes important components: 1) Stalk for attaching capping agent to nanopore surface. 2) Capping agent to control the nanopore entrance and act as a gatekeeper, capable of opening and blocking the entrance reversibly upon stimulation. 3) Solid support to contain the cargo molecules as container, capable of providing controlled release and holding the capping agent and is a biocompatible material providing easy surface modification. The pH sensitive nano valve as biomaterial supporting mechanized release of cargo can be prepared. The nano assembly consists of mesoporous silica nanoparticles (MSNPs) as solid support, 1-methyl-1H-benzimidazole (MBI) stalk and βCyD the capping agent.[84] The capping agent can be covalently attached over the solid silica support. Under neutral pH, due to the noncovalent interaction between the gatekeepers surrounding the stalks, nanopores remain closed and cargo molecules can be retained well within the container of nanovalve. Upon reaching endosomal pH acidic
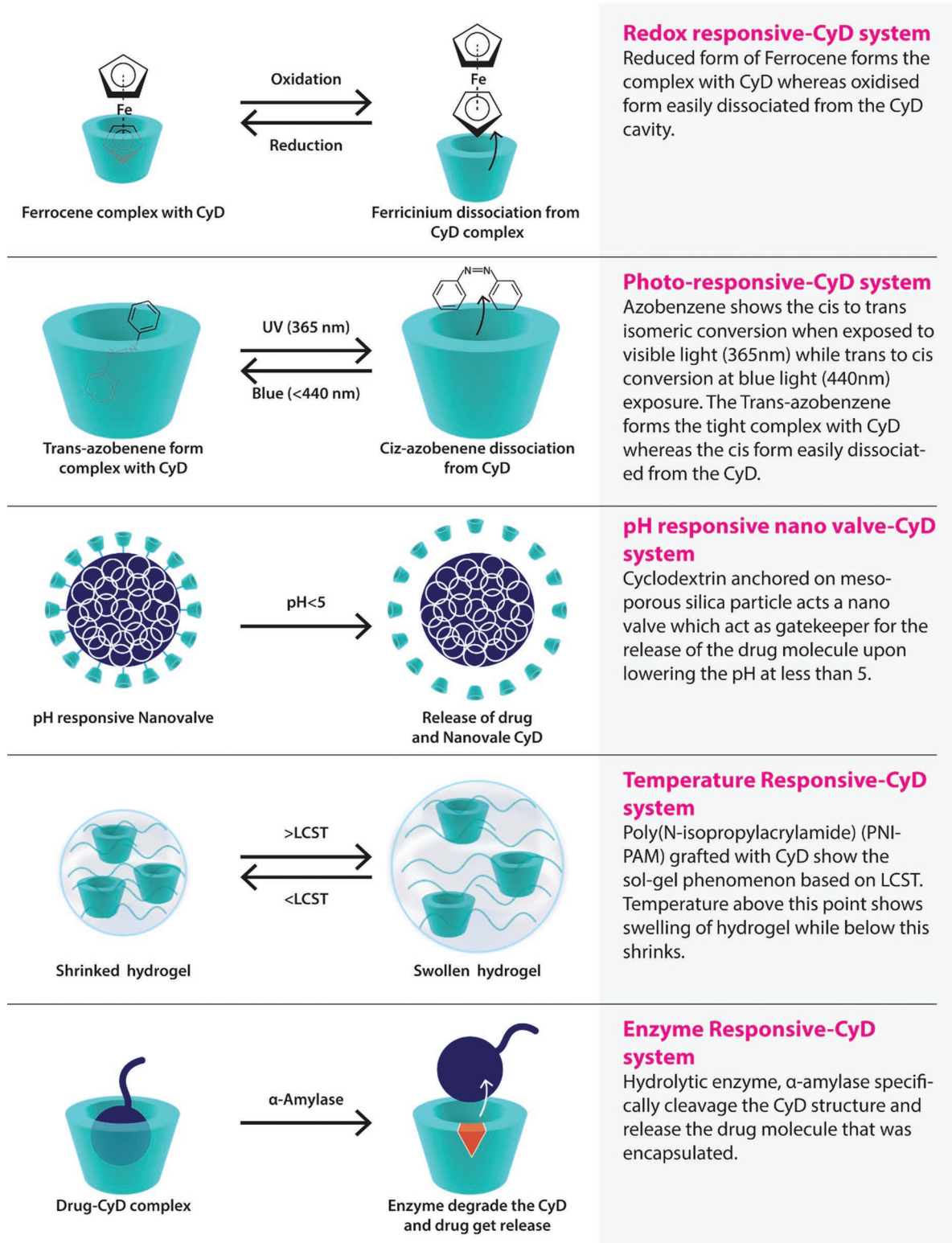
Redox responsive-CyD system
Reduced form of Ferrocene forms the complex with CyD whereas oxidised form easily dissociated from the CyD cavity.

Photo-responsive-CyD system
Azobenzene shows the cis to trans isomeric conversion when exposed to visible light (365nm) while trans to cis conversion at blue light (440nm) exposure. The Trans-azobenzene forms the tight complex with CyD whereas the cis form easily dissociated from the CyD.

pH responsive nano valve-CyD system
Cyclodextrin anchored on mesoporous silica particle acts a nano valve which act as gatekeeper for the release of the drug molecule upon lowering the pH at less than 5.

Temperature Responsive-CyD system
Poly(N-isopropylacrylamide) (PNIPAM) grafted with CyD show the sol-gel phenomenon based on LCST. Temperature above this point shows swelling of hydrogel while below this shrinks.

Enzyme Responsive-CyD system
Hydrolytic enzyme, α-amylase specifically cleavage the CyD structure and release the drug molecule that was encapsulated.

Figure 6. Cyclodextrin based host–guest complex trigger by the different stimuli and releases the guest molecules.

conditions in the tumor, the protonation of amines in the stalk can take place, leading to decapping of the valve with subsequent opening of the nanopore surface and release of the payload (drug) out in the environment.[85]

6.1.3. Targeted Delivery in Tumor via pH Sensing Nanovalves

The efficacy of therapeutics against tumor cells can be increased by tumor-specific ligands, aptamers, peptides, antibodies and
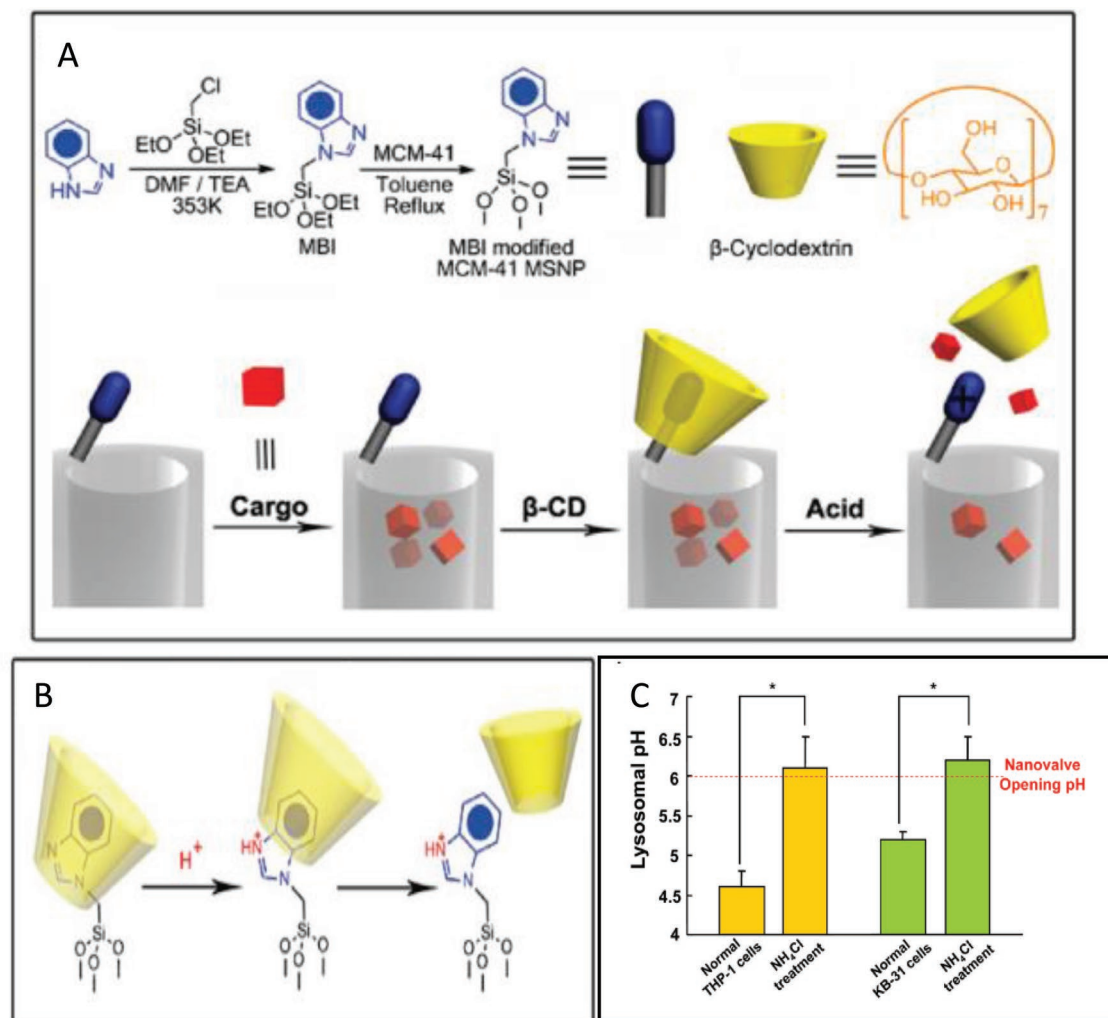
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Figure 7. Pictorial Illustrations of pH-responsive mesoporous silica nanoparticles (MSNP) containing nanovalve. A) Creation of the stalk, drug encapsulation, pore capping, and cap release in acidic condition. B) Description about stalk that undergoes protonation and CyD release. C) Determination of pH in cell lysosome (*$p < 0.05$). Reproduced with permission.[84] Copyright 2010, American Chemical Society.

growth factors predominantly overexpressed on the surface of tumor cells. Acetonated cyclodextrin (Ac-αCyD) as a pH sensitive material can be used for encapsulation of paclitaxel (PTX) into nanoparticles for encapsulation for improved therapeutics in vitro and in vivo.[23] HApt (Anti-HER2 aptamer) mediated targeting in HER 2 sensitive cancers such as human ovarian, breast, lung and gastric cancer cells can selectively kill tumor cells through inhibition of cell proliferation and cell death. Benzimidazole modified MSNPs, capped by βCyD and functionalized HApt SH (anti-HER2 aptamer) can create a nano assemblage for Doxorubicin (DOX) delivery for targeted delivery in breast cancer cells.[86] In the preparation process, modified MSN pores were made ready and capped by βCyD-SH groups. Upon reaching the tumor site, endosomal uptake takes place. Where in this HApt aptamers will combine at the target site corresponding to high expression at the tumor site and the acidic pH causes the disruption of βCyD cap with the release of DOX from the cavity of MSN pores as shown in **Figure 7**. The specificity of cellular uptake by HER2 receptor-mediated

endocytosis is one of the successful approaches to delivery of cytotoxic drugs at the tumor site.[86]

6.1.4. pH Sensitive Gene Delivery Nano Vector

Developing the safe, stable, and effective nonviral nanovectors is a prime need of the biotechnology industry aiming for effective gene therapeutics. Some of the delivery systems such as liposomes, lipoplexes, polymeric particles, cationic polymers, microcapsules, nanoemulsions, and micelles are explored for delivery of the siRNA, double stranded DNA, RNA, and miRNA. These delivery systems often encounter issues with biocompatibility, safety, toxicity and instability in in vivo.[87] The functional nanovector of acetalated αCyD material (Ac-αCyD), low MW polyethylenimine (PEI1800) and antisense oligonucleotide Bcl-xl allows the transfection and apoptosis in human lung carcinoma cells.[88] The acetalated CyD is acid soluble and biocompatible having high transfection ability and is effective

against the cations including PEI25000 and lipofectamine 2000. The acetalated CyD system allows transfection of even multidrug resistant (MDR) tumor cells by decreasing Pgp expression, Pgp ATPase attenuation, reduced ATPase activity with less cytotoxicity and pH dependent intracellular release in tumor cells.[89]

