

SELF-ASSEMBLY OF SUPRAMOLECULAR AMPHIPHILIC BLOCK COPOLYMERS

Abstract

Self-assembled aggregates of supramolecular amphiphilic block copolymers (ABCs), in aqueous solutions, have received ever-increasing interest in the recent years due to their advantages viz. easy preparation, efficient loading of drug without any chemical change, and controlled drug release. In specific, self-assembly of cyclodextrin (CD) based ABCs has been a challenging topic in the field of supramolecular chemistry since it provides the spontaneous generation of well-defined aggregations containing functional host sites with potential applications as drug-carrier systems. CDs, with a hydrophobic central cavity and a hydrophilic outer surface, are a series of natural cyclic oligosaccharides. Due to their biocompatibility, low toxicity, and complexation ability with a variety of hydrophobic moieties, they have been most widely employed as host units to construct polymeric micelles. In this chapter, we discuss the basic concepts and recent developments on self-assembly aggregates of cyclodextrin based ABCs.

Keywords: Amphiphilic Block Copolymers; B-Cyclodextrin; Self—Assembly; Stimuli-Responsive Polymeric Micelles.

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I. INTRODUCTION

Self-assembled nanostructures containing dense aqueous insoluble cores with diffuse outer shell surroundings can be fabricated from conventional amphiphilic block copolymers (ABCs). These self-assembled nanostructures, such as polymeric micelles, can be employed as carriers in biomedical applications for drug and gene delivery, maximize therapeutic effects of drugs and to minimize the negative side effects of chemotherapy, protein encapsulation, targeted release of the drugs in cancer cells and broadly used in pharmaceutical industries [1-4]. Development of stimuli-responsive supramolecular micelles, having therapeutic applications, received much interest in recent years [5]. Developing dynamic and reversible aggregates which are capable of releasing encapsulated cargos under desired environment is very important to enhance their application in the controlled release systems. Synthetic organic receptors like calixarenes, crown ethers, cucurbiturils and cyclodextrins (CDs) have been widely used as molecular receptors, since the origin of molecular recognition chemistry, in host—guest interactions [6, 7]. Cyclodextrins are a series of natural cyclic oligosaccharides. The hosting properties of cyclodextrins play crucial role in obtaining host—guest supramolecular polymers. Because of their unique capability of forming host—guest complexes, and many other useful biological and physicochemical properties, these natural CDs and their derivatives, have been recognized as important natural host molecules in the field of supramolecular chemistry [8,9]. Recent investigations have proved the promising applications of cyclodextrin based host—guest complexes, particularly in the areas of biomedicine and biotechnology [10]. These molecules form very stable host—guest complexes, which guarantee high degree of polymerization [11-13]. β -cyclodextrin (β -CD) based inclusion complexes, among other supramolecular based inclusion complexes, have received much attention due to their high association constant with guest molecules such as adamantane (AD). In order to obtain supramolecular micelles, various stimuli-responsive polymers can be constructed through host—guest interactions. Micelles produced by self—assembly of supramolecular amphiphilic copolymers containing hydrophilic and hydrophobic segments are stimuli responsive under the environmental changes such as pH, redox, enzymes and temperature [14-16]. Various coupling reactions (click chemistry) and polymerization techniques like atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer polymerization (RAFT) and ring-opening polymerization (ROP) are employed in the construction of supramolecular ABCs. These strategies make good control over the degree of polymerization and thus molecular weight of the constructed polymers [17, 18]. These biocompatible and biodegradable supramolecular ABC micelles can be efficient in drug loading, without causing any chemical change in the parent drug, and controlled drug release [14]. In this chapter, we have mainly focused on β -CD based supramolecular amphiphilic block copolymers and their self—assembly study.

- 1. Cyclodextrins:** In supramolecular chemistry, α -, β -, and γ - cyclodextrins (CDs), a series of α -1,4-linked cyclic oligosaccharides composed of 6, 7, or 8 D-(+)-glucose repeat units respectively (Figure 1), are widely used as the functional macrocyclic host molecules due to their water solubility, biocompatible properties and low cost. Various fermented consumer products, such as beer, contain small amounts of these natural products. Although the unsubstituted α -CD, β -CD, and γ -CD, and their complexes are hydrophilic, their solubility is somewhat limited in aqueous solutions (especially that of β -CD) [19, 20]. The molecules are commonly described as truncated cone, bucket-like or donut-

shaped, with a hydrophilic outer surface and a relatively hydrophobic inner cavity that allows entrapment of small hydrophobic drug molecules or hydrophobic moieties of larger molecules [21]. To construct host—guest delivery carriers, CDs have been used as host units. A variety of lipophilic drugs which are able to fit inside the hydrophobic cavity can be accommodated inside the cavity of CDs, and the solubility of hydrophobic drugs and the stability of labile drugs can be improved due to the hydrophobic interactions [22]. The interior of CDs is somewhat hydrophobic as the inner walls of CDs are formed by the hydrophobic carbon backbones of glucopyranose monomers. This structural feature of CDs predetermined their application as solubilizers for poorly water-soluble drugs. CDs are non-toxic towards humans. Simple dissolution of solid drug/CDs complexes and dilution of aqueous complexation media are the major driving forces for drug release from the CDs complex [23].

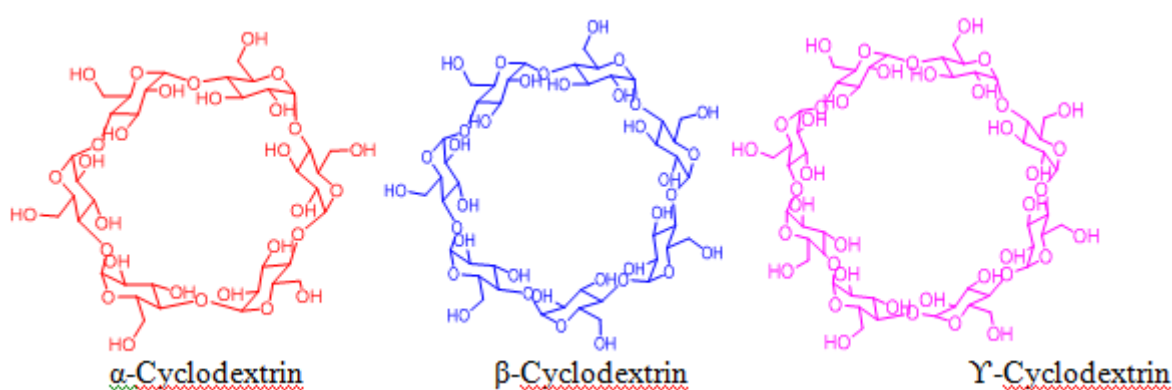


Figure 1: Structures of Various Cyclodextrins

- β-Cyclodextrin:** β-Cyclodextrin (Figure 2), one of the cyclodextrins, can accommodate various guest molecules into its truncated cone-shaped hydrophobic cavity. It is a cyclic oligosaccharide consisting of 7-D (+)-glucopyranose units with 7- primary and 14-secondary alcoholic –OH functional groups [24]. β-CD originating from starch is eco-friendly, renewable, cost-effective, and easily soluble and has non-immunogenicity, good biocompatibility and low toxicity [25]. β-CD possesses a hydrophilic exterior surface and hydrophobic interior cavity, and has been widely recognized as a host for many guest molecules. Moreover, the ideal cavity sizes of CDs allow these supramolecules to include a variety of guest hydrophobic molecules in their bucket shaped interior. Adamantane (AD), one of the potential guest molecules, has complementary size for β-CD and high hydrophobicity. For this reason, AD has great affinities towards β-CD ($K_{eq} \approx 10^5 M^{-1}$) [26].

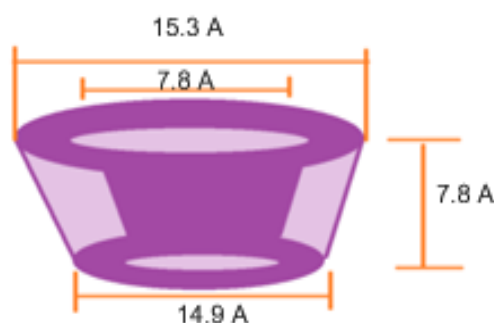


Figure 2: Cavity Sizes of β-Cyclodextrin

- 3. Amphiphiles:** Amphiphiles are compounds possessing both hydrophilic (water-loving) and hydrophobic (water-hating) components. In conventional head/tail(s) amphiphiles, the hydrophobic part consists generally of a long (saturated or unsaturated) hydrocarbon chain, while the hydrophilic head can be either nonionic or ionic. Amphiphiles are often called as surfactants due to their ability to reduce the interfacial tension. This ability of amphiphilic molecules enable them to play an important role as detergents, dispersants, emulsifiers, and wetting and foaming agents in several applications [27]. Self-assembling systems based on amphiphilic compounds find wide application in different fundamental and practical areas due to their unique ability to form nanoscale aggregates with gradients of polarity, viscosity, electric charge and other properties [28].
- 4. Amphiphilic Block Copolymer:** Amphiphilic block copolymers are of great interest owing to their unique chemical structure with hydrophilic and hydrophobic segments (Figure 3). They can form micelles in selective solvents, with soluble and insoluble segments forming the core and shell, respectively [29]. In aqueous solution, the hydrophobic chain core is efficiently encapsulated and stabilized by the hydrophilic shell [30]. ABCs consist of at least two regions of distinct chemical nature that undergo phase separation as a result of chain association in solvents that selectively dissolve one of the blocks. This unique architecture enables polymeric micelles to serve as nanoscopic depots or stabilizers for poorly water-soluble compounds. There has been great interest in the use of polymeric micelles as drug carriers. The functional properties of micelles based on ABCs, render them ideal for encapsulation and delivery of hydrophobic drugs [31].

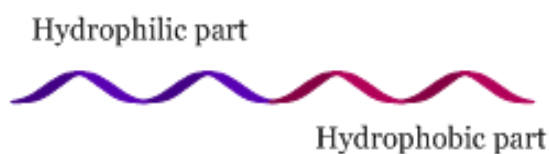


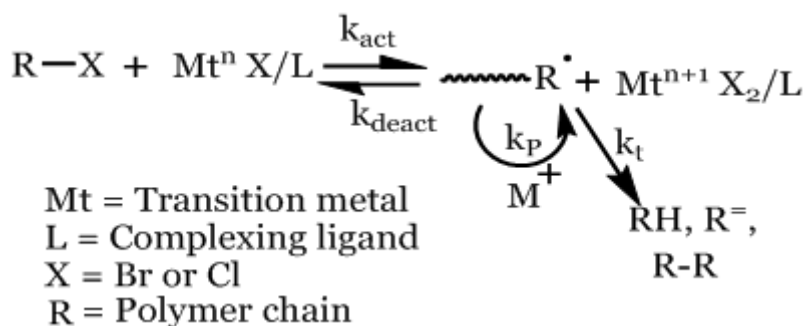
Figure 3: Structure of Amphiphilic Block Polymer

- 5. Supramolecular Amphiphilic Block Copolymer:** Supramolecular polymerization has been recognized as one of the significant approaches to design delivery systems. The self-assembling ability allows the formation of polymeric nanoparticles with various components offering required binding strength which is from non-covalent interactions [6]. It is important to note here that, this research area has progressed from regular amphiphiles, such as surfactants, towards giant amphiphiles, such as ABCs, and further to supra-amphiphiles. Conventional amphiphiles are constructed on the basis of covalent bonds whereas in supra-amphiphiles, the amphiphiles comprise dynamic covalent bonds or noncovalent interactions [32]. On the other hand, host—guest complexes are formed by the combination of geometric fitting within the interaction structure and hydrophobic interactions. There has been emerging interest, in the recent years, in polymeric supramolecular micelles based amphiphilic block copolymer with supramolecular interactions of promising application of pharmaceutical in drug carriers and drug delivery system [33]. Because of the growing interest of the scientists in the areas of micelles, vesicle, grafting and hydrogel, and so on, the supramolecular polymeric materials have been reviewed for several times. In this chapter, we focused mainly on the recent stimuli-responsive supramolecular amphiphilic block copolymers [34].

II. METHODS FOR SYNTHESIS OF BLOCK COPOLYMERS

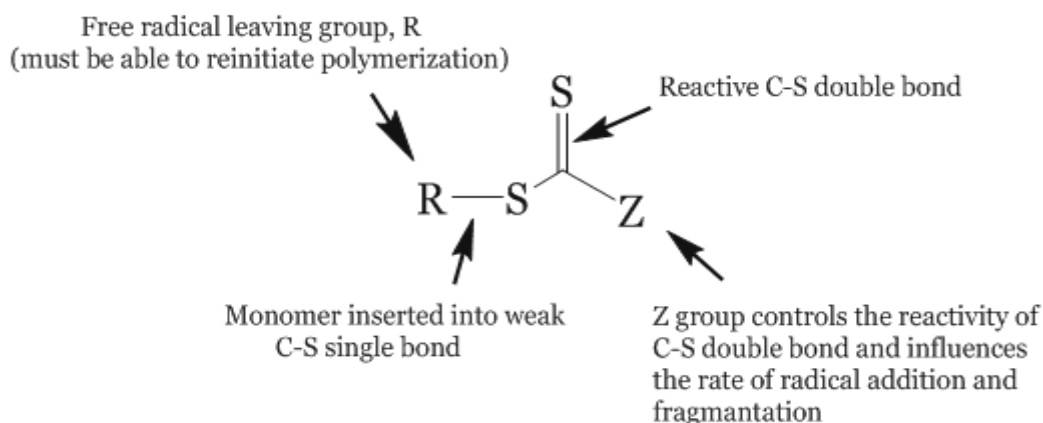
Block copolymers are a specific class of copolymers, in which the chemically distinct monomer units are grouped in discrete blocks along the polymer chain. Recently, a variety of techniques have been devised for the creation of block copolymers, ranging from the combination of controlled and/or live polymerizations with block copolymers with predictable molecular weights and homogenous chain lengths [35]. Controlled/living radical polymerizations like atom transfer radical polymerization, reversible addition-fragmentation chain-transfer polymerization and ring opening polymerization enabled the scope of combination polymerization to reach new dimensions in the preparation of block copolymers [36].

1. **ATRP:** Atom transfer radical polymerization is a controlled/living radical polymerization that produces block copolymers and star copolymers, as well as polymers with high molecular weights, narrow molecular weight ranges, and sophisticated macromolecular structures. The equilibrium process of ATRP is controlled by a transition metal complex. Through a reversible redox process, the transition metal complex ($Mt^n X/L$), acting as an activator, causes the homogenous cleavage of the alkyl halide bond ($R-X$). The rate constants for activation and deactivation reactions of this equilibrium are k_{act} and k_{deact} , respectively. The ratio of the number of bimolecular termination reactions will decrease and the polymerization process will resemble a living system when $k_{deact} \gg k_{act}$, and the rate of initiation is significantly greater than the rate of propagation. The termination and propagation rate constants are represented in the provided (Scheme 1), by k_t and k_p , respectively [37, 38].

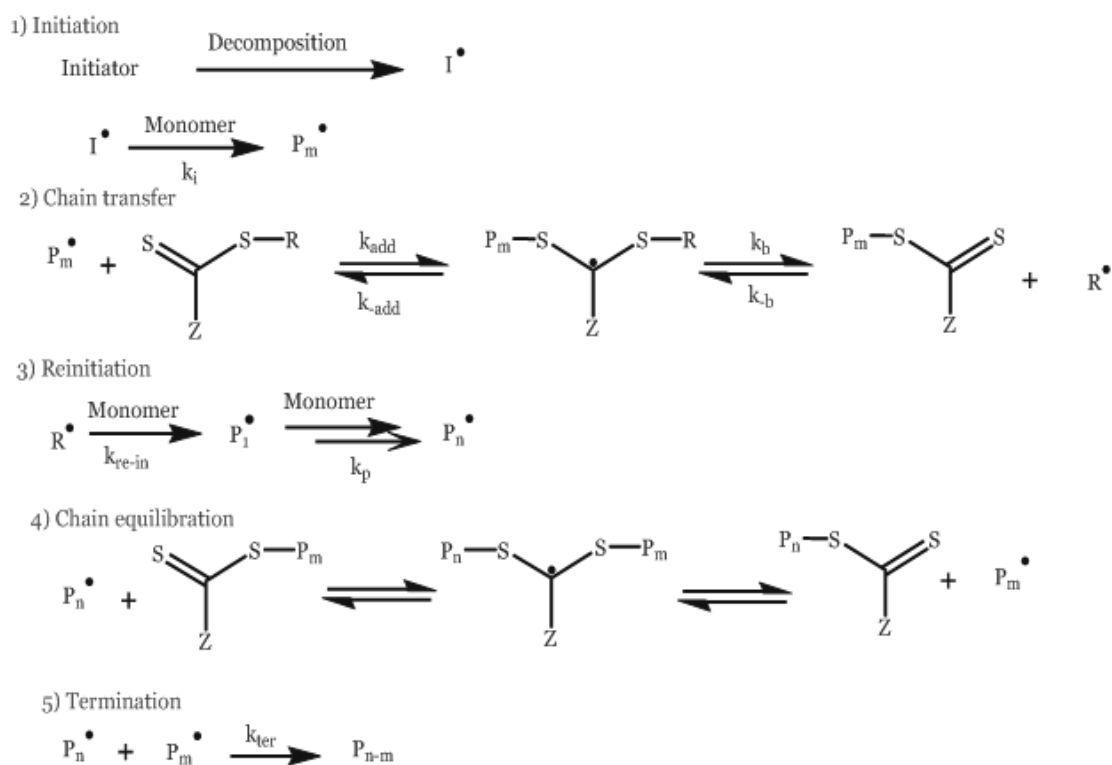


Scheme 1: Reversible Equilibrium of Metal Complex Mediated ATRP

2. **RAFT Polymerization:** Reversible addition-fragmentation chain transfer polymerization enables the synthetic creation of macromolecules with elaborate architectures, such as block, graft, and star structures with specified molecular weight, terminal functionality, and confined molecular weight dispersion. These polymerizations should ideally yield polymer products that are able to be reactivated for chain extension or block synthesis, give molecular weights that are specified by reagent concentrations and conversion, and enable very narrow polydispersities. RAFT agents are organic compounds possessing a thiocarbonylthio moiety [39]. The generic structure of RAFT agents is shown in Scheme 2.



Scheme 2: Generic Structure of RAFT Agent

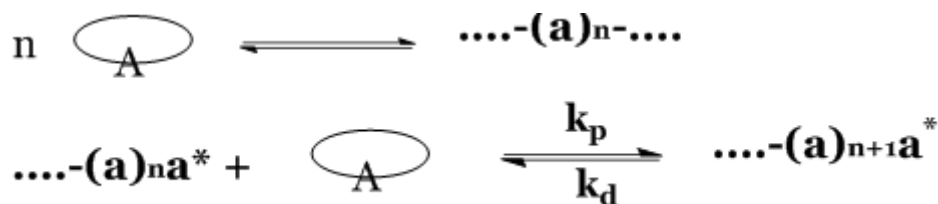


Scheme 3: Mechanism of RAFT Polymerization

The mechanism of RAFT polymerization is shown in Scheme 3. A radical is produced in the initiation step from initiator and it attacks on monomer to yield a propagated radical (step 1). A radical intermediate is created when this radical reacts with the RAFT agent. This radical intermediate has the ability to split into the original RAFT agent and an oligomeric radical species, or it can split back into the original radical agent and a reinitiating R radical species. R should be built with a good reinitiating group in mind. Additionally, it must fragment at least as quickly as the polymer chains or initiator from the stabilized radical intermediate (step 2). Following the initialization step, polymer chains expand by adding monomer (step 3), and they quickly exchange between the thiocarbonylthio group-capped species (step 4) and any increasing radicals that are

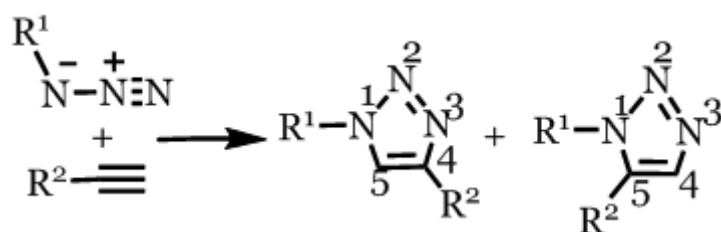
already present (as in the propagation step). The quick interchange in the chain transfer step is demonstrated by the smaller concentration of developing radical chains than that of stabilized radical intermediates, which restricts the termination reactions. Although limited but the termination reactions still occur via combination or disproportionation mechanisms (step 5).

3. **ROP:** In ring-opening polymerization, a reactive centre on one polymer chain's terminal end interacts with a different cyclic monomer to open the ring system and create a longer polymer chain. Ionic, cationic, or radical reactive centre can all be found at the terminal end of polymer chains. These cyclic monomers typically have heteroatoms, alkenes, or alkanes in the ring. Depending on the kind and size of the ring structure, polymerization capacity and the accompanying driving force differ. Many useful polymers, such as polyesters, have been produced by ring-opening polymerization from cyclic ester (lactones) [40]. Cyclic monomers should have the ability to polymerize in accordance with ring opening polymerization (Scheme 4), which transforms the monomer molecule into repeating units of the polymer. Where "A" represents for the monomer, "a" is the repeating unit of a macromolecule formed from the A monomer, and "n" is the number of monomers. While the basic reaction for the growth of the macromolecule chain can be expressed as, where a* denotes the active species, and k_p and k_d are the rate constant of propagation and de-propagation, respectively.



Scheme 4: Chain Growth Ring Opening Polymerization Technique

4. **Click Chemistry:** Click chemistry concept has been introduced by Sharpless and his coworkers. The term "click" describes chemical reactions that have the potential to be used extensively in synthetic chemistry because they are effective, versatile, particular, and energetically favored. For low molecular weight organic synthesis, click chemistry was initially proposed. However, it subsequently achieved enormous popularity in the polymer and materials sciences [41]. The best example of a click reaction is definitely Huisgen's 1, 3-dipolar cycloaddition of alkynes and azides to give triazoles [42]. Triazoles that are 1, 4- and 1, 5- disubstituted are produced as a result of the reaction (Scheme 5).



Scheme 5: Huisgen 1, 3-Dipolar Azide–Alkyne Cycloaddition

III. CRITERIA FOR SELF—ASSEMBLY OF AMPHIPHILIC BLOCK COPOLYMER

Polymeric micelles (PMs), which are a promising class of carriers for the intravenous delivery of hydrophobic drugs, are generated by the self-assembly of amphiphilic block copolymers in aqueous solutions. Several micellar formulations are currently being investigated in clinical trials [43]. The critical micelle concentration (CMC) or critical aggregation concentration (CAC) for polymeric micelles is now well established as the concentration above which micellization occurs in diluted solutions of block copolymers in a selective solvent at a given temperature (Figure 4) [44]. Amphiphilic di- or tri-block copolymers can typically be larger than 100 nm and yet be regarded as micelles. Designing PMs often involves using di-block copolymers of the A-B type, where A stands for a hydrophilic block and B for a hydrophobic block, whereas tri-block copolymers are made up of two types of polymers (A-B-A) or three types of polymers (A-B-C). Due to the confined association between the properties of micelles and the structure of polymers, A-B or A-B-A type block copolymers have been examined for the majority of drug carrier applications [45].

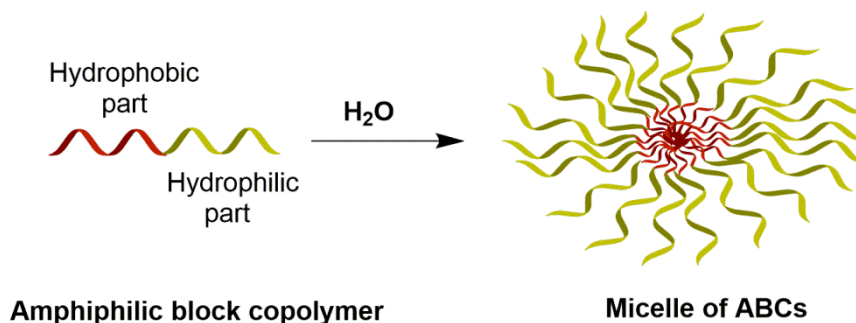


Figure 4: Self—Assembly of Amphiphilic Block Copolymers

- 1. Self—Assembly of Supramolecular Amphiphilic Block Copolymer:** A novel research field was born by the combination of supramolecular chemistry with traditional ABCs to yield supramolecular ABCs. Supramolecular ABCs are constructed, in contrast to conventional amphiphiles, on the basis of noncovalent interactions [7]. These advanced supramolecular amphiphiles, along with the enrichment of the family of conventional amphiphiles, provide a new bridge between the colloidal and supramolecular sciences. In particular, the biocompatibility and inclusion complexation abilities of CDs and their derivatives make them extremely attractive in developing therapeutic nanoparticles. Nano entities such as micelles, nanospheres, and vesicles can be formed from CD-based materials including amphiphilic CDs and CD-polymers. Nano assemblies thus formed can be potential nanocarriers for both hydrophilic and hydrophobic bioactive molecules due to their multiple hydrophilic/hydrophobic domains and recognition sites [10]. To a hydrophobic moiety, CDs can be chemically attached through chemical bonds or physically attached by host—guest interaction, to yield a classic amphiphile in which the CDs outer surface acts as a hydrophilic moiety. Macrocyclic amphiphiles derived from cyclodextrins have been widely used in self—assembly processes to fabricate supramolecular nanostructures [46]. For example, the β -CD-PNAM-b-AD-PDLLA supramolecular ABCs prepared by the inclusion complexation between adamantine-terminated linear poly(D,L-lactide) (AD-PDLLA) and β -cyclodextrin terminated poly(N-acryloylmorpholine) (β -CD-PNAM) form micelles in aqueous solution. In order to have

spontaneous formation of the micelles, AD-PDLLA solution was slowly, drop wise, added into the β -CD-PNAM aqueous solution. The resultant micelles contain the hydrophobic linear PDLLA core and the hydrophilic PNAM shell [14]. Similar observations were reported on the preparation of supramolecular amphiphilic block copolymers through the host—guest interaction of β -CD and AD. We reported, in our previous work [47], the fabrication of amphiphilic miktoarm star polymers, through the host-guest interactions of adamantane ended poly(methyl methacrylate) (AD-PMMA) separately with β -CD based PAM (β -CD-PAM) and β -CD trimer based PAM (3- β -CD-PAM) star polymers, and also their micellization in water. Since these inclusion complexes contain hydrophobic AD-PMMA part and hydrophilic β -CD-PAM or 3- β -CD-PAM polymer chains, they are amphiphilic in nature and form nanostructured aggregates of the polymers in aqueous solutions. To estimate the CMC of these complexes, fluorescence spectroscopic analysis with pyrene probe was used. Then the semi logarithmic plot of the fluorescence excitation intensity ratio (I_3/I_1) of pyrene observed at $\lambda_{em} = 394$ nm vs. concentration of the polymers revealed the CMC values as the concentrations correspond to points of intersection of the best-fit tangents.

IV. CHARACTERIZATION OF POLYMERIC MICELLES

Pyrene fluorescence spectroscopy probe techniques can be used to examine the self-assembly behavior of ABCs, and to estimate their critical micelle concentration. As the concentration of the copolymer added to pyrene solution increases, micelles start to form, and pyrene, which is hydrophobic in nature, will be encapsulated into the hydrophobic micro domains of hydrophobic polymer [16, 18]. For chemical structure characterization of polymers, ^1H nuclear magnetic resonance (NMR) spectroscopy and Infrared spectroscopy (IR) can be employed [48]. The self-aggregates can be characterized by dynamic light scattering (DLS), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). The micellar size analysis methods can be categorized as follows: (i) ensemble techniques and (ii) counting techniques. Ensemble techniques provide high statistical accuracy and a wide dynamic size range, whereas the counting techniques give low statistical accuracy and a narrow dynamic size range. The former technique family includes DLS, which is also known as photon correlation spectroscopy, and the later technique family includes TEM [49]. Hydrodynamic spherical size might be estimated by DLS, and TEM can be used for identifying the nano-shapes [50]. High-resolution transmission electron microscopy (HR-TEM) has been transformative to the field of supramolecular polymeric micelles, enabling the direct imaging of molecular structures. In contrast with conventional microscopic techniques, this does not use absorption for creating images instead uses interference in the image plane. Due to the high resolution it offers, HR-TEM is an invaluable tool for studying the nanoscale properties of materials. With this high resolution, it is possible to image crystal structures, defects in the crystal, and individual atoms [51]. HR-TEM can give information regarding nanoparticle growth and structure-related properties [52]. Also, understanding the microphase separation of the di- and tri-block copolymers were aided by TEM [53, 54]. We have compared the observed sizes of the aggregates formed by 3- β -CD-PAM-b-AD-PMMA and β -CD-PAM-b-AD-PMMA. This observation supported the fact that 3- β -CD-PAM-b-ADM-PMMA has a larger hydrophobic part area than that of β -CD-PAM-b-ADM-PMMA (Figure 5) [47]. Differential scanning calorimetry (DSC), dynamic mechanical analysis (DMA), thermal gravimetric analysis and thermal mechanical analyzer

(TMA) methods are used for characterization of thermal properties of polymeric micelles [39].

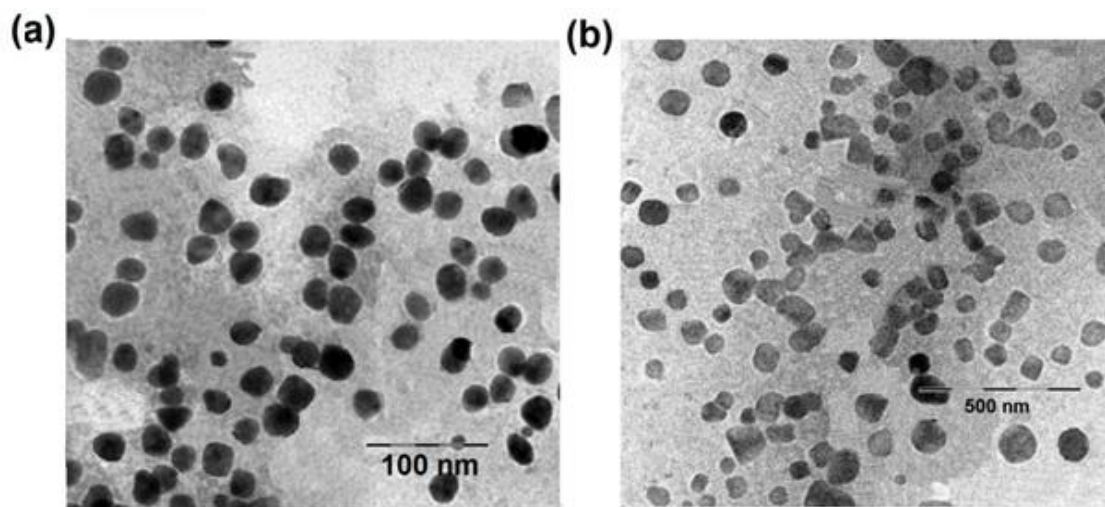


Figure 5: TEM Images of (A) B-CD-PAM-B-AD-PMMA and (B) 3-B-CD-PAM-B-AD-PMMA Micelles

V. DRUG ENCAPSULATION AND DELIVERY TECHNIQUES

Chemical conjugation or physical entrapment techniques can be used for the encapsulation of hydrophobic drugs by using polymeric micelles. Interaction between hydrophobic block copolymer and drugs is the main factor for the solubilization and stabilization of drugs loaded in polymeric micelle. Thus, the stability of hydrophobic drugs, loaded inside the core of micelle, can be enhanced with proper choice of the hydrophobic block copolymer. Chemical conjugation, in the drug encapsulation technique, is about the formation of covalent bond between particular groups of drugs and hydrophobic core of polymeric micelle [55]. ABCs based micelles are being investigated as drug carriers to increase the solubility and decrease the toxicity of hydrophobic drugs. Among these, a unique class is of ABCs aggregate to form nano-scale carriers (~10—200 nm) that can accommodate the hydrophobic drugs in the core and allow them for biocompatible modifications at the surface [56]. Some of the drugs most commonly explored for delivery in block copolymer micelle systems like Doxorubicin (DOX), Paclitaxel (PTX), etc. In order to understand the relationships between the copolymer and the physicochemical properties of the drug, it is necessary to first consider the partitioning behavior of the drug between, micelles and its various responsive stimuli of the environment [57]. Interestingly, biocompatible and biodegradable self-assembly of supramolecular amphiphilic block copolymer micelles can be very useful due to their biomedical and pharmaceutical applications, owing to enhanced therapeutic loading properties and tunable stimuli responsive release [14]. Figure 6 portrays the example of drug loaded supramolecular amphiphilic block copolymer.

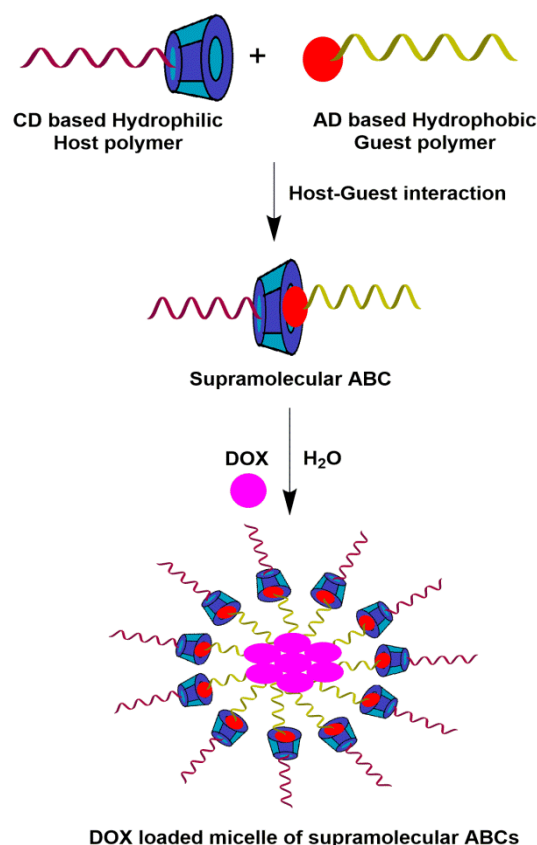


Figure 6: DOX- Loaded Supramolecular Abcs

VI. STIMULI RESPONSIVE POLYMERIC MICELLES

The development of stimuli-responsive polymeric micelles as drug delivery systems has received a lot of attention in recent years. These micelles are self-assembled from supramolecular amphiphilic block copolymers. By utilizing a change in environmental stimulus, these polymeric drug nanocarriers are able to deliver the hydrophobic drugs they are encapsulating rapidly. Here we have discussed some temperature, photo, redox, and pH responsive supramolecular amphiphilic block copolymers and ultrasound and enzyme stimuli responsive ABCs with examples.

- 1. Thermo-Responsive Supramolecular based Abcs:** Recently, thermally induced phase changes of covalent polymers have been treated by supramolecular inclusion with CDs. One of the most widely used and well researched thermo-responsive polymers is poly(N-isopropylacrylamide, or PNIPAAm). The interactions of thermo-responsive poly(N-isopropylacrylamide) (PNIPAAm) with various guests are the main basis for the supramolecular aggregates' ability to exhibit phase transition temperature [58, 59]. The development of nanocarriers for use in drug delivery applications depend significantly on the thermos-responsive features of PNIPAAm [60]. Amphiphile encompassing poly(ethylene glycol) (PEG) and PNIPAAm copolymers is one of the well-known nanocarriers of drug investigated. While the PNIPAAm part of the copolymer serves as the hydrophobic core for drug loading, the PEG part acts as the hydrophilic shell to stabilize the micelle. A system based on the interaction between a well-defined β -CD

based PNIPAAm host polymer and an adamantyle (AD) containing poly(ethylene glycol) AD-PEG guest polymer was proposed by Kim et al. The host polymer's PNIPAAm arms exhibit hydrophobic behavior at 37 °C, and as PEG is hydrophilic by nature, the β -CD-(PNIPAAm)-b-AD-PEG block copolymer will exhibit amphiphilic behavior and take part in micellization. Thus, drug can be loaded at 37 °C during micellization. When the temperature is reduced to 25 °C the hydrophobic PNIPAAm part will become hydrophilic and thus micelle gets opened. By utilizing this technique, targeted delivery of drug can be done by changing the temperature. Thermo-responsive supramolecular micelles have got great potential for drug delivery and therapeutic effects [61].

2. Photo-Responsive Supramolecular based Abcs: Light-responsive polymers have found potential use in a wide range of biomedical applications due to the ability of their micelles to encapsulate and retain hydrophobic drugs in their core. Upon exposure to specific light, the hydrophobic part of the amphiphilic block copolymers convert into a hydrophilic one. This results the disassembly of polymeric self aggregates. In several light-responsive polymeric micelle systems, ultraviolet (UV) light promotes domains containing photochromic azo containing compounds and 2-diazo-1,2-naphthoquinone (DNQ) to shift polarity or transition from hydrophobicity to hydrophilicity, which causes drug release [62]. In this case, the ability of azobenzene to respond to light and confine host-guest interaction in CDs has been used to create light-responsive micelles and drug delivery systems. The hydrophobic and van der Waals interactions play a major role in the host-guest relationship between CDs and trans-azobenzene [63, 64]. Azo-containing amphiphilic block copolymers are able to modify from spherical micelles to irregular micelles by simply altering the chain length of the hydrophilic and hydrophobic blocks. The micelles can also be broken up by adding various concentrations of β -cyclodextrin. Construction of light-responsive supramolecular aggregates like micelles has made great use of this particular photo-controlled host-guest interaction. The dual hydrophobic azo-containing di-block copolymer poly[6-(4-(phenyldiazenyl)phenoxy)hexyl acrylate]-b-polystyrene (PAzo-b-PS) is capable of self-assemble into micelles in water via β -CD-Azo host-guest interconnection[65].

3. Redox-Responsive Supramolecular based Abcs: The most important redox-responsive polymeric micelles drug delivery technology relies on redox potentials for triggered intracellular drug release because tumor tissues have high redox potentials, especially inside tumor cells. The oxidation-responsive polymers with ferrocene (Fc) as a component have received the most research attention. These materials have a wide range of uses, including biomedicine, biosensors, actuators, liquid crystal displays, electronics, and other related fields [66]. The hydrophobic ferrocene groups can be rapidly oxidised to hydrophilic ferrocenium and then reversibly recovered by chemical and electrochemical reduction method. This reversible ferrocene/ferricinium redox conversion without major structural change is followed by different alterations of properties [67]. Zuo et al fabricated Fc-containing block polymers for the development of a self-assembling, stimuli-responsive drug delivery system. For glutathione-triggered responsiveness and reactive oxygen species, respectively, β -CD/Fc pair and disulfide-bridge were simultaneously included into the copolymer structure of redox responsive supramolecular ABCs. The resulting supramolecular ABCs consist of a supramolecular hydrophobic component (Fc-SS- β -CD) that is coupled at both the β -CD and Fc termini by a central disulfide connection. Due of the well-known host-guest interaction between β -CD and Fc,

hydrophobic Fc-SS- β -CD was combined to create supramolecular amphiphilic block copolymers with noncovalent β -CD/Fc junctions [68].

- 4. pH-Responsive Supramolecular based Abcs:** In the area of drug delivery, pH-responsive micelles have generated extensively of attention. The acidic tumor microclimate is most common in solid tumors. Because of this reason, the approach of pH targeting is observed to be a more general strategy than the strategy of conventional specific tumor cell surface targeting approaches [15]. Zhang et al developed, PEG and poly(L-lactide)-based supramolecular micelles that are pH-responsive. Benzimidazole (BM) ended PEG (PEG-BM) formed complex with PLLA modified with β -cyclodextrin (β -CDPLLA). The DOX-loaded PEG-BM/CD-PLLA supramolecular micelles were found to release the encapsulated doxorubicin in 24 hours at pH 5.5. The pH-insensitive DOX-loaded PEG-b-PLLA micelles were likewise shown to not release the medication when the pH was lowered from 7.4 to 5.5. As a result, it is reasonable to assume that the supramolecular micelles' drug release at pH 5.5 was caused by the acid-induced breakdown of the micelles. The decomplexation of the BM/CD complexes caused the micelles to break down. Supramolecular micelles made of the pH-responsive polymers PEG-BM/CD-PLLA have the potential to transport anticancer drugs [69].
- 5. Ultrasound-Responsive Abcs:** Drug release from micelles can be triggered by ultrasound because it could physically break the micelle. High intensity focused ultrasound (HIFU) is another possible external trigger for the drug release from self-aggregates. HIFU has the advantages such as deep penetration, focused tiny area, non-invasiveness and remote controllable properties [70]. Investigations on ultrasound-triggered release from liposomes, polyelectrolyte micro-containers, multilayered capsules, micro emulsions, and micelles have recently been conducted. Ultrasound technology in general encompasses both high-frequency diagnostic ultrasound and low-frequency power ultrasound [71]. Liang et al studied the self-assembly of block copolymers of PPG-[Ru]-PEG that have a hydrophobic core and binds to terpyridines of the element Ru(II). Because the labile ether bonds attached to the pyridine ring cleave when these spherical micelles are exposed to HIFU, the amphiphilic structures are broken. The micelles are therefore broken apart, which causes the cargo to be enclosed to be released [72]. Ultrasound responsive supramolecular based ABCs are also expected to show promising applications and this area has to be developed in near future.
- 6. Enzyme-Responsive Polymeric Micelles:** The use of enzymes as a trigger for the stimuli-responsive degradation and disassembly of polymeric micelles has a number of important benefits, including their great selectivity and universal presence in every living organism [73]. Combinations of a stimuli-responsive dendron with enzyme-cleavable hydrophobic end groups and linear polyethylene glycol make up enzyme-responsive amphiphilic hybrids. These PEG-dendron hybrids that are hydrophilic in the PEG shell and hydrophobic in the water self-assemble into micelles. These self-aggregates can potentially be utilized to deliver hydrophobic cargos. The hydrophobic end groups get cleaved from the dendron, in the presence of the activating enzyme, making the dendron more hydrophilic. Thus, the micellar aggregates get destabilized. This causes the micelles to disassemble, releasing the enclosed cargo along with soluble PEG-dendron hybrids [74]. This is also an area which can be further improved by using cyclodextrins.

VII. CONCLUSION

In summary, there has been a significant amount of advancement in the field of supramolecular amphiphiles based on host-guest molecular reputation motifs during the past decade. We have discussed about the different types of ABCs, their micellization properties, supramolecular ABCs based on the host-guest interlinkage, and the ability efforts of the ensuing self-aggregates, including nanocarriers for the delivery of anticancer drugs and biomolecules, that could respond to internal or external stimuli (temperature, light, redox, and pH). These stimuli-responsive supramolecular ABCs hold significant promise for hydrophobic drug encapsulation and tailored drug delivery. In supramolecular self-aggregates and their in-addition classes, cyclodextrins play incredibly important functions. The introduction of any revolutionary macrocycle technology can advance supramolecular chemistry and open up novel possibilities for substance research. In future research in the field of self-assembly, amphiphilic block copolymers have great advantage in pharmaceutical areas. The improvement and development of stimuli responsive supramolecular amphiphilic block copolymers plays extra vital feature in in-vivo and in-vitro systems drug capsulation, drug and gene delivery. Cost effectiveness, easy accessibility and feasibility of supramolecular ABCs could be challenging aspects to move this field forward.

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