**Self―Assembly of Supramolecular Amphiphilic Block Copolymers**

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**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 several advantages such as simple preparation, efficient drug loading without chemical modification of the parent drug, 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 are a series of natural macrocyclic oligosaccharides with a hydrophobic interior cavity and a hydrophilic interior. 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.

***Key Words:*** *Amphiphilic block copolymers; β-Cyclodextrin; Self―assembly; Stimuli-responsive polymeric micelles*.

**1. Introduction**

Self–assembled nanostructures containing dense cores, of the insoluble blocks in aqueous medium, surrounded by diffuse outer shells (coronas) can be formed from conventional amphiphilic block copolymers (ABCs). These self−assembled nanostructures, such as polymeric micelles, may have promising biomedical applications in drug and gene delivery, protein encapsulation, maximize therapeutic effects of drugs and to minimize the negative side effects of chemotherapy, targeted release of the drugs in cancer cells and broadly used in pharmaceutical industries [1-4]. There has been considerable interest, in recent years, in the development of supramolecular micelles with stimuli-responsive nature, which enable a wide range of therapeutic applications including drug delivery and gene transport systems [5]. Developing dynamic and reversible aggregates which are capable of falling apart and releasing encapsulated cargos under appropriate conditions is very important to enhance their application in the controlled release systems. Since the origin molecular recognition chemistry, a wide variety of synthetic organic receptors like calixarenes, crown ethers, cucurbiturils and cyclodextrins (CDs) have been widely used as molecular receptors, in host―guest interactions, to construct supramolecular amphiphiles [6, 7]. Cyclodextrins are a series of natural cyclic oligosaccharides. Host―guest supramolecular polymers can be obtained by using the hosting properties of cyclodextrins. These natural CDs and their derivatives, because of their unique capability of forming inclusion complexes in the inner cavities and many other favorable physicochemical and biological properties, have been recognized as important natural host molecules in the field of supramolecular chemistry [8, 9]. Recent investigations have proved that the CDs based inclusion complexes have many promising applications, particularly in the areas of biotechnology and biomedicine [10]. These molecules give rise to very stable inclusion complexes that, when employed in the polymerization, should guarantee high polymerization degrees [11-13]. Among supramolecular interactions, β-cyclodextrin (β-CD) based inclusion complexation is often employed owing to the high association constant with guest molecules such as adamantine (AD). Various stimuli-responsive polymers can be constructed trough host―guest interactions, in order to obtain supramolecular micelles. Micelles formed by self―assembly of supramolecular amphiphilic copolymers containing hydrophilic and hydrophobic segments are responsive to environmental stimuli, such as pH, redox, enzymes and temperature [14-16]. Various coupling reactions (click chemistry) and polymerization techniques like ring-opening polymerization (ROP), reversible-deactivation radical polymerization techniques are reversible addition-fragmentation chain transfer polymerization (RAFT) and atom transfer radical polymerization (ATRP) are employed in the construction of supramolecular ABCs. These strategies make good control over the molecular weight of the synthesized polymers [17, 18]. Interestingly, biocompatible and biodegradable supramolecular ABC micelles can be very useful, from the point of their pharmaceutical and biomedical lowing to enhanced self―assemble character of supramolecular ABCs, inefficient drug loading without chemical modification of 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.

**i) 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].



 α-Cyclodextrin β-Cyclodextrin ϒ-Cyclodextrin

Figure 1. Structures of various cyclodextrins.

**ii) 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 (Keq ≈ 105 M−1) [26].



Figure 2. Cavity sizes of β-cyclodextrin.