6.2. Photoresponsive CyD Systems

Photoresponsive supramolecular biomaterial employs azobenzene chemistry with host–guest interactions. Azobenzene is a photo responsive compound which undergoes reversible isomerization into *cis* and *trans* isomers on illumination with ultraviolet light. The photo isomerization of *trans* to *cis* isomer [π–π^* (S_2 state) transition] occurs upon irradiation with wavelength 350 nm while *cis* relaxes back to *trans* at 455 nm [n–π^* (S_1 state) transition] corresponding to energy gaps. The rod-shaped nonpolar *trans* isomer forms stable complex with host, αCyD and βCyD while the bent polar *cis*-form is less stable and unable to fit in either type of cyclodextrin cavity. This photo isomerization chemistry is used to form various light stimulated delivery of host molecules and molecular shuttles.[90]

Photo isomerization of azobenzene forms the principle of supramolecular chemistry involved in photo responsive host–guest interaction with molecules such as CyDs. The photo responsive interaction of amphiphilic CyD vesicles with bifunctional guest molecules suggested the aggregation of vesicles. The process of aggregation is concentration-dependent and selective in that only *trans* can result in aggregation of the CyD vesicles through the complex formation with guest molecules, unlike *cis* isomer.[91]

6.2.1. Smart Photosensitive Hydrogels

Photo switchable hydrogels can be formed from modified cyclodextrins and guest containing azo moieties. Upon mixing the modified curdlan cyclodextrin CUR-CyD with azobenzene-modified {poly-(acrylic acid, AA) (pAC12Azo)}, the viscosity increases and results in hydrogel formation. Photo-irradiation of UV light (λ 365 nm) caused photo isomerization of azobenzene from the *trans* azo into *cis* azo in gel form, while exposure to light (λ 430 nm) or heating results in transformation of *cis* into *trans* and converts the gel into sol form.[92]

6.2.2. Self-Assembled Photoresponsive Hydrogels

The host–guest complexation of α/βCyD (host) and a photoresponsive azobenzene compounds (guest) can result in self-assembled hydrogel.[93] Upon irradiation with UV light, *trans-cis* photo-isomerization of the azobenzene occurs which results in dissociation of the assembled gels. Due to the lack of inclusion complex formation with *cis*-azo form result in easy detachment of *cis*-azo-gel by simply dispensing in water while the *trans*-azo gel based complex retained the native gel structure despite of forced shaking in water. The separated αCyD-gels and azo-gels were found to reassemble on visible light (wavelength at 430 nm). After light irradiation (λ 365 nm), the azobenzene undergoes photo-isomerization from *trans* to *cis* form, which result in dissociation of the native assembled gel structures. The photosensitive hydrogel process is reversible and reproducible.[93]

6.2.3. Smart Capsules with On/Off Photo Switches for Drug Delivery

Photo stimulated host–guest interaction can be used to develop an intelligent microcapsule for controlled drug release application. The assembly formed on the principle of UV sensitive interaction between guests AD, azo compounds and βCyD acting as a switch with on/off control over drug release from the capsule.[94] The microcapsule works on photoisomerization where *trans* azo interacts with βCyD, the model drug cannot pass under normal visible light. The exposure to UV light leads to ending of the interaction between CyD and azo, and the negatively charged polyelectrolyte chains cannot hold the drug, hence the drug is released. The process is reversible in visible light with an on/off switch controlling the drug delivery. Cyclodextrin host and azobenzene or ferrocene as guest to produce a dual effect as light and redox-sensitive systems respectively.[95] The nanocapsules (NCs) were prepared by deposition of host and guest through employing thiolated gold nanoparticles on previously thiolated CyD polymer followed by core removal. Both azobenzene and ferrocene interact with CyD using different chemistry and final particle size. The light-responsive NCs were fabricated using a *p*-tertbutyl-azobenzene-modified polymer. The host cavity forms the tight and stable inclusion complexes with the *trans* isomeric form. The complementary host–guest polymers can be detached and reattached on employing the light stimulus.

6.2.4. Self-Healing Material Systems

A self-healing material based on host–guest interactions which, after being cut, recover its original strength even by rejoining again.[96] The supramolecular hydrogels were formulated by utilizing radically copolymerized hydrophobic guest monomers (*n*-butyl acrylate and *N*-adamantane-1-yl-acrylamide) in water which forms the inclusion complexes with α the βCyD-Ad gel. These two types of self-standing gels possess a self-healing property as a result of the reversible and reproducible host–guest interactions. After the initial cut, surfaces attach to each other indicating host and guest affinity and adhesion. A rupture experimental study was used to calculate the initial stress strength (S0) of individual hydrogel where, with αCyD-*n* Bu hydrogel shows the adhesive strength on the joint surface that increases with time (74% of the initial strength) is restored as compared to with βCyD-Ad gel (99% of the initial strength) shown in **Figure 8**A.

6.2.5. Photo Sensitive Self-Expansion and Contraction Material Systems

The biomaterial supramolecular hydrogel systems operate with self-expansion and contraction properties by utilizing a reversible crosslinking between αCyD and azobenzene.[97] Upon UV

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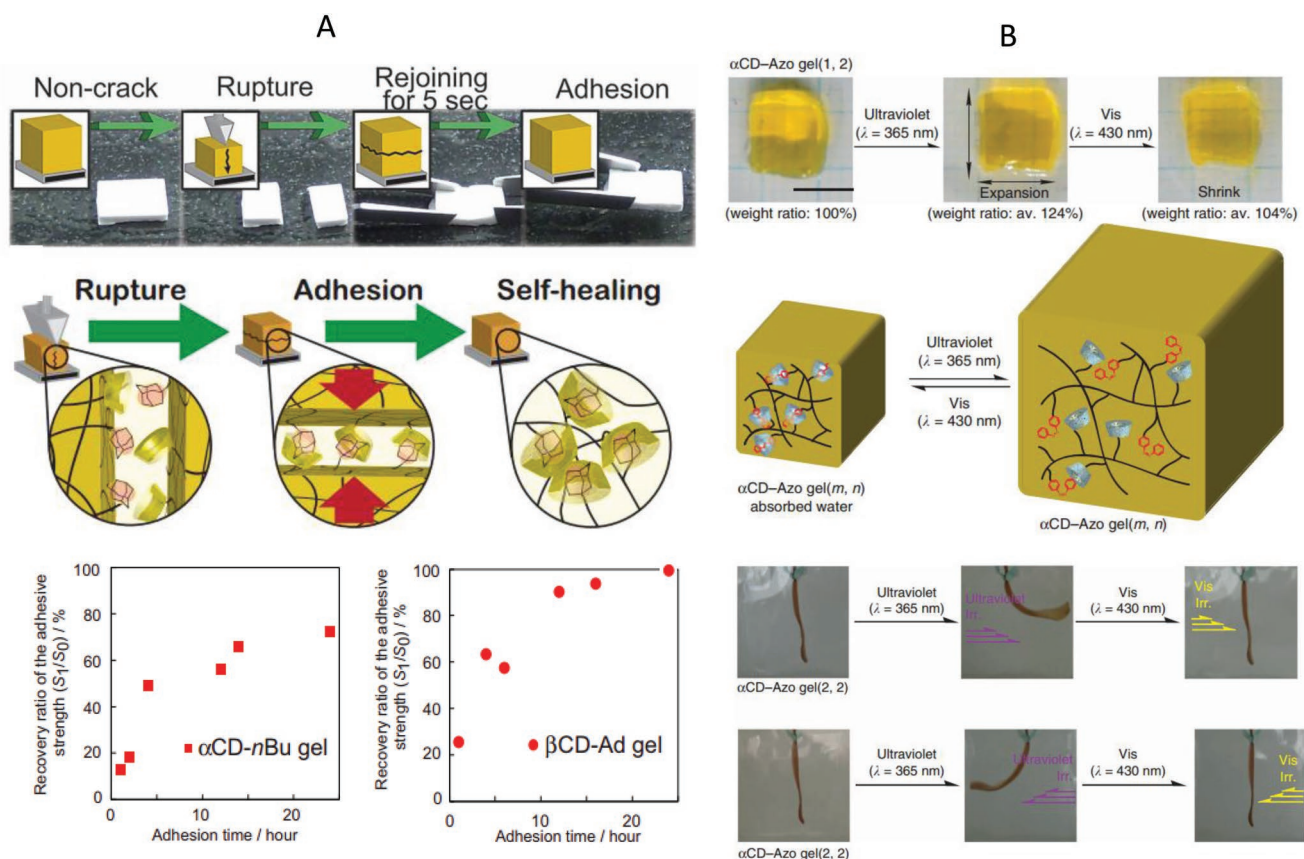MATERIALS**

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Figure 8. A) Schematic representation of self-healing material. The original stress strength (S0) was calculated after cutting the hydrogel into two pieces. The pieces were permitted to reattached for the sufficient time and adhesion strength (S1) was measured. The adhesive strength recovery ratio[(S1/So b)] was determined for α CyD-*n* Bu gel and βCyD–Ad gel. Reproduced with permission.[96] Copyright 2013, Wiley-VCH Verlag GmbH & Co. KGaA. B) Pictures representing the volume difference (αCyD-azo gel) when exposed to UV–vis light and Representation of the hydrogel expansion–contraction phenomenon upon UV–vis light illumination. Reproduced with permission.[97] Copyright 2012, Springer Nature.

light irradiation (λ 365 nm), azobenzene undergoes an isomeric conversion of the *trans*-azo into the *cis*-azo form resulting in increased weight over that with visible light (λ 430 nm). The volume and weight changes are monitored for the bending of the gel to the opposite side on irradiating the plate gel and this was observed corresponding to the interaction shown in Figure 8B.

6.2.6. Light Controlled Cell Adhesion

Another interesting area that utilizes these photocontrollable switches make use of this azobenzene cyclodextrin chemistry for cell selection, isolation, or screening, and adhesion of tumor or specific cells;[98] for example, MCF-7 breast cancer cells utilizing DNA aptamer (specific sequence capable of binding) via light-triggered mismatch chemistry of *cis/trans* isomers with cyclodextrins.[99] The azobenzene-modified cell capture agent aptamer (DNA or RNA sequence capable of binding) to target was designed onto a modified CyD surface to produce the light responsive surface that control the cell adhesion. After UV light illumination, the azobenzene changed from *trans* to *cis*-isomeric configuration and the *cis*-azo form is unable to recognized by CyD molecules because of the mismatched pair and captured MCF-7 cells would be discharged. Cell adhesion and migration

are regulated by various regulating molecules such as integrins through noncovalent interactions with biomolecules such as fibronectin, peptides containing RGD sequence at extracellular membrane. The smart system using smart template containing αCyD with terminally modified alkane silane allows assembly of the azobenzene with peptide, glycine-arginine-glycine-aspartate-serine (azo-GRGDS) via host–guest interactions to control reversible cell adhesion upon UV/visible illumination.[100]

6.3. Thermo Responsive CyD Biomaterials

Temperature-sensitive carriers can help in tumor treatment through swelling/shrinking or via cooling/heating behavior. The polyacrylamide gels have a tendency to undergoes the temperature/fluid composition responsive phase transition.[101] The other materials which shows the similar properties are *N*-substituted thermoresponsive polyacrylamides that can be potential drug carriers include the poly(*N,N*-diethylacrylamide and poly(*N*-vinyl caprolactam).The NIPAAm-based polymers are hydrophilic and biodegradable with high LCST.[102] Poly (*N*-isopropylacrylamide) is the representative polymer and most studied thermoresponsive polymer used commonly for preparation of temperature-sensitive hydrogels. The PNIPA hydrogels maintain the transition

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temperature (LCST) at around 33 °C and below which it retains water and swells, while it becomes opaque, shrinks and loses strength upon exceeding LCST temperature in surroundings.[103]

6.3.1. Smart Hydrogels (PNIPA Hydrogels)

Hydrogels provide such a controlled delivery system and, in particular, smart hydrogels are a stimuli-controlled delivery system providing the controlled release of drugs by tuning the environmental factor such as pH, light, temperature, magnetic, chemical or redox systems.[104] Amphiphilicity of cyclodextrins can be combined with PNIPA macro hydrogels via host–guest interaction to increase the thermal induced swelling. The thermoresponsive βCyD/PNIPAM nanogel prepared by in situ polymerization where βCyD can enhance the thermo-induced complexation with PNIPAM upon heating, and decomplexation with cooling. The increased hydrophobicity and complexation with βCyD above LCST, while with decreased temperature, PNIPM molecules in gel become hydrophilic and are forced to shuttle from the cavity of βCyD leading to the shrinking of gel while CyD maintains the high rigid nanogel at normal temperature. The resulting gel is capable of controlled delivery in response to thermal change as illustrated in **Figure 9**.[105] Supramolecular hydrogels are constructed using inclusion complex formation of adamantyl-modified copolymers with CyD dimers. Adamantyl groups can be strongly interacted with CyD and the resulting gel can be highly crosslinked. The phase transition temperatures (LCST) of the supramolecular assembly consisting of NIPAAM copolymers and CyD dimers are considerably lower and are transparent over a low temperature range and can easily be formed from less viscous aqueous solutions.[67]

6.3.2. Thermosensitive Block Copolymers and Star Polymers

Triblock polymers produced by atom transfer radical polymerization (ATRP) with entrapped CyDs and end capping with polymer blocks can be used as thermo-sensitive material. Supramolecular hydrogels with tunable crosslinking structures using polypseudorotaxanes (PPRs) and F127 triblock copolymer terminally conjugated with bromopropionyl bromides can control hydrophilicity.[106] The thermosensitive behavior of hydrogels is due to the aggregation PPO blocks in networks. αCyD was found to decrease the swelling of hydrogels. There are abundant supramolecular structures that can be formed from block polymers using CyD as linker. For example, two poly (N-(2-hydroxypropyl)methacrylamide) (PHPMA) exterior blocks with a poly (N,N-dimethylacrylamide) (PDMAAm) or poly (N,N-diethylacrylamide) (PDEAAm) interior block via CyD host–guest complexation can be connected. PDMAAm, being an inner block for thermoresponsive property, holds guest molecules and outer block PDEAAm to form aggregates via supramolecular interactions. The thermo responsivity of polymers was observed with changing temperature and photo isomerization of azobenzene at 360 nm is due to reversible transition of *cis trans* isomers on illumination with UV or visible light.[107] Star-shaped polymers are the branched polymers containing several (usually greater than three chain) linear chains radiating from or linked to a central core. These arms can be chemically identical (homostars) or

different (heteroarm stars). Star-shaped polymers can be created by commonly employed techniques such as the arm-first approach where living chains acts as the initiators, and a core-first approach where core act as a initiator. Star polymers were produced using CyD as core material and thermo or photo responsive polymers as arm material. The example is poly(N-isopropylacrylamide) (star-PNIPAm) and star-PNIPAm with CyD end groups (star-PNIPAm-CyD) through ATRP.[108]

6.4. Redox Responsive CyD Drug Delivery

Electrofunctional materials which are responsive to altered electronic states are called electrically switchable materials or redox stimulated systems. Ferrocene is the most frequently utilized molecule in redox tuned drug delivery systems. Ferrocene is a d6 Fe (II) 18-electron neutral sandwich like molecular structure (orange) which undergoes oxidation at moderate potential of around +0.4 V versus to a green d5 Fe (III) 17-electron cationic form, called as a ferricinium (Fcium). This is then restored into its native neutral form using a reducing agent.[109] The redox-sensing properties of ferrocene and reaction as hydrophobic guest with β cyclodextrin as reversible ferrocene/ferricinium redox system is widely used in biomedical, electrochemistry, material science and chemical science applications. The ferrocene (stimuli component) and host–guest molecules (delivery component) together can achieve stimuli-based drug delivery aimed at the targeted site. The synthesis of different kinds of Fc polymers through modifications, the applications of Fc based polymers in redox based biomaterial for drug delivery and its applications can be found in the literature.[110]

6.4.1. Redox Sensitive Sol–Gel Materials

Ferrocene (Fc) molecules have redox-sensitive properties and have been frequently used in the preparation of responsive material. Hydrogels of poly acrylic acid pAA modified CyD pAA-6βCyD (guest) and pAA-Fc (host) show sol–gel transition upon host–guest interaction as supramolecular chemistry.[111] The mixing results in host–guest interaction and increased viscosity with hydrogel formation. The presence of oxidant or reductant can control the sol–gel transition. Addition of the NaClO aq. to the hydrogel causes phase transition to the sol state, and constant addition of glutathione (GsH) to the sol restored an elasticity, which led to formation of the hydrogel again. For instance, in an example, βCyD shows greater affinity toward the reduced state of the Fc because of its hydrophobicity, and remain as gel in presence of GsH (reductant) while it loses elasticity and exists as sol in presence of oxidant due to less affinity of cationic Fc for βCyD cavity as shown in **Figure 10**.

For producing an oxidation-responsive system, boronic esters can be used to prepare functionalized CyD material, where, the 4-phenylboronic acid pinacol ester (PBAP) chemically reacted with hydroxyl groups of CyD to allow the fabrication of oxidant responsive CyD (Ox-βCyD). This further treated for the generation of core shell nanoparticles by a nanoprecipitation technique using lipids like lecithin, DSPE PEG and PEG 2000.[112] Hydrolysis of such components depends on the number of PBAP
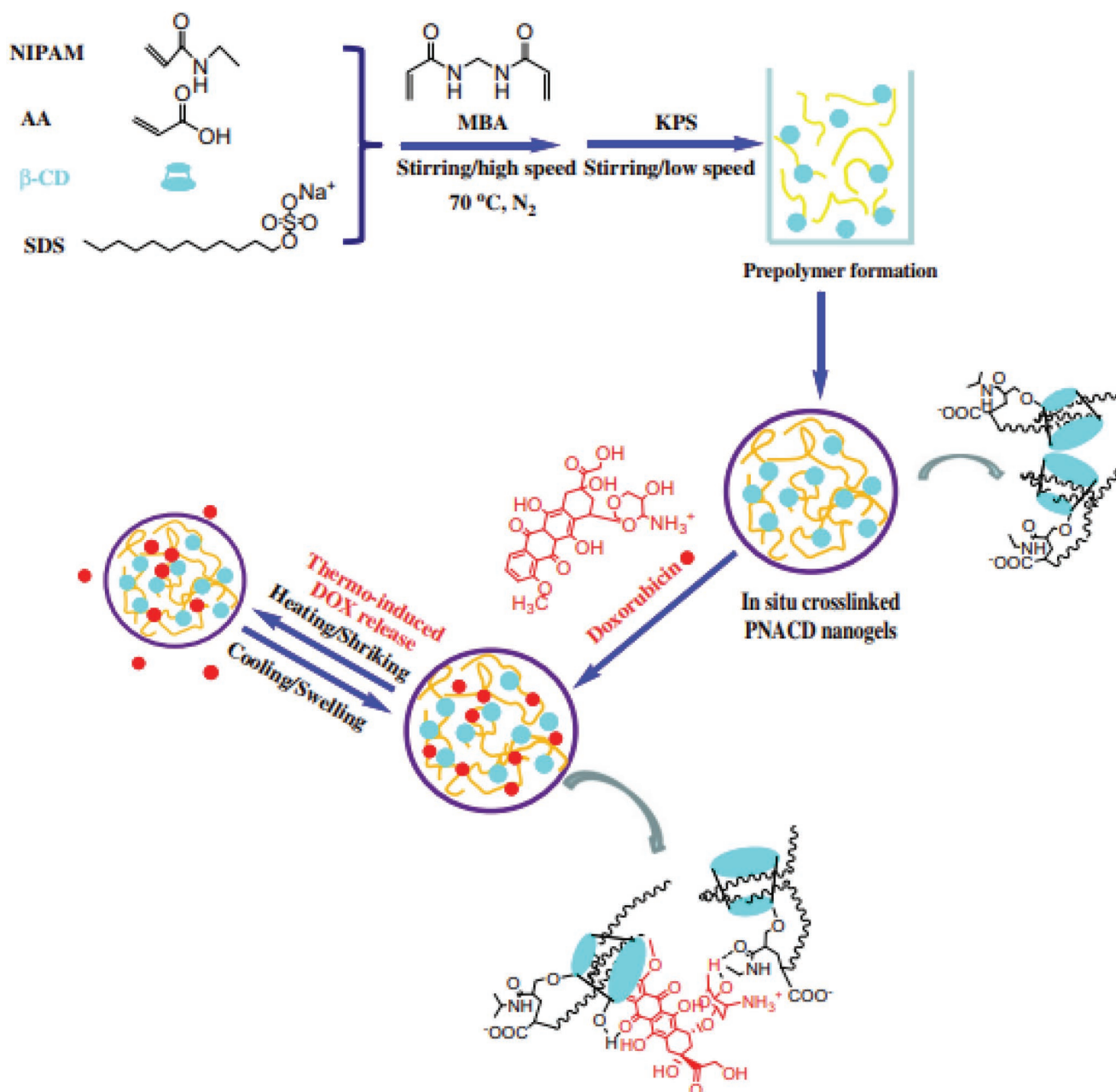
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Figure 9. Scheme representing hydrogel prepared by in situ polymerization utilizing *N*-isopropylacrylamide (NIPAM), AA as a polymer source, [initiator-potassium persulfate (KPS)] and [crosslinker-*N*,*N*′-methylenebisacrylamide] and swelling or shrinking of hydrogel upon heating or cooling or complexation decomplexation with CyD and subsequent drug release (MBA). Reproduced with permission.[105] Copyright 2017, Elsevier B.V.

conjugated to CyD. The higher the number of PBAP units there are, the higher will be the hydrophobic nature and hence delayed hydrolysis and can be used for controlling oxidative stress in inflammation by inhibiting the secretion of proinflammatory cytokines, chemokines, and oxidative mediators.[113] Ox-*β*CyD NP can be used for docetaxel therapy in tumor cells. A host component comprised of *β*CyD-polyethylenimine (low MW) conjugated with recognition ligand, MC11 peptide (MQLPLATGGGC) that can target FGFRs and guest component consists of adamantyl modified PEG linked through a disulfide bond. PEGylation of MPC (MC11 peptide-PEI-*β*CyD) offer the extracellular

stabilization of DNA polyplexes and at the same time responsible for intracellular cleavage that results in the greater transfection efficiency than those of non-PEGylated MPC.[114]

6.5. Enzymatic Activity Programmed Material

Enzymes play a key role in controlling cell metabolism and regulation. Increased enzymatic activity at the target site may be utilized as an opportunity to control the drug release by designing a carrier that can release the drug upon enzymatic
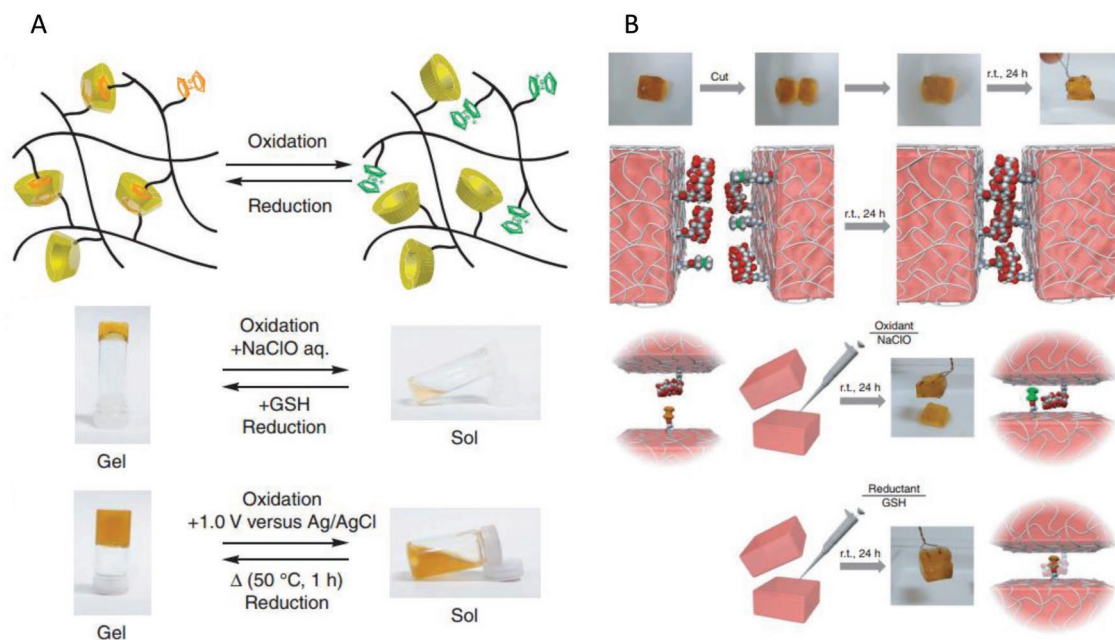
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Figure 10. A) Redox-responsive sol–gel experiments and B) Self-healing experiments. a) Cutting of pAA-6βCyD/pAA-Fc hydrogel into two pieces was joined after 24 h and form the self-healing native hydrogel structure. b) Redox-responsive healing of the pAA-6βCyD/pAA-Fc hydrogel was observed when treated with oxidant (NaClO aq)/reductant (GsH aq). Reproduced with permission.[111] Copyright 2011, Springer Nature.

conversion or detection. High enzymatic levels are also important as a diagnostic tool for some diseases; for example, proteases such as esterase or urease are overexpressed in tissues with tumor, and therefore form an important target. Programming of the nanomaterial for payload release (drug) with active encounter of the enzyme which degrades the polymeric material shell is one of the most widely known approaches. In other cases, nanomaterial shell that are nonresponsive to enzymes can be modified with molecules that alter the physical properties of the nanoparticle solution upon enzymatic transformation for the release of therapeutic and diagnostic agents.[115] For example, the high level of esterase present at the tumor site, maleic anhydride can form an ester linkage between CyD and paclitaxel, release of drug at the tumor site upon enzyme activity and cleavage of ester bonds. The system improves the stability in blood due to negative carboxylate ions and multivalent host–guest interaction.[116]

6.5.1. Enzymatic Luminescent Material

Levels of enzyme such as amylase and lipase are increased during pathophysiological conditions in acute pancreatitis. Enzyme responsive release of guest molecules includes the valve containing silica container, stalk hydrolyzed by lipase, casein as guest molecules and CyD as gatekeeper hydrolyzing in presence of α amylase as displayed in **Figure 11**A.[117] The CyD molecules were attached on the surface by click chemistry of monoazide CyD and the ester group was introduced in the stalk providing the controlled release of guest measured by fluorescence intensity. The luminescent material made up of luminol functionalized CyD responsive to altered ROS and myeloperoxidase (MPO) levels can create luminescence better than luminol in both cellular

environment and in vivo murine models. The nanoparticles of modified cyclodextrin conjugated to hydrophilic luminol represents sustainable luminescence which was enhanced in presence of MPO and MPO/Cl and can be correlated to the degree of inflammation by neutrophil count as shown in Figure 11B.[118]

6.5.2. Enzyme Sensitive Cancer Treatment

The enzymes upon acting on nanocarriers can deliver a payload at the target site, for example at the tumor site. The design of such a system is based on hydrolytic reactions to degrade the polysaccharide such as βCyD and chitosan coated over magnetic nanoparticles designed to target tumor cell lines. The hydrolytic enzymes such as α-amylase and chitosanase causes the enzymatic degradation of drug loaded CyD and chitosan-based carrier and release the drug. The microscopic study confirmed that both, CyD and chitosan coated nanocarrier reveals the target specific controlled drug release with enhanced intracellular drug uptake.[119]

6.5.3. Nanovalves Operating on Enzymatic Releasing Guest Molecules at Target Site

The working principle of the designed enzyme stimuli sensitive nano cargo using CyD supramolecular chemistry is based on designing specific targeted, cell-penetrating drug delivery in tumor cells to prevent side effects in normal tissue. The system can be highly effective since it corresponds to high-level expression of an enzyme such as cathepsin B overexpressed in endosomes and lysosomes at the tumor site leading to cell death in tumor cells and acts as a highly versatile designed nano system for controlled and targeted delivery in cancer. The
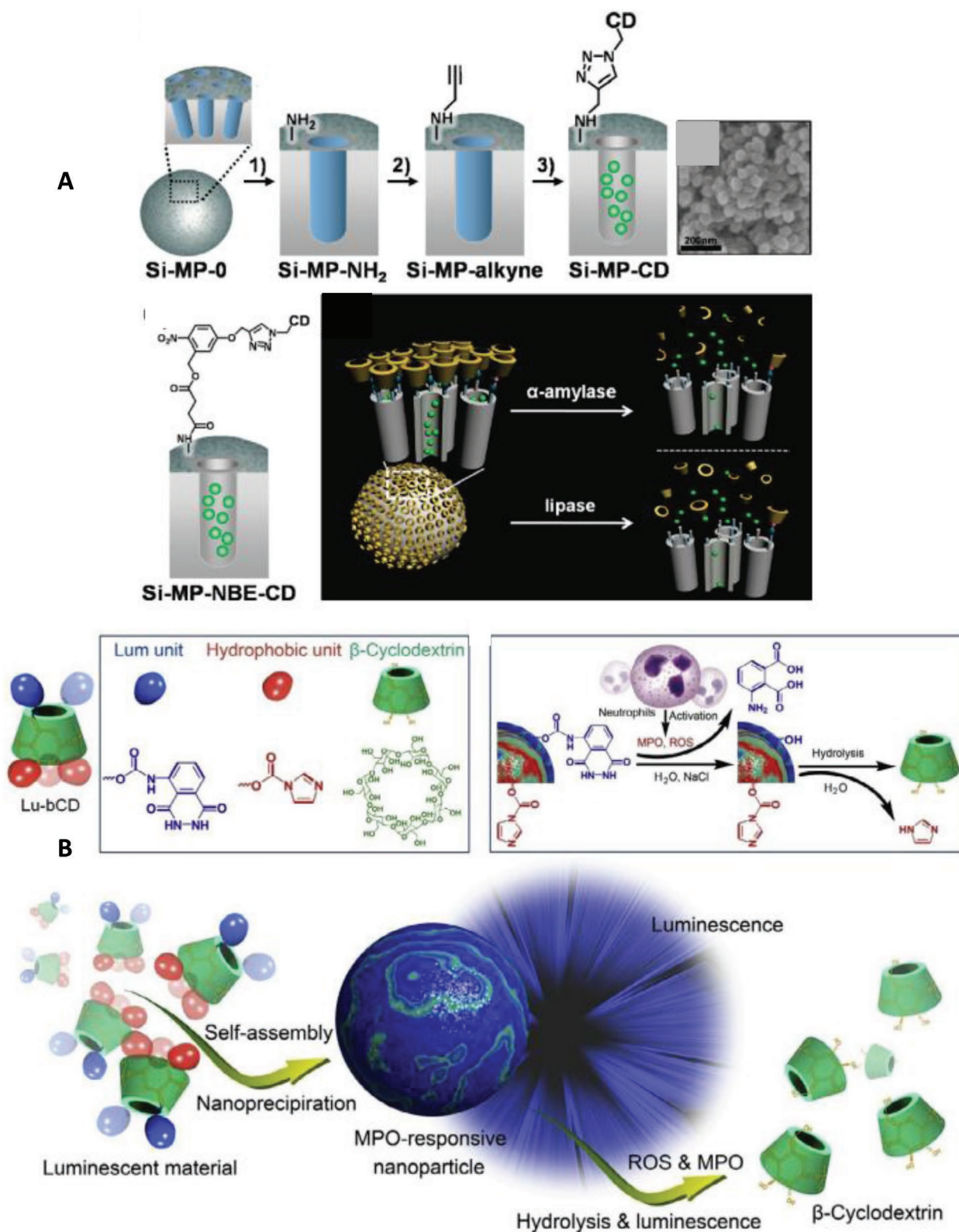
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Figure 11. A) Synthesis of Si-MP-CyD 1–3) and FE-SEM picture of Si-MP-CyD, the structural motifs on the surface of Si-MP-NBE-CyD and scheme representing the enzyme-triggered (α-amylase and lipase) release of the guest molecules from the pore of CyD-based nanocontainers. Reproduced with permission.[117] Copyright 2009, American Chemical Society. B) Lay out of a myeloperoxidase (MPO)-responsive biodegradable and luminescent system. a) The structural composition of the luminol (Lum)-conjugated βCyD (Luβ-CyD) based luminescent material. b) Enzyme-responsive hydrolysis of luminescent material. c) CyD-engineered MPO-responsive luminescent nanocarrier. Reproduced with permission.[118] Copyright 2017, Elsevier Ltd.

concept forms a working mechanism of CyD nano valves using MSN nanoparticles as a solid container to carry guest molecules DOX. Rotaxane of alkoxysilane and αCyD plays a role of gatekeeper to control the release of DOX from orifices and the multifunctional peptide unit containing arginine (R7) sequence (cell penetratingR7) targeting moiety peptide of RGDS and enzyme sensitive peptide of Gly-PheLeu-Gly (GFLG) sequence for targeted delivery in tumor.[120]

6.6. Chemical Responsive CyD Biomaterial

The solubility issues facing by single-walled carbon nanotubes (SWNTs) can be solved by utilizing reaction with pyrene molecule that leads to the π–π interaction between pyrene containing ionic groups and SWNTs. The research group of Harada had reported the preparation of chemically advanced responsive SWNT hydrogel through SWNTs functionalized CyD. Water-soluble SWNT bearing CyDs are produced by manipulating π–π interaction between pyrene conjugated αCyDs and SWNTs. CyD act as host and can allow the guest molecules over the SWNT surface. Py-αCyD/SWNTs were prepared and π–π interaction was analyzed by different techniques like UV, fluorescence quenching and $1H$ NMR suggesting strong absorption of Py-αCyD on the SWNT surface. Poly (acrylic acid) with high molecular weight (MW 250 000) consisting of dodecyl groups were used to prepare the hydrogel. The dodecyl groups in the polymer interact with CyD as guest to prepare host–guest complexes in which, upon mixing the PAA with Py-αCyD/SWNT hydrogel, is formed. SWNT hydrogels comprised of Py-αCyD/SWNT hybrids and PAA2 are converted to sol through the addition of competitive guests/host molecules. Upon adding of adamantane carboxylate AdCNa to dodecyl groups, transition of gel to sol state occurs because it interacts strongly with CyD compared to dodecyl group and, on adding βCyD as competitive host, gel converts to sol as dodecyl forms a bond with βCyD rather than with αCyD.[121]

6.7. Magnetic Responsive CyD-Based Biomaterial

Magnetic nanoparticles (MNPs) provide a versatile tool as a targeted delivery in the tumor site due to unmatched advantages as magnetism, biocompatibility, size and targeting stimuli-based therapy.[122] The surfaces of the MNPs can be modified easily using various functional bioactive molecules to achieve stability and reduce toxicity and targeting ability to achieve effective therapeutic goals in drug delivery.[123]

6.7.1. Tumor Targeted Drug Delivery and Imaging

Targeted delivery with magnetic nanoparticles was attempted using targeting ligand such as peptides, antibodies, and polymers to provide controlled and targeted release at target tissue-specific site. Polypyrole (PPy), a near infrared light-absorbing polymer, has been exploited to functionalized MNPs for near infrared light stimulated drug release in antitumor therapy. The powerful ability to absorb the near-infrared light, good biocompatibility, and stability behavior made polypyrole as

a suitable candidate for drug delivery and diagnostics. Polypyrrole coated magnetic nanocomposites conjugated with βCyD and HA adds targeting ability to grafted MNPs. The pH sensitivity for drug release and increased uptake by specific tumor cells further improves efficiency of the delivery system.[124] Despite high magnetic properties, easy preparation and biocompatibility, the issues of aggregation, poor dispersion in physiological conditions, and oxidation into Fe^{2+} ions can lead to issues through which magnetic particles lose their magnetism and effectiveness in the drug delivery system. To improve these properties, magnetic particles should be grafted with molecules that improve the stability, biocompatibility, and toxicity by providing the hydrophilic surfaces via additional functional groups and increase stability in physiological conditions. MNPs grafted with βCyD can bring immense benefit for the delivery of hydrophobic drugs, while additional mucoadhesive properties can be achieved by adding chitosan to the CyD as this may result in improved hydrophilicity and sustained release properties. For hydrophobic drugs, the amplification of electrostatic interaction and inclusion complexation introduced by the chitosan layer and the βCyD layer can control the initial burst release followed by sustained release.[125] Supramolecular paramagnetic nanoparticles prepared from adamantane (Ad MNPs). The nanoparticles prepared by molecular association between Ad and CyD motifs for DOX delivery with provided magnetic field stimulus achieve the controlled drug delivery at tumor site.[126]

The multiple advantages of the system with mucoadhesive property, inclusion ability, controlled and targeting effects of MNPs can be achieved through grafting CyD MNPs by gums such as gum Arabic.[127] CyD assembled MNP nanoparticles synthesized using the layer-by-layer technique for delivery provides the inclusion properties of CyD and targeted delivery of MNP to improve the drug delivery of DOX and EPI with high drug loading. This is due to the different conformation of inclusion, excellent biocompatibility and pH dependent drug release at the tumor site which suggests a promising approach for drug delivery against tumor cells.[128]

7. Advancements in Biomedical Applications of Cyclodextrin Systems

Natural/marine/microbial-derived polymeric materials provide a number of advantages over those of artificial polymers such as their biocompatibility, biodegradability, and biological activity, as most of them occur in the structural tissues of living organisms. Biocompatible polymers such as dextrans, alginates, hyaluronan, and chitosan etc. can be built into drug active or passive devices/ drug delivery systems or coated device in order to reduce the risk of rejection when implanted into the body. With for CyDs to be useful pharmaceutical excipients, they must be biocompatible; however, the associated toxicities are based on the route of administration. In general, CyDs have resistance to human enzymatic degradation. Nevertheless, bacterial or fungal enzymes, such as amylases, can degrade CyD complexes/conjugates. CyDs administered intravenously (IV) into an individual are thus largely excreted through renal clearance. It is reported that (LD$_{50}$) of α, β and γCyDs are $\approx$1.0, 0.79, and more than 4.0 g kg^{-1}, respectively, after parenteral injections in rodents.[6,129]

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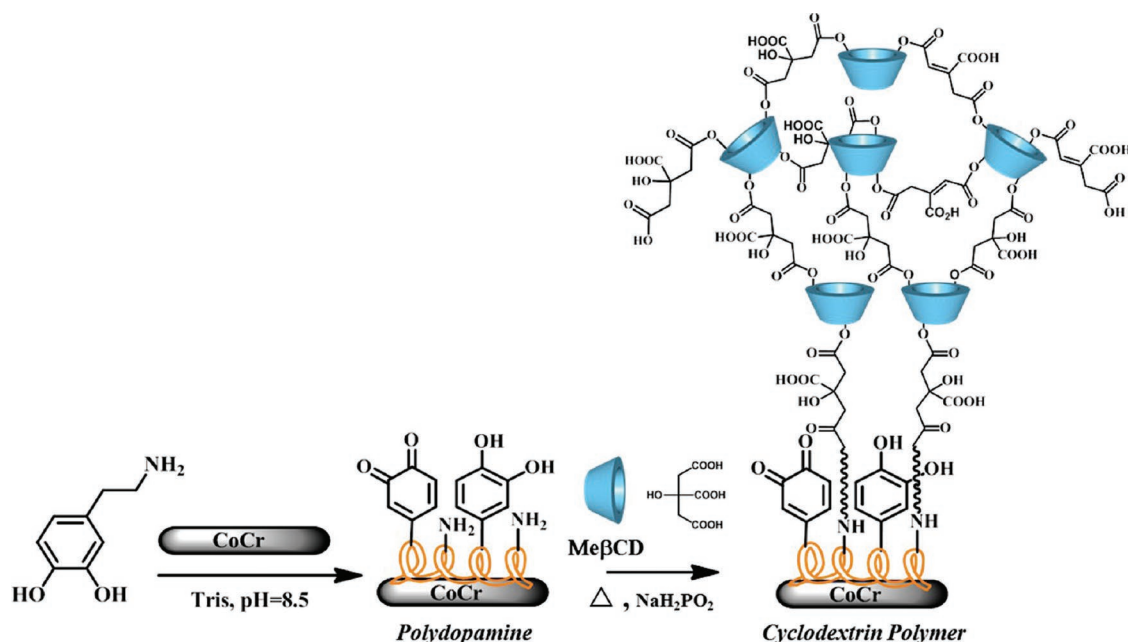*ADVANCED*
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Figure 12. Illustration of the plan utilized for the generation of functionalized CoCr vascular device with PDA and therapeutic agent loaded cyclodextrin polymer. Reproduced with permission.[132] Copyright 2014, American Chemical Society.

7.1. Cyclodextrin-Based Device Coating: Active Drug Delivery Devices

Extensive attempts have been made to utilize cyclodextrins as coating polymers on medical devices. These coating are designed to improve the loading of an active component (therapeutic agent) and its prolonged release from the medical devices to help in creating biocompatible layers on vascular stents, and to prevent postoperative infections on orthopedic implants etc. However, these methodologies are often material and its chemistry specific and not commonly relevant to many other biomedical devices.[130]

Over recent years, infections triggered by nosocomial bacteria persist as a serious problem in orthopedic surgery. To date, various approaches for the localized delivery of antibiotics have been developed to counter these types of infections. Mattioli-Belmonte et al. created a antibiotics, ciprofloxacin loaded chitosan nanoparticle-based coating over the titanium exploiting an antibiotic delivery with a combine action of sulfobutyl ether β-cyclodextrin (SBE βCyD) and β-cyclodextrin (βCyD).[131] This novel approach with effective combination of SBE βCyD (act as a counter ion for chitosan) and βCyD (antibiotic host) nanoparticle coating reduces bacterial infection and considered as a potential biocompatible antibiotic delivery method for orthopedic or dental surgical applications.

Over the past few decades, drug-eluting stent devices have been used widely for coronary artery-related diseases with associated limitations such as late acute thrombosis. Recent studies aimed to deliver the required therapeutics (e.g., antiproliferative drug—paclitaxel) in a sustained manner to improve the long-term safety, and efficacy of the devices. Sobocinski et al., 2014 fabricated the cobalt–chromium (CoCr) vascular metallic stents with surface functionalization by polydopamine (PDA) and drug loading ability of CyD polymers allows the constant release of prohealing arterial drugs (**Figure 12**). However, this study is still ongoing to evaluate the potential of an in vivo rat model.[132]

Historically, countless efforts have been made to load/functionalize/make antibiotics matrix systems onto medical devices to counteract associated infections; nonetheless these findings have resulted in only moderately short drug release patterns.[133] During the process for improving strategies, cyclodextrin polymer coatings used on the devices to improve the drug encapsulation and prolonged drug delivery. Thatiparti et al., 2010 evaluated the CyD-drug conjugate coatings to deliver the drug from the device surface gels in a sustained manner for around 200 h.[134]

Macocinschi et al., 2014 fabricated a composite system with polyurethane/β-cyclodextrin/ciprofloxacin films by ciprofloxacin as a model drug with encouraging antibacterial activity, and dynamic constitutional behavior with solid thin layer protecting systems for various medical device applications.[135] In another study, Lavoine et al., 2014 developed a new paper-based controlled release system of antibacterial agent chlorhexidine digluconate (CHX), using micro fibrillated cellulose (MFC) and CyD as coating material. Controlled release of low proportions of drug accomplished using coated-CyD, higher proportions of drug were released by utilizing the MFC and CyD together.[136]

7.2. Cyclodextrins in Bio Imaging and Therapeutic Applications

A substantial effort of research has led to an improvement in the design of the cyclodextrins based probe for in vitro cellular targeting and in vivo imaging applications as these CyD carrier can provide the sites for conjugation and accommodation of targeting ligands/drug. These are easy in surface functionalization and in constructing disease responsive moieties loaded complex structures. Cyclodextrin forms inclusion
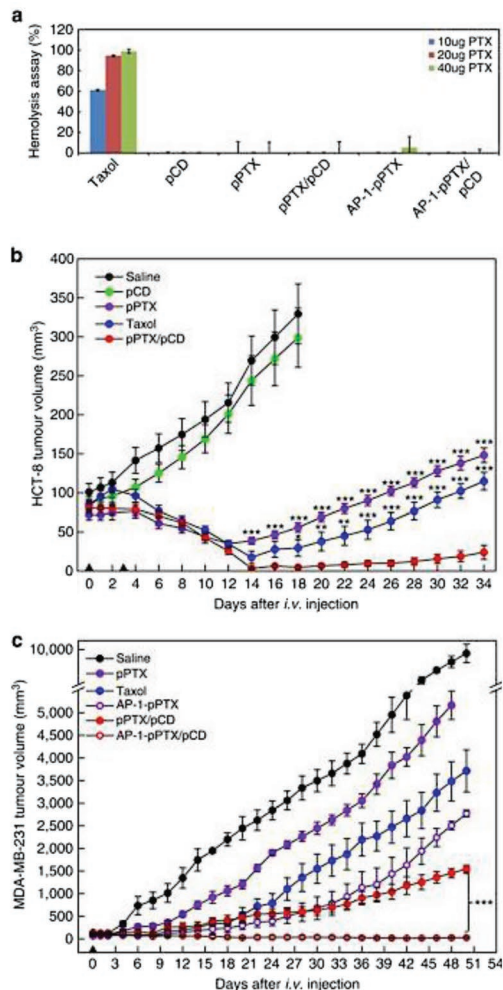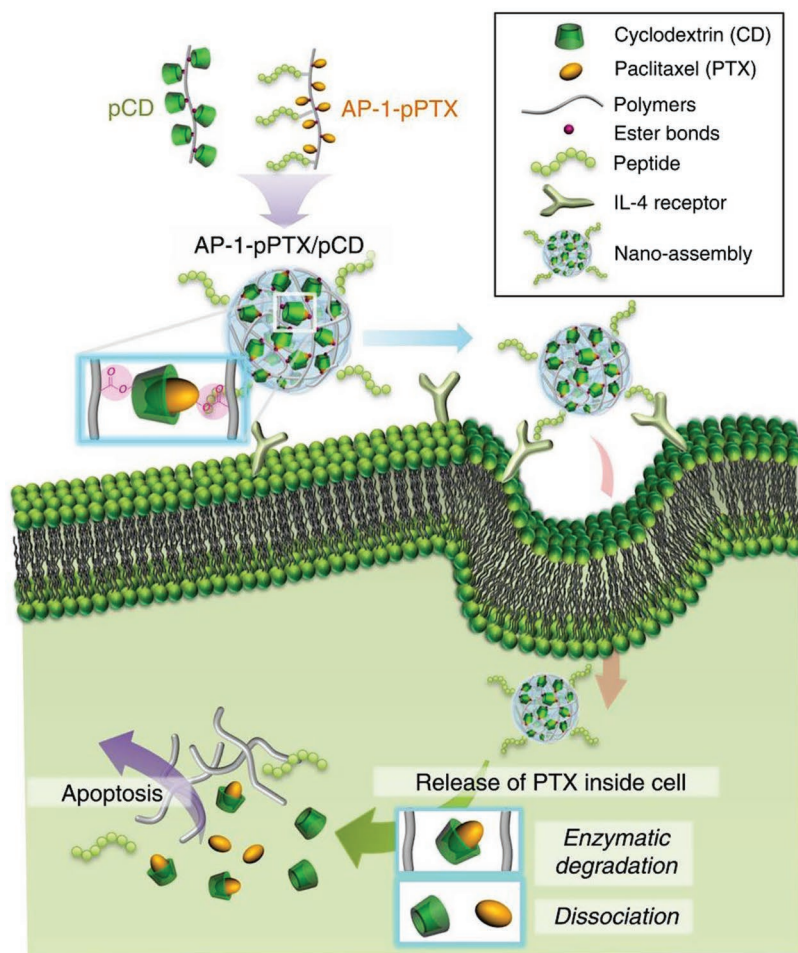
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Figure 13. Schematic picture of the nano-assembly of pCyD and pPTX and its targetability toward cancer cells with enhanced therapeutic efficacy, in vivo. Reproduced with permission.[116] Copyright 2014, Nature Publishing Group, Macmillan Publishers Limited.

complexes with a variety of hydrophobic drugs and this property was used in developing multivalent inclusion complexes that provide high drug stability during circulation and efficient drug uptake by the targeted cancer cells (reported by Namgung et al., 2014). The ester linkages between the anticancer drug (paclitaxel) and the polymer backbone facilitate effective release of paclitaxel in cellular environment by degradation and exhibits significant anti-tumor activity in in vivo (**Figure 13**).[116]

However, the in vivo antitumor targetability (might be via EPR effect) and receptor level interaction of the conjugate system for uptake mechanism is still unclear for such a type of conjugate. Another study, conducted by Bartelett et al., 2007, has shown the in vivo biodistribution and effective action of nanoparticles prepared by employing cyclodextrin-holding polycations and siRNA using positron emission tomography (PET) and bioluminescent imaging. The experimental results explain the utility of noninvasive imaging technologies for the parallel investigation about an impact of cell-specific targeting ligands on the in vivo biodistribution and the function of target specific siRNA nanocarriers (**Figure 14**).[137]

In addition to the pharmaceutical applications, βCyD also influence the extraction of cholesterol from the cell membrane with associated cellular interactions. These mechanisms enrich the opportunities that cyclodextrin molecules not only enhance solubility of hydrophobic drugs but also enhance the permeation of drug molecules across the membrane.[138] Fenyves et al., 2014 investigated the penetration activity of fluorescently labeled randomly methylated-beta-cyclodextrin (FITC-RAMEB) on Caco-2 cell layer and studied the cellular permeability of CyD on intestinal cells. The possible reported mechanism of the cellular uptake of the water-soluble FITC-RAMEB was by fluid phase endocytosis in Caco-2 cells.[139]

7.3. Diagnostics Application: Probe for the Encapsulation of Diagnostics Biomarker

Over the last decade, β-cyclodextrins have received huge interest and have been explored in self-assembly, catalysis, enhancing solubility and in sensing applications. Of those, βCyDs have a highly organized molecular system, with possible molecular

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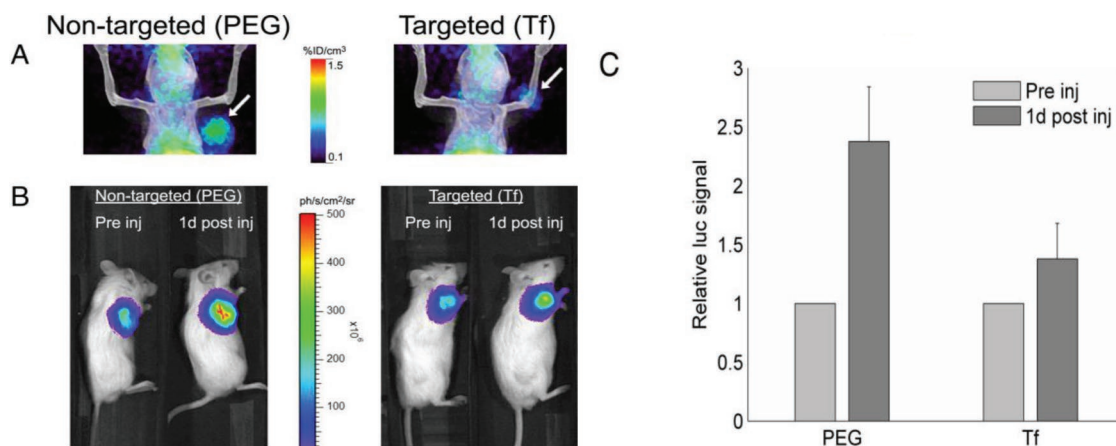**ADVANCED
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Figure 14. Multimodal in vivo imaging focusing on the biodistribution siRNA-nanoparticle and function using micro-PET/CT (positron emission tomography/computer tomography (CT) and BLI (bioluminescent imaging). Reproduced with permission.[137] Copyright 2007, The National Academy of Sciences.

interactions, host–guest complexation, reversibility of the host–guest interactions, and specific biorecognition ability that helps to design novel sensor-based devices. Ortiz et al., 2011 demonstrated the applicability of supramolecular self-assembly of conjugates on CyD surfaces for the detection of autoantibodies in human serum. The sensing element was built on thiolated βCyD polymer (CyDPSH) with modified gold electrodes and on the surface of the supramolecular self-assembled adamantane-carboxymethylcellulose-gliadin (ADA-CMC-GLI) polymers for the detection of antigliadin IgA and IgG autoantibodies from celiac disease patient samples.[140]

In a similar study, polypyrrole-cyclodextrin modified surfaces expended in sensing of antibody related to the celiac disease, in which polypyrole-CyD modified electrodes were employed as structures for the immobilization of a bifunctionalized polysaccharide having adamantane units (for docking to the CyD surface) and gliadin units on disposable screen-printed electrodes.[141] By utilizing pristine-βCyD as reducing-cum-stabilizing agent, a one-pot synthetic method was used for preparing gold nanoclusters (AuNCs) for a selective sensing of dopamine (DA) in plasma serum of human serum and parenteral

formulation, which applied for DA detection in biological and pharmaceutical applications.[142] Recently, in another study Chekin et al., 2019 developed dopamine-functionalized CyDs to a reduced state of the graphene oxide result in the fabrication of the electrochemical transducer for the real sensing of folic acid in human serum as shown in **Figure 15**.[143]

8. Conclusion

The native cyclodextrin has been established as a pharmaceutical solubilizer to enhance the solubility of hydrophobic drugs. Native cyclodextrin, α, β and γCyD have seen successfully used for modification to improve the properties of native cyclodextrin such as limited aqueous solubility of βCyD which was improved with HP-βCyD and Sulfobutylether βCyD. They have a significantly higher aqueous solubility profile than that of native βCyD and are used in drug formulation. Worldwide, around 35 formulations containing cyclodextrin were approved. The major focus was on creating the cyclodextrin that has high water solubility and negligible toxicity. The last two decades
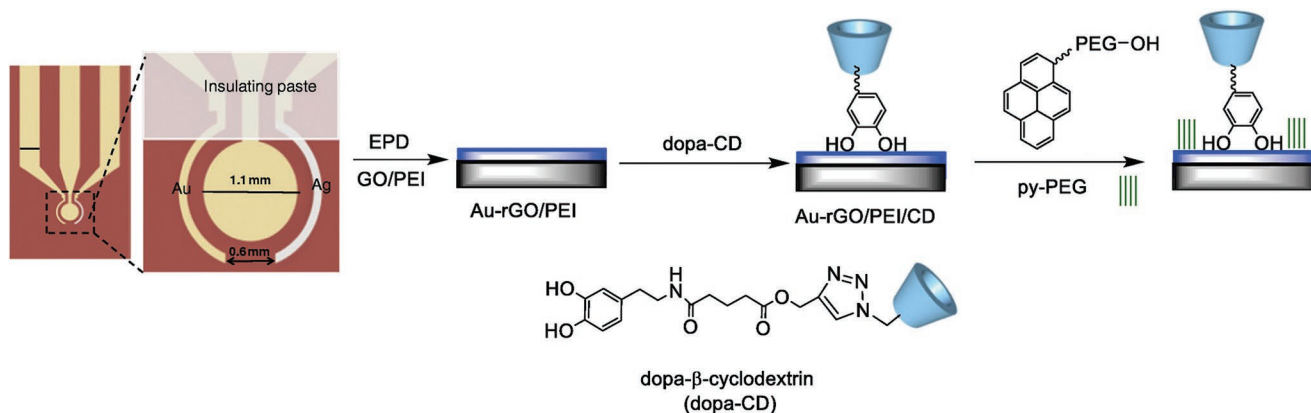

Figure 15. Pictorial illustration of assembled electrochemical sensor system consisting of reduced state of graphene oxide (rGO) fabricated by electrophoretic deposition (EPD) method which later modified with dopamine-conjugated βCyD (dopa-CyD) and O-(2-aminoethyl) polyethylene glycol modified pyrene (py-PEG). Reproduced with permission.[143] Copyright 2019, Springer Nature.

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were significant for cyclodextrin based derivatives and systems. Their potential for the formation of noncovalent interaction through the inclusion complex formation has been widely explored to develop the various nanosystems based on cyclodextrin. Polycondensation of cyclodextrin with epichlorohydrin leads to the generation of a cyclodextrin polymer which has an ability to form the self-assembled nanoparticle containing the multiple cyclodextrin unit in structure. The polymeric CyD are improved therapeutics vehicles compared to native cyclodextrin. The noncovalent interaction which is fundamental to cyclodextrin utilization in pharmaceutical and biomedical engineering has been investigated using the combined efforts of spectroscopic techniques such as UV, CD, NMR, HPLC, and fluorescence spectroscopy.

Over the preceding decade, huge interest was shown in developing the molecular machine where cyclodextrin's ability to include complex formation via noncovalent interaction has played a significant role in creating the interlocked molecular structures such as polyrotaxane, polypseudorotaxane, and polycatenane. The cyclodextrin has been a central molecule in the fabrication of supramolecular nanoassembly with noncovalent interaction via grafting with different linear and branched chain polymeric materials such as chitosan, polyethylenimine, alginate, poly(N-isopropylacrylamide), hyaluronic acid, and metallic organic framework.

The fabrication of smart and intelligent drug delivery systems is currently needed to minimize the discomfort associated with conventional drug a formulation such as a nonspecific drug distribution other than at target sites and inadequately controlled over release patterns of the drug which leads to the serious dose-related issues. Huge interest has been found in the scientific community to develop cyclodextrin-based smart and stimulus-responsive biomaterials for drug delivery and biomedical application (tissue engineering, medical devices, biosensor, and imaging). Specifically, cyclodextrin's ability of inclusion complex formation involving the association and dissociation of guest molecules with applying the stimuli such as redox (Ferrocene), light (azobenzene), pH (cyclodextrin-MSPs nanovalve), thermoresponsive polymer and enzyme responsive have been investigated to develop smart biomaterial. Moreover, cyclodextrin is an interesting material for medical devices and diagnostics. Cyclodextrin has been coupled with several biopolymers and is explored in designing the drug active medical device. Cyclodextrin has also been utilized for the encapsulation of dyes that are clinically relevant in diagnosis. Cyclodextrin is biocompatible and biodegradable with a well-established safety profile in clinical use for human and has, so far, played a major role in pharmaceutical and biomedical applications.

Conflict of Interest

The authors declare no conflict of interest.

[1] a) S. V. Kurkov, T. Loftsson, *Int. J. Pharm.* **2013**, *453*, 167; b) L. Ding, J. He, L. Huang, R. Lu, *J. Mol. Struct.* **2010**, *979*, 122.
[2] J. Li, X. J. Loh, *Adv. Drug Delivery Rev.* **2008**, *60*, 1000.
[3] T. Loftsson, P. Jarho, M. Masson, T. Järvinen, *Expert Opin. Drug Delivery* **2005**, *2*, 335.
[4] C. Alvarez-Lorenzo, C. A. García-González, A. Concheiro, *J. Controlled Release* **2017**, *268*, 269.
[5] K. Uekama, F. Hirayama, T. Irie, *Chem. Rev.* **1998**, *98*, 2045.
[6] M. E. Davis, M. E. Brewster, *Nat. Rev. Drug Discovery* **2004**, *3*, 1023.
[7] M. V. Rekharsky, Y. Inoue, *Chem. Rev.* **1998**, *98*, 1875.
[8] P. Buchwald, *J. Phys. Chem. B* **2002**, *106*, 6864.
[9] J. Wankar, G. Salzano, E. Pancani, G. Benkovics, M. Malanga, F. Manoli, R. Gref, E. Fenyvesi, I. Manet, *Int. J. Pharm.* **2017**, *531*, 568.
[10] G. Salzano, J. Wankar, S. Ottani, B. Villemagne, A. R. Baulard, N. Willand, P. Brodin, I. Manet, R. Gref, *Int. J. Pharm.* **2017**, *531*, 577.
[11] G. M. Hendy, C. B. Breslin, *J. Electroanal. Chem.* **2011**, *661*, 179.
[12] P. Mura, *J. Pharm. Biomed. Anal.* **2014**, *101*, 238.
[13] P. Mura, *J. Pharm. Biomed. Anal.* **2015**, *113*, 226.
[14] A. R. Khan, P. Forgo, K. J. Stine, V. T. D'Souza, *Chem. Rev.* **1998**, *98*, 1977.
[15] M. E. Brewster, T. Loftsson, *Adv. Drug Delivery Rev.* **2007**, *59*, 645.
[16] A. Harada, Y. Takashima, M. Nakahata, *Acc. Chem. Res.* **2014**, *47*, 2128.
[17] S. Pereva, V. Nikolova, S. Angelova, T. Spassov, T. Dudev, *Beilstein J. Org. Chem.* **2019**, *15*, 1592.
[18] J. Wankar, F. Bonvicini, G. Benkovics, V. Marassi, M. Malanga, E. Fenyvesi, G. A. Gentilomi, P. Reschiglian, B. Roda, I. Manet, *Mol. Pharmaceutics* **2018**, *15*, 3823.
[19] V. r. Setnička, M. Urbanová, V. r. Král, K. Volka, *Spectrochim. Acta, Part A* **2002**, *58*, 2983.
[20] J. C. De Miranda, T. E. A. Martins, F. Veiga, H. G. Ferraz, *Braz. J. Pharm. Sci.* **2011**, *47*, 665.
[21] E. Renard, A. Deratani, G. Volet, B. Sebille, *Eur. Polym. J.* **1997**, *33*, 49.
[22] Y. Çirpanli, E. Bilensoy, A. L. Doğan, S. Çaliş, *Eur. J. Pharm. Biopharm.* **2009**, *73*, 82.
[23] H. He, S. Chen, J. Zhou, Y. Dou, L. Song, L. Che, X. Zhou, X. Chen, Y. Jia, J. Zhang, *Biomaterials* **2013**, *34*, 5344.
[24] N. Erdoğar, G. Esendağlı, T. T. Nielsen, M. Şen, L. Öner, E. Bilensoy, *Int. J. Pharm.* **2016**, *509*, 375.

[25] R. Cavalli, M. Donalisio, A. Civra, P. Ferruti, E. Ranucci, F. Trotta, D. Lembo, *J. Controlled Release* **2009**, *137*, 116.

[26] F. Perret, C. Marminon, W. Zeinyeh, P. Nebois, A. Bollacke, J. Jose, H. Parrot-Lopez, M. Le Borgne, *Int. J. Pharm.* **2013**, *441*, 491.

[27] N. C. Bellocq, S. H. Pun, G. S. Jensen, M. E. Davis, *Bioconjugate Chem.* **2003**, *14*, 1122.

[28] F. Quaglia, L. Ostacolo, A. Mazzaglia, V. Villari, D. Zaccaria, M. T. Sciortino, *Biomaterials* **2009**, *30*, 374.

[29] T. Liu, X. Li, Y. Qian, X. Hu, S. Liu, *Biomaterials* **2012**, *33*, 2521.

[30] F. Liu, J. Antoniou, Y. Li, H. Majeed, R. Liang, Y. Ma, J. Ma, F. Zhong, *Food Hydrocolloids* **2016**, *57*, 291.

[31] M. Nahaei, H. Valizadeh, B. Baradaran, M. Nahaei, D. Asgari, S. Hallaj-Nezhadi, S. Dastmalchi, F. Lotfipour, *Drug Res.* **2013**, *63*, 7.

[32] M. d. Mariangela de Burgos, L. Tasic, J. Fattori, F. H. Rodrigues, F. C. Cantos, L. P. Ribeiro, V. de Paula, D. Ianzer, R. A. Santos, *Int. J. Nanomed.* **2011**, *6*, 1005.

[33] M. Sivasubramanian, T. Thambi, J. H. Park, *Carbohydr. Polym.* **2013**, *97*, 643.

[34] H.-Q. Tao, Q. Meng, M.-H. Li, H. Yu, M.-F. Liu, D. Du, S.-L. Sun, H.-C. Yang, Y.-M. Wang, W. Ye, *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2013**, *386*, 61.

[35] E. Bilensoy, O. Gürkaynak, M. Ertan, M. Şen, A. A. Hıncal, *J. Pharm. Sci.* **2008**, *97*, 1519.

[36] P. Mura, F. Maestrelli, M. Cecchi, M. Bragagni, A. Almeida, *J. Microencapsulation* **2010**, *27*, 479.

[37] A. Trapani, J. Sitterberg, U. Bakowsky, T. Kissel, *Int. J. Pharm.* **2009**, *375*, 97.

[38] E. Vega, M. A. Egea, A. C. Calpena, M. Espina, M. L. García, *Int. J. Nanomed.* **2012**, *7*, 1357.

[39] A. Harada, *Acc. Chem. Res.* **2001**, *34*, 456.

[40] L. Garcia-Rio, F. J. Otero-Espinar, A. Luzardo-Alvarez, J. Blanco-Mendez, *Curr. Top. Med. Chem.* **2014**, *14*, 478.

[41] A. Harada, J. Li, M. Kamachi, *Nature* **1992**, *356*, 325.

[42] G. Wenz, B.-H. Han, A. Müller, *Chem. Rev.* **2006**, *106*, 782.

[43] J. Li, C. Yang, H. Li, X. Wang, S. H. Goh, J. L. Ding, D. Y. Wang, K. W. Leong, *Adv. Mater.* **2006**, *18*, 2969.

[44] M. Arunachalam, H. W. Gibson, *Prog. Polym. Sci.* **2014**, *39*, 1043.

[45] X. Liao, G. Chen, X. Liu, W. Chen, F. Chen, M. Jiang, *Angew. Chem., Int. Ed.* **2010**, *49*, 4409.

[46] Y. Wang, H. Wang, Y. Chen, X. Liu, Q. Jin, J. Ji, *Chem. Commun.* **2013**, *49*, 7123.

[47] M. Adeli, F. Hakimpoor, M. Parsamanesh, M. Kalantari, Z. Sobhani, F. Attyabi, *Polymer* **2011**, *52*, 2401.

[48] H. Tong, Y. Wang, H. Li, Q. Jin, J. Ji, *Chem. Commun.* **2016**, *52*, 3966.

[49] H. Yamaguchi, A. Harada, *Encyclopedia of Polymeric Nanomaterials* (Eds: S. Kobayashi, K. Müllen), Springer, Berlin, Heidelberg **2015**, pp. 1796–1802.

[50] S. A. Nepogodiev, J. F. Stoddart, *Chem. Rev.* **1998**, *98*, 1959.

[51] T. Higashi, K. Morita, X. Song, J. Zhu, A. Tamura, N. Yui, K. Motoyama, H. Arima, J. Li, *Commun. Chem.* **2019**, *2*, 78.

[52] J. Zhou, H. Ritter, *Polym. Chem.* **2010**, *1*, 1552.

[53] a) B. V. Schmidt, C. Barner-Kowollik, *Angew. Chem., Int. Ed.* **2017**, *56*, 8350; b) B. V. K. J. Schmidt, M. Hetzer, H. Ritter, C. Barner-Kowollik, *Prog. Polym. Sci.* **2014**, *39*, 235.

[54] H. Hamedi, S. Moradi, S. M. Hudson, A. E. Tonelli, *Carbohydr. Polym.* **2018**, *199*, 445.

[55] T. M. M. Ways, W. M. Lau, V. V. Khutoryanskiy, *Polymers* **2018**, *10*, 267.

[56] H. Izawa, K. Yamamoto, S. Yoshihashi, S. Ifuku, M. Morimoto, H. Saimoto, *Polym. J.* **2016**, *48*, 203.

[57] Z. Yuan, Y. Ye, F. Gao, H. Yuan, M. Lan, K. Lou, W. Wang, *Int. J. Pharm.* **2013**, *446*, 191.

[58] a) B. A. Aderibigbe, B. Buyana, *Pharmaceutics* **2018**, *10*, 42; b) J. Venkatesan, I. Bhatnagar, P. Manivasagan, K.-H. Kang, S.-K. Kim, *Int. J. Biol. Macromol.* **2015**, *72*, 269.

[59] W. Pluemsab, N. Sakairi, T. Furuike, *Polymer* **2005**, *46*, 9778.

[60] T. Hosseinifar, S. Sheybani, M. Abdouss, S. A. Hassani Najafabadi, M. Shafiee Ardestani, *J. Biomed. Mater. Res., Part A* **2018**, *106*, 349.

[61] S. Vaidyanathan, J. Chen, B. G. Orr, M. M. Banaszak Holl, *Mol. Pharmaceutics* **2016**, *13*, 1967.

[62] H. Lv, S. Zhang, B. Wang, S. Cui, J. Yan, *J. Controlled Release* **2006**, *114*, 100.

[63] S. H. Pun, N. C. Bellocq, A. Liu, G. Jensen, T. Machemer, E. Quijano, T. Schluep, S. Wen, H. Engler, J. Heidel, *Bioconjugate Chem.* **2004**, *15*, 831.

[64] J. T. Zhang, Y. N. Xue, F. Z. Gao, S. W. Huang, R. X. Zhuo, *J. Appl. Polym. Sci.* **2008**, *108*, 3031.

[65] R. Suntornnond, J. An, C. K. Chua, *Macromol. Mater. Eng.* **2017**, *302*, 1600266.

[66] H.-D. Wang, L.-Y. Chu, X.-Q. Yu, R. Xie, M. Yang, D. Xu, J. Zhang, L. Hu, *Ind. Eng. Chem. Res.* **2007**, *46*, 1511.

[67] O. Kretschmann, S. W. Choi, M. Miyauchi, I. Tomatsu, A. Harada, H. Ritter, *Angew. Chem., Int. Ed.* **2006**, *45*, 4361.

[68] M. Hemshekhar, R. M. Thushara, S. Chandranayaka, L. S. Sherman, K. Kemparaju, K. S. Girish, *Int. J. Biol. Macromol.* **2016**, *86*, 917.

[69] G. Mattheolabakis, L. Milane, A. Singh, M. M. Amiji, *J. Drug Targeting* **2015**, *23*, 605.

[70] J. E. Mealy, C. B. Rodell, J. A. Burdick, *J. Mater. Chem. B* **2015**, *3*, 8010.

[71] A. Charlot, A. Heyraud, P. Guenot, M. Rinaudo, R. Auzély-Velty, *Biomacromolecules* **2006**, *7*, 907.

[72] C. B. Rodell, A. L. Kaminski, J. A. Burdick, *Biomacromolecules* **2013**, *14*, 4125.

[73] P. Horcajada, T. Chalati, C. Serre, B. Gillet, C. Sebrie, T. Baati, J. F. Eubank, D. Heurtaux, P. Clayette, C. Kreuz, J.-S. Chang, Y. K. Hwang, V. Marsaud, P.-N. Bories, L. Cynober, S. Gil, G. Férey, P. Couvreur, R. Gref, *Nat. Mater.* **2010**, *9*, 172.

[74] S. S. Nadar, L. Vaidya, S. Maurya, V. K. Rathod, *Coord. Chem. Rev.* **2019**, *396*, 1.

[75] a) T. Rajkumar, D. Kukkar, K.-H. Kim, J. R. Sohn, A. Deep, *J. Ind. Eng. Chem.* **2019**, *72*, 50; b) Y. Han, W. Liu, J. Huang, S. Qiu, H. Zhong, D. Liu, J. Liu, *Pharmaceutics* **2018**, *10*, 271.

[76] K. J. Hartlieb, D. P. Ferris, J. M. Holcroft, I. Kandela, C. L. Stern, M. S. Nassar, Y. Y. Botros, J. F. Stoddart, *Mol. Pharmaceutics* **2017**, *14*, 1831.

[77] X. Li, T. Guo, L. Lachmanski, F. Manoli, M. Menendez-Miranda, I. Manet, Z. Guo, L. Wu, J. Zhang, R. Gref, *Int. J. Pharm.* **2017**, *531*, 424.

[78] R. Langer, *Sci. Am.* **2003**, *288*, 50.

[79] E. S. Gil, S. M. Hudson, *Prog. Polym. Sci.* **2004**, *29*, 1173.

[80] S. Ganta, H. Devalapally, A. Shahiwala, M. Amiji, *J. Controlled Release* **2008**, *126*, 187.

[81] Y. Liu, W. Wang, J. Yang, C. Zhou, J. Sun, *Asian J Pharm. Sci.* **2013**, *8*, 159.

[82] Z. Li, N. Song, Y.-W. Yang, *Matter* **2019**, *1*, 345.

[83] S. Saha, K. F. Leung, T. D. Nguyen, J. F. Stoddart, J. I. Zink, *Adv. Funct. Mater.* **2007**, *17*, 685.

[84] H. Meng, M. Xue, T. Xia, Y.-L. Zhao, F. Tamanoi, J. F. Stoddart, J. I. Zink, A. E. Nel, *J. Am. Chem. Soc.* **2010**, *132*, 12690.

[85] L. Bai, Q. Zhao, J. Wang, Y. Gao, Z. Sha, D. Di, N. Han, Y. Wang, J. Zhang, S. Wang, *Nanotechnology* **2015**, *26*, 165704.

[86] Y. Shen, M. Li, T. Liu, J. Liu, Y. Xie, J. Zhang, S. Xu, H. Liu, *Int. J. Nanomed.* **2019**, *14*, 4029.

[87] H. Tian, J. Chen, X. Chen, *Small* **2013**, *9*, 2034.

[88] H. Chen, X. Liu, Y. Dou, B. He, L. Liu, Z. Wei, J. Li, C. Wang, C. Mao, J. Zhang, *Biomaterials* **2013**, *34*, 4159.

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[89] Q. Shi, L. Zhang, M. Liu, X. Zhang, X. Zhang, X. Xu, S. Chen, X. Li, J. Zhang, *Biomaterials* **2015**, *67*, 169.

[90] J. Deng, X. Liu, W. Shi, C. Cheng, C. He, C. Zhao, *ACS Macro Lett.* **2014**, *3*, 1130.

[91] S. K. M. Nalluri, B. J. Ravoo, *Angew. Chem., Int. Ed.* **2010**, *49*, 5371.

[92] S. Tamesue, Y. Takashima, H. Yamaguchi, S. Shinkai, A. Harada, *Angew. Chem., Int. Ed.* **2010**, *49*, 7461.

[93] H. Yamaguchi, Y. Kobayashi, R. Kobayashi, Y. Takashima, A. Hashidzume, A. Harada, *Nat. Commun.* **2012**, *3*, 603.

[94] H. Lin, W. Xiao, S.-Y. Qin, S.-X. Cheng, X.-Z. Zhang, *Polym. Chem.* **2014**, *5*, 4437.

[95] E. Wajs, T. T. Nielsen, K. L. Larsen, A. Fragoso, *Nano Res.* **2016**, *9*, 2070.

[96] T. Kakuta, Y. Takashima, M. Nakahata, M. Otsubo, H. Yamaguchi, A. Harada, *Adv. Mater.* **2013**, *25*, 2849.

[97] Y. Takashima, S. Hatanaka, M. Otsubo, M. Nakahata, T. Kakuta, A. Hashidzume, H. Yamaguchi, A. Harada, *Nat. Commun.* **2012**, *3*, 1270.

[98] Y. Hao, H. Cui, J. Meng, S. Wang, *J. Photochem. Photobiol., A* **2018**, *355*, 202.

[99] Q. Bian, W. Wang, S. Wang, G. Wang, *ACS Appl. Mater. Interfaces* **2016**, *8*, 27360.

[100] Y.-H. Gong, C. Li, J. Yang, H.-Y. Wang, R.-X. Zhuo, X.-Z. Zhang, *Macromolecules* **2011**, *44*, 7499.

[101] T. Tanaka, *Phys. Rev. Lett.* **1978**, *40*, 820.

[102] S. D. Fitzpatrick, L. E. Fitzpatrick, A. Thakur, M. A. J. Mazumder, H. Sheardown, *Expert Rev. Med. Devices* **2012**, *9*, 339.

[103] X. S. Wu, A. S. Hoffman, P. Yager, *J. Polym. Sci., Part A: Polym. Chem.* **1992**, *30*, 2121.

[104] S.-k. Ahn, R. M. Kasi, S.-C. Kim, N. Sharma, Y. Zhou, *Soft Matter* **2008**, *4*, 1151.

[105] P. Yi, Y. Wang, P. He, Y. Zhan, Z. Sun, Y. Li, Y. Zhang, *Mater. Sci. Eng., C* **2017**, *78*, 773.

[106] Y. Zhou, X. Fan, D. Xue, J. Xing, J. Kong, *React. Funct. Polym.* **2013**, *73*, 508.

[107] B. V. Schmidt, M. Hetzer, H. Ritter, C. Barner-Kowollik, *Macromolecules* **2013**, *46*, 1054.

[108] Y.-Y. Liu, Y.-B. Zhong, J.-K. Nan, W. Tian, *Macromolecules* **2010**, *43*, 10221.

[109] D. Astruc, *Eur. J. Inorg. Chem.* **2017**, *2017*, 6.

[110] H. Gu, S. Mu, G. Qiu, X. Liu, L. Zhang, Y. Yuan, D. Astruc, *Coord. Chem. Rev.* **2018**, *364*, 51.

[111] M. Nakahata, Y. Takashima, H. Yamaguchi, A. Harada, *Nat. Commun.* **2011**, *2*, 511.

[112] D. Zhang, Y. Wei, K. Chen, X. Zhang, X. Xu, Q. Shi, S. Han, X. Chen, H. Gong, X. Li, *Adv. Healthcare Mater.* **2015**, *4*, 69.

[113] Q. Zhang, F. Zhang, Y. Chen, Y. Dou, H. Tao, D. Zhang, R. Wang, X. Li, J. Zhang, *Chem. Mater.* **2017**, *29*, 8221.

[114] Y. Ping, Q. Hu, G. Tang, J. Li, *Biomaterials* **2013**, *34*, 6482.

[115] R. De La Rica, D. Aili, M. M. Stevens, *Adv. Drug Delivery Rev.* **2012**, *64*, 967.

[116] R. Namgung, Y. M. Lee, J. Kim, Y. Jang, B.-H. Lee, I.-S. Kim, P. Sokkar, Y. M. Rhee, A. S. Hoffman, W. J. Kim, *Nat. Commun.* **2014**, *5*, 3702.

[117] C. Park, H. Kim, S. Kim, C. Kim, *J. Am. Chem. Soc.* **2009**, *131*, 16614.

[118] J. Guo, H. Tao, Y. Dou, L. Li, X. Xu, Q. Zhang, J. Cheng, S. Han, J. Huang, X. Li, *Mater. Today* **2017**, *20*, 493.

[119] B. Rastegari, H. R. Karbalaei-Heidari, S. Zeinali, H. Sheardown, *Colloids Surf., B* **2017**, *158*, 589.

[120] Y.-J. Cheng, G.-F. Luo, J.-Y. Zhu, X.-D. Xu, X. Zeng, D.-B. Cheng, Y.-M. Li, Y. Wu, X.-Z. Zhang, R.-X. Zhuo, F. He, *ACS Appl. Mater. Interfaces* **2015**, *7*, 9078.

[121] T. Ogoshi, Y. Takashima, H. Yamaguchi, A. Harada, *J. Am. Chem. Soc.* **2007**, *129*, 4878.

[122] M. Arruebo, R. Fernández-Pacheco, M. R. Ibarra, J. Santamaría, *Nano Today* **2007**, *2*, 22.

[123] O. Veiseh, J. W. Gunn, M. Zhang, *Adv. Drug Delivery Rev.* **2010**, *62*, 284.

[124] S. Hong, Z. Li, C. Li, C. Dong, S. Shuang, *Appl. Surf. Sci.* **2018**, *427*, 1189.

[125] P. Chen, H. Song, S. Yao, X. Tu, M. Su, L. Zhou, *RSC Adv.* **2017**, *7*, 29025.

[126] J. H. Lee, K. J. Chen, S. H. Noh, M. A. Garcia, H. Wang, W. Y. Lin, H. Jeong, B. J. Kong, D. B. Stout, J. Cheon, *Angew. Chem., Int. Ed.* **2013**, *52*, 4384.

[127] S. S. Banerjee, D.-H. Chen, *Chem. Mater.* **2007**, *19*, 6345.

[128] C. Wang, L. Huang, S. Song, B. Saif, Y. Zhou, C. Dong, S. Shuang, *Appl. Surf. Sci.* **2015**, *357*, 2077.

[129] a) D. Frank, J. Gray, R. Weaver, *Am. J. Pathol.* **1976**, *83*, 367; b) in *Cyclodextrins in Pharmaceutics, Cosmetics, and Biomedicine: Current and Future Industrial Applications* (Ed: E. Bilensoy), 1st ed., John Wiley & Sons, Inc, **2011**, p. 91, https://doi.org/10.1002/9780470926819.

[130] A. Concheiro, C. Alvarez-Lorenzo, *Adv. Drug Delivery Rev.* **2013**, *65*, 1188.

[131] M. Mattioli-Belmonte, S. Cometa, C. Ferretti, R. Iatta, A. Trapani, E. Ceci, M. Falconi, E. De Giglio, *Carbohydr. Polym.* **2014**, *110*, 173.

[132] J. Sobocinski, W. Laure, M. Taha, E. °Courcot, F. Chai, N. Simon, A. Addad, B. Martel, S. Haulon, P. Woisel, *ACS Appl. Mater. Interfaces* **2014**, *6*, 3575.

[133] a) M. M. Tambuwala, M. C. Manresa, E. P. Cummins, V. Aversa, I. S. Coulter, C. T. Taylor, *J. Controlled Release* **2015**, *217*, 221; b) N. Blanchemain, S. Haulon, B. Martel, M. Traisnel, M. Morcellet, H. Hildebrand, *Eur. J. Vasc. Endovasc. Surg.* **2005**, *29*, 628.

[134] T. R. Thatiparti, A. J. Shoffstall, H. A. Von Recum, *Biomaterials* **2010**, *31*, 2335.

[135] D. Macocinschi, D. Filip, S. Vlad, C. G. Tuchilus, A. F. Cristian, M. Barboiu, *J. Mater. Chem. B* **2014**, *2*, 681.

[136] N. Lavoine, N. Tabary, I. Desloges, B. Martel, J. Bras, *Colloids Surf., B* **2014**, *121*, 196.

[137] D. W. Bartlett, H. Su, I. J. Hildebrandt, W. A. Weber, M. E. Davis, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 15549.

[138] Z. Hammoud, N. Khreich, L. Auezova, S. Fourmentin, A. Elaissari, H. Greige-Gerges, *Int. J. Pharm.* **2019**, *564*, 59.

[139] F. Fenyvesi, K. Réti-Nagy, Z. Bacsó, Z. Gutay-Tóth, M. Malanga, É. Fenyvesi, L. Szente, J. Váradi, Z. Ujhelyi, P. Fehér, *PLoS One* **2014**, *9*, e84856.

[140] M. Ortiz, A. Fragoso, C. K. O'Sullivan, *Anal. Chem.* **2011**, *83*, 2931.

[141] E. Wajs, N. Fernández, A. Fragoso, *Analyst* **2016**, *141*, 3274.

[142] M. I. Halawa, F. Wu, T. H. Fereja, B. Lou, G. Xu, *Sens. Actuators, B* **2018**, *254*, 1017.

[143] F. Chekin, V. Mishyn, A. Barras, J. Lyskawa, R. Ye, S. Melinte, P. Woisel, R. Boukherroub, S. Szunerits, *Anal. Bioanal. Chem.* **2019**, *411*, 5149.

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