**iii) 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].

**iv) 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.

**v) Supramolecular amphiphilic block copolymer**

Supramolecular polymer has been recognized as a significant approach in the design of delivery systems. The ability to self―assemble readily allows the formation of macromolecular nanoparticles with multiple components offering the appropriate binding strength resulting from non-covalent interactions in specific circumstances [6]. It is important to note here that, this line of research has progressed from regular amphiphiles, such as surfactants, toward giant amphiphiles, such as ABCs, and further to supra-amphiphiles. Conventional amphiphiles comprise covalent bonds whereas in the emerged new field of supra-amphiphiles, the amphiphiles are constructed on the basis of noncovalent interactions or dynamic covalent bonds [32]. Formation of such exotic structures is primarily driven by the immiscibility of a specific block in a block selective solvent and also determined by the hydrophobic/hydrophilic block ratios. Formation of the host―guest complex requires combination of several elemental noncovalent interactions such as hydrophobic interactions and geometric fitting within the interaction structure. Taking such inspiration from nature, in the recent past, there has been emerging interest in polymeric supramolecular micelles based amphiphilic block copolymer with supramolecular interactions of promising application of pharmaceutical in drug carriers and drug delivery system [33]. These supramolecular polymeric materials have been reviewed several times owing to the growing interest of the scientists in the areas of micelles, vesicle, grafting and hydrogel and so on. In this brief account, we will mainly focus on the recent stimuli-responsive functional supramolecular amphiphilic block copolymers in aqueous solution and present some perspectives of their future development as well [34].

**2. 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 many methods have been developed for the preparation of block copolymer ranging from the combinations of synthesis of block copolymers with predictable molecular weighs and uniform chain lengths are controlled and/or living polymerizations [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].

**i) Atom transfer radical polymerization**

Atom transfer radical polymerization is a controlled/living radical polymerization that affords polymers of high molecular weight, narrow molecular weight distributions, and advanced macromolecular architectures such as block copolymers and star copolymers. A transition metal complex is used as controlling agent in the equilibrium process in atom transfer radical polymerization. Transition metal complex (MtnX/L), as an activator, is responsible for homogeneous cleavage of alkyl halide bond (R-X) through a reversible redox process. The rate constants for activation and deactivation reactions of this equilibrium are kact and kdeact, respectively. When kdeact>>kact and the rate of initiation is much more than the rate of propagation, the number of bimolecular termination reactions will be reduced and the polymerization resembles a living system. In the given scheme, kt and kp represent the termination and propagation rate constants, respectively (Scheme 1) [37, 38].



Scheme 1. Reversible equilibrium of metal complex mediated ATRP.

**ii) Reversible addition fragmentation chain transfer**

Reversible addition-fragmentation chain transfer polymerization allows the synthetic tailoring of macromolecules with complex architectures including block, graft, comb, and star structures with predetermined molecular weight, terminal functionality, and narrow molecular weight distribution. Ideally, these polymerizations provide molecular weights that are predetermined by reagent concentrations and conversion, make very narrow polydispersities possible, and, most importantly, give polymer products that can be reactivated for chain extension or block synthesis. 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. In the initiation step a radical is created from initiator and it attacks on monomer to yield a propagated radical (step 1). This radical reacts with the RAFT agent and a radical intermediate will be formed. This radical intermediate can fragment to yield an oligomeric RAFT agent and a reinitiating R radical species or fragment back to the original RAFT agent and an oligomeric radical species. The structure of R should be such that it is a good reinitiating group. Also it should fragment at least as quickly as the initiator or polymer chains from the stabilized radical intermediate (step 2). Initialization step is followed by polymer chains growth via adding monomer (step 3), and they rapidly exchange between existing growing radicals (as in the propagation step) and the thiocarbonylthio group capped species (step 4). The lower concentration of growing radical chains than that of the stabilized radical intermediates evidences the rapid interchange in the chain transfer step and this limits the termination reactions. Although limited but the termination reactions still occur via combination or disproportionation mechanisms (step 5).

**iii) Ring opening polymerization**

In ring-opening polymerization, one polymer chain has a reactive center on its terminal end that reacts with another cyclic monomer, and opens its ring system to form a longer polymer chain. The reactive center on the terminal end of the polymer chain can be ionic, cationic, or radical. These cyclic monomers usually contain alkenes, alkanes, or heteroatoms in the ring. The ability of polymerization and the corresponding driving force varies depending on the type and size of the ring structure. Ring-opening polymerization has been applied to produce many commercially important polymers including polyesters from cyclic ester (lactones) [40]. The ability of cyclic monomer to polymerize according to ring opening polymerization (Scheme 4) the corresponding polymerization mechanism should exist, that conversion of the monomer molecule into the polymer repeating units. Where ‘A’ denotes the monomer molecule, and ‘a’ is the macromolecule repeating unit derived from the A monomer and n is the number of monomers. Whereas elementary reaction of the macromolecule chain growth can be written as, where a\* denotes the active species, and kp and kd are the rate constant of propagation and de-propagation, respectively.





Scheme 4. Chain growth ring opening polymerization technique.

**iv) Click chemistry**

Click chemistry concept has been introduced by Sharpless and his coworkers. The term ‘‘click’’ refers to the chemical reactions which are versatile, efficient, specific and energetically favored, and could become universal tools in synthetic chemistry. Click chemistry was first proposed for low molecular weight organic synthesis. However, it later became extremely popular in polymer and materials′ sciences [41]. Huisgen’s 1, 3-dipolar cycloaddition of alkynes and azides yielding triazoles is, undoubtedly, the premier example of a click reaction [42]. Cycloaddition of unsaturated species: 1, 3-dipolar cycloaddition. The reaction generates a mixture of 1, 4- and 1, 5-disubstituted triazoles (Scheme 5).



Scheme 5. Huisgen 1, 3-dipolar azide–alkyne cycloaddition.

**3. Criteria for self–assembly of amphiphilic block copolymer**

Polymeric micelles (PMs) formed by the self–assembly of amphiphilic block copolymers in aqueous solutions, are an attractive class of carriers for the intravenous delivery of hydrophobic agents and several micellar formulations are currently being evaluated in clinical trials [43]. It is now well established that micellization occurs in dilute solutions of block copolymers in a selective solvent at a fixed temperature above a concentration called the critical micelle concentration (CMC) or critical aggregation concentration (CAC) for polymeric micelles (Figure 4) [44]. Amphiphilic copolymers which constitute PMs are usually block copolymers. Block copolymers can be di-block copolymers or tri-block copolymers. In general, amphiphilic di- or tri-block copolymers can be greater than 100 nm in size and still be considered micelles. Generally, di-block copolymers of the *A-B* type, where A represents a hydrophilic block and B represents a hydrophobic block, are commonly used to design PMs, whereas tri-block copolymers consist of two types of polymers (*A-B-A*) or three types of polymers (*A-B-C*). Most drug carrier applications have been studied with *A-B* or *A-B-A* type block copolymers due to the close relationship between the properties of micelles and the structure of polymers [45].

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Figure 4. Self–assembly of amphiphilic block copolymers.

**i) Self–assembly of supramolecular amphiphilic block copolymer**

By combining supramolecular chemistry and traditional ABCs, supramolecular ABCs, a novel research field, was born under the widespread attention of scientists. In contrast to conventional amphiphiles, supramolecular ABCs referring to ABCs are constructed on the basis of noncovalent interactions [7]. The advance of supramolecular amphiphiles will not only enrich the family of conventional amphiphiles, but also provide a new bridge between the colloidal and supramolecular sciences. In particular, the well-recognized biocompatibility and inclusion capability of CDs and their derivatives make them extremely attractive in developing therapeutic nanoparticles. Nano entities such as nanospheres, micelles, 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. Macro cyclic amphiphiles derived from cyclodextrins or calixarenes have been widely used to construct supramolecular nanostructures via self–assembly processes [46]. For example, the β-CD-PNAM-b-AD-PDLLA supramolecular ABCs prepared by the inclusion complexation between β-cyclodextrin terminated poly(N-acryloylmorpholine) (β-CD-PNAM) and adamantine-terminated linear poly(D,L-lactide) (AD-PDLLA) 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]. Identical observations were reported by other investigators 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 adamantine 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. β–CD–PAM (50 mg) and AD–PMMA (10 mg) were added to 2 mL of DMSO, for the fabrication of inclusion complex based on β–CD–PAM and PAM (β–CD–PAM–b–AD–PMMA), and this mixture was added with 18 mL of deionized water drop wise under stirring. Further, sonicated the mixture for 0.5 h and stirred for 6 h at RT. Then, DMSO was removed by dialysis in deionized water. Unencapsulated AD–PMMA was simply removed by filtration. The filtrate, thus, containing inclusion complex was precipitated by adding it drop wise into excess of acetone. The complex was dried in vacuum oven at 40 ◦C for 48 h. The similar procedure was employed for the preparation of 3–β–CD–PAM–b–AD–PMMA. Since these inclusion complexes contain both hydrophobic and hydrophilic 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 (I3/I1) of pyrene observed at λem = 394 nm vs. concentration of the polymers revealed the CMC values as the concentrations correspond to points of intersection of the best-fit tangents.

**4. Characterization of polymeric micelles**

There are various methods and instruments available for the characterization of polymeric micelles, and different methods are used for different purposes. To examine the self–assembly behavior of micelles and to estimate critical micelle concentration, pyrene fluorescence spectroscopy probe techniques can be used. As the concentration of the copolymer added to pyrene solution increases, micelles start to form, and the hydrophobic pyrene will be encapsulated into the hydrophobic micro domains of hydrophobic polymer [16, 18]. For chemical structure characterization of polymeric materials ultraviolet visible (UV) spectroscopy analysis DOX concentration was calculated based on the absorbance intensity, DOX-loaded micelles, consistent with based on 1H nuclear magnetic resonance (NMR) spectroscopy shifting chemical shift data and Infrared spectroscopy (IR) was employed in the present study to investigate the Poly (ϵ-Caprolactone) PCL crystallinity and intermolecular hydrogen-bonding between PCL and DOX [48]. The self–aggregates can be characterized by scanning electron microscopy (SEM), transmission electron microscopy (TEM), and dynamic light scattering (DLS). 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 microscopy, this does not use absorption for creating images instead images are created from interference in the image plane. This method is an invaluable tool for studying the nanoscale properties of materials due to the high resolution it offers. 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]. For characterization of thermal properties of polymeric micelles, thermal gravimetric analysis, differential scanning calorimetry (DSC), thermal mechanical analyzer (TMA), and dynamic mechanical analysis (DMA) methods are used [39].



Figure 5.TEM images of (a) β‒CD‒PAM‒b‒AD‒PMMA and (b) 3‒β‒CD‒PAM‒b‒AD‒PMMA micelles.

**5. Drug encapsulation and delivery techniques**

Hydrophobic drugs encapsulation techniques using polymeric micelles can be done by chemical conjugation or physical entrapment. The main factor for the solubilization and stabilization of drugs loaded in polymeric micelle is the interaction between hydrophobic block copolymer and drugs. 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 physicochemical properties of the drug and the copolymer of the drug loading and deliver properties of the micelle, 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 from the point of their pharmaceutical and biomedical 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.

**6. Stimuli responsive polymeric micelles**

Stimuli-responsive polymeric micelles self–assembled from supramolecular amphiphilic block copolymers as drug delivery vehicles have attracted extensive attention in the past few decades. These polymeric drug nanocarriers can rapidly deliver the encapsulated hydrophobic drugs by means of the change in environmental stimuli. Here we have discussed some temperature, photo, redox, and pH responsive supramolecular amphiphilic block copolymers and ultrasound and enzyme stimuli responsive ABCs with examples.

**i) Thermo-responsive supramolecular based ABCs**

Supramolecular inclusion with CDs has recently been applied to thermally induced phase transitions of covalent polymers. Poly(N-isopropylacrylamide) (PNIPAAm) is one of the most popular and extensively-studied thermo-responsive polymers. The principle for the supramolecular aggregates to show phase transition temperature mainly relies on the interactions of thermo-responsive poly(N-isopropylacrylamide) (PNIPAAm) with different guests [58, 59]. The thermo-responsive properties of PNIPAAm play key role to develop nanocarriers for drug delivery applications [60]. One of the well known nanocarriers of drug studied is amphiphile containing poly(ethylene glycol) (PEG) and PNIPAAm copolymers. In this copolymer, PEG part serves as the hydrophilic shell for stabilizing the micelle while PNIPAAm part functions as the hydrophobic core for drug loading. Kim et al proposed the system based on the host–guest interaction between a well-defined β-CD based PNIPAAm host polymer and adamantyle (AD) containing poly(ethylene glycol) AD-PEG guest polymer. At 37 oC, the PNIPAAm arms of the host polymer show hydrophobic nature and since PEG is hydrophilic in nature, β-CD-(PNIPAAm)-b-AD-PEG block copolymer will show amphiphilic behavior and thus participate in micellization. Thus drug can be loaded at 37 oC during micellization. When the temperature is reduced to 25 oC 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].

**ii) 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 many light-responsive polymeric micelle systems, Ultraviolet (UV) light triggers a change in polarity or a transition from hydrophobicity to hydrophilicity in domains bearing photo-chromic azo containing compound and 2-diazo-1,2-naphthoquinone (DNQ), which leads to drug release [62]. For example, the light-responsive inclusion of azobenzene, containing host-guest interaction in CDs, has been exploited to make light-responsive micelles and drug-delivery vehicles. The host–guest interaction between CDs and trans-azobenzene is mainly governed by hydrophobic and *vander* Waals interactions [63, 64]. Azo-containing amphiphilic block copolymers from spherical micelles to irregular micelles transitions by facilely adjusting the chain length of hydrophilic and hydrophobic blocks, and micelles get dissociated by addition of different amounts of β-cyclodextrin. This unique photo-controlled host–guest interaction has been extensively used to construct light-responsive supramolecular aggregates such as micelles. The double hydrophobic azo-containing di-block copolymer poly[6-(4-(phenyldiazenyl)phenoxy)hexyl acrylate]-b-polystyrene (PAzo-b-PS) can self–assemble into micelles in water through β-CD–Azo host–guest interaction [65].

**iii) Redox-responsive supramolecular based ABCs**

The basic principle of redox-responsive polymeric drug delivery systems is to utilize redox potentials for triggered intracellular drug release owing to high redox potentials in tumor tissues, particularly inside tumor cells. Ferrocene (Fc)-containing polymers have been the most studied species among the oxidation-responsive polymers, with applications ranging from biomedicine, biosensors, actuators, and liquid crystals to electronics and other related areas [66]. This reversible ferrocene/ferricinium redox conversion without main structural change is accompanied by various changes of properties hydrophobic ferrocene groups can be quickly oxidized to hydrophilic ferrocenium, and then reversibly recovered by chemical and electrochemical reduction method [67]. Zuo et al fabricated Fc-containing block polymers for the construction of stimuli-responsive drug delivery system through self–assembly techniques. β-CD/Fc pair and disulfide-bridge were introduced into the copolymer structure of redox responsive supramolecular ABCs, simultaneously for reactive oxygen species and glutathione-triggered responsiveness, respectively. The supramolecular ABCs thus fabricated contain a supramolecular hydrophobic part with both β-CD and Fc termini connected by a central disulfide link (Fc-SS-β-CD). Due to the well-documented host−guest interaction between β-CD and Fc, supramolecular amphiphilic block copolymers with noncovalent β-CD/Fc junctions were prepared by mixing hydrophobic Fc-SS-β-CD [68].

**iv) pH-responsive supramolecular based ABCs**

pH-responsive micelles have received great attention in the field of drug delivery. 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 pH-responsive supramolecular micelles based on PEG and poly(L-lactide) (PLLA). The pH-dependent association/dissociation of the complexes formed by benzimidazole (BM) terminated PEG (PEG-BM) and β-cyclodextrin modified PLLA (β-CDPLLA). It was observed that the encapsulated doxorubicin was released from the DOX-loaded PEG-BM/CD-PLLA supramolecular micelles in 24 h at pH 5.5. It was also noticed that the pH-insensitive DOX-loaded PEG-b-PLLA micelles did not release the drug when the pH was reduced from 7.4 to 5.5. Hence, the drug release of the supramolecular micelles upon reducing the pH to 5.5 can be reasonably attributed to the acid-induced decomposition of the supramolecular micelles. The micelles got decomposed due to the decomplexation of the BM/CD complexes. pH-responsive PEG-BM/CD-PLLA supramolecular micelles hold potential for anticancer drug delivery [69].

**v) Ultrasound-responsive ABCs**

Drug release from micelles can be triggered by ultrasound because it could physically break the micelle. Another promising external trigger for the drug release from self-aggregates is high intensity focused ultrasound (HIFU). HIFU has the advantages such as deep penetration, focused tiny area, non-invasiveness and remote controllable properties [70]. Recently, ultrasound-triggered release from liposomes, polyelectrolyte micro containers, multilayered capsules, micro emulsions, and micelles has been investigated. Generally, ultrasound technology includes low-frequency power ultrasound and high-frequency diagnostic ultrasound [71]. Liang et al studied the self-assembly of PPG-[Ru]-PEG block copolymers containing a hydrophobic core with Ru(Ⅱ) -terpyridine bonds. When these spherical micelles are subjected to HIFU, the amphiphilic structures are broken due to the cleavage of labile ether bonds connected to the pyridine ring. Thus, disruption of the micelles takes place, which leads to the release of the encapsulated cargo [72]. Ultrasound responsive supramolecular based ABCs are also expected to show promising applications and this area has to be developed in near future.

**vi) Enzyme-responsive polymeric micelles**

Enzymes as a trigger for stimuli-responsive degradation and disassembly of polymeric micelles have several significant advantages such as their high selectivity and natural existence in all living organisms [73]. Enzyme-responsive amphiphilic hybrids are composed of linear polyethylene glycol and a stimuli-responsive dendron with enzyme-cleavable hydrophobic end groups. In water, these amphiphilic PEG-dendron hybrids self -assemble into micelles with a hydrophobic core and a hydrophilic PEG shell. 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 leads to the disassembly of the micelles and release of the encapsulated cargo and soluble PEG-dendron hybrids [74]. This is also an area which can be further improved by using cyclodextrins.

**7. Conclusion**

In summary, a good-sized development with inside the discipline of supramolecular amphiphiles primarily based on host−guest molecular reputation motifs has been done during the last decade. We have discussed various types of ABCs, micellization characteristics of ABCs, and supramolecular ABCs based on host−guest interactions, and the ability programs of the consequent self–aggregates, including nanocarriers for the shipping of anticancer drugs and bio-molecules, that could reply to inner or outside stimuli (temperature, light, redox and pH). These stimuli responsive supramolecular ABCs have great potential in encapsulation of hydrophobic drugs and targeted drug deliver. Cyclodextrins play extraordinarily crucial roles in supramolecular self–aggregates and their in-addition programs. The arrival of any novel technology of these macrocycles can boost up the improvement of supramolecular chemistry and offer new possibilities for substances science. 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.

**References**

[1] Zhang, X.Z., Liu, L.K., and Li, J., Macromolecules, 44, (2011), 1182-1193.

[2] Shuai, Y., Zhou, M., and Qian, X., Advanced materials research, 487, (2012), 663-667.

[3] Fetsch, C., Gaitzsch, J., Messanger, L., Battaglia, G., and Luxenhofer, R., Scientific reports, 6, (2016), 33491.

[4] Xiong, B.X., Binkhathlan, Z., Molavi, O., and Lavasanifar, A., Acta biomaterialia, 8, (2012), 2017-2033.

[5] Noh, H., Myung, S., Kim, J.M., and Yang, K.S., Polymer, 175, (2019), 65-70.

[6] Hu, D.Q., Tang, P.G., and Chu, K.P., Account of chemical research, 47, (2014), 2017-2025.

[7] Yu, G., Jie, K., and Huang, F., Chemical reviews, 115, (2015), 7240-7303.

[8] Wanker, J., KOTLA, G.N., Gera, S., Rasala, S., Pandit, A., and Rochev, A.Y., Advanced functional materials, 30, (2020), 1909049.

[9] Chen, G., and Jiang, M., Chemical society reviews, 40, (2011), 2254-2266.

[10] Zhang, X.J., and Ma, X.P., Advanced drug delivery, 65, (2013), 1215-1233.

[11] Leggio, C., Anselmi, M., Nola, D.A., Galantini, L., Jovar, A., Meijide, F., Pavel, V.N., Tellini, S.H.V., and Tato, V.J., Macromolecules, 40, (2007), 5899-5906.

[12] Ciferri, A., Macromolecular rapid communications, 23, (2002), 511-529.

[13] Ohga, K., Takashima, Y., Takashi, H., Kawaguchi, Y., Yamaguchi, H., and Harada, A., Macromolecules, 38, (2005), 5897-5904.

[14] Ramesh, K., Anugrah, B.S.D., and Lim, T.K., Reactive and functional polymers, 131, (2018), 12-21.

[15] Zhang, Z., Diang, J., Chen, X., Xiao, C., He, C., Zhuang, X., Chen, L., and Chen, X., Polymer chemistry, 4, (2013), 3265-3271.

[16] Xu, F., Li, H., Luo, L.Y., and Tang, W., Applied materials interfaces, 9, (2017), 5181-5192.

[17] McCormick, L.C., Kirkland, E.S., and York, W.A., Macromolecular science, 46, (2006), 421-443.

[18] Adeli, F., Abbasi, F., Babazadeh, M., and Davaran, S., Journal of nanobiotechnology, 20, (2022), 91.

[19] Saokham,P., Muankaew, C., Jansook, P., and Loftsson, T., Molecules, 23, (2018), 1161.

[20] Sun, T., Guo, Q., Zhang,C., Hao,J., Xin, P., Su, J., Li, S., Hao, A., and Liu, G., Longmuir, 28,(2012), 8625-8636.

[21] Munkaew, C., and Loftsson, T., Basic and clinical pharmacology and toxicology, 122, (2017), 46-55.

[22] Yuan,Z., Ye,Y., Gao, F., Yuan, H., Lan, M., Lou, K., and Wang, W., International journal of pharmaceutics, 446, (2013), 191-198.

[23] Kurkov, V.S., and Loftsson, T., International journal of pharmaceutics, 453, (2012), 167-180.

[24] Tungala, K., Adhikary, P., and Krishnamoorthi, S., Carbohydrates, 95, (2013), 295-298.

[25] Tungala, K., Adhikary, P., Azmeera, V., Kumar,K., and Krishnamoorthi,S., New journal chemistry, 41, (2017), 611-618.

[26] Rodell, B.C., Mealy, J., and Burdick, A.J., Bioconjugate Chemistry, 26, (2015), 2279-2289.

[27] Lombardo, D., Kiselev, A.M., Magazu, S., and Calandra, P., Advanced in condensed matter physics, 11, (2015), 151683.

[28] Kashapov, R., Gaynanova,G., Gabdrakhmanov, D., Kuznetsov, D., Pavlov, R., Petrov, K., Zakharova, L., and Sinyashin, O., International journal of molecular sciences, 21, (2020), 6961.

[29] Bas, S., and Souck, D.M., Polymer journal, 44, (2012), 1087-1097.

[30] Bu, X., Ji, N., Dai, L., Dong, X., Chen, L., Xiong, L., and Sun, Q., Trends in food and technology, 114, (2021), 386-393.

[31] Adams, L.M., Lavasanifar, A., and Kwon, S.G., Journal of pharmaceutical sciences, 92, (2003), 1343-1355.

[32] Wang, C., Wang, Z., and Zhang, X., Accounts of chemical research, 45, (2012), 608-618.

[33] Rajak, A., Karan, K. C., Theato, P., and Das, A., Polymer chemistry, 11, (2020), 695-703.

[34] Ma, X., and Tian, H., Accounts of chemical research, 47, (2014), 1971-1981.

[35] Feng, H., Lu, X., Wang, W., Wang, G.N., and Mays, W.J., Polymers, 9, (2017), 494.

[36] Asmita, D., Haldar, U., and De, P., Frontiers in Chemistry, 9, (2021), 644547.

[37] Krysztof, M., and Xia, J., Chemical reviews, 101, (2001), 2921-2990.

[38] Mamaqani, R.H., Asl, H.V., Najafi, M., and Kalajahi, S.M., Polymer composites, 31, (2010), 1829-1837.

[39] Moad, G., Chiefari, J., Chong, Y.K.B., Krstina, J., Mayadunne, T.A.R., Postma, A., Rizzardo, E., and Thang, H.S., Polymer international, 49, (2000), 993-1001.

[40] Deb, K.P., Kokaz, F.S., Abed, N.S., Paradkar, A., and Tekade, K.R., Basic fundamental of drug delivery, 6, (2019), 203-267.

[41] Lutz, F.J., and Schlaad, H., Polymer, 49, (2008), 817-824.

[42] Kolb, C.H., and Sharpless, B.K., Drug discovery today, 8, (2003), 1128-1137.

[43] Avsar, Y. S., Kyropoulou, M., Leone, D. S., Schoenenberger, C.A., Meier, P.W., and Palivan, G.C., Frontiers in chemistry, 6, (2019), 645.

[44] Talelli, M., Rijcken,F. J.C., Oliveira, S., Meel, D.V.R., Henegouwen, E.B.V.M.P.P., Lammers,T., Nostrum, V.F.C., Storm, G., and Hennink, E.W., Journal of controlled release, 153, (2011), 93-102.

[45] Xu,W., Ling, P., and Zhang, T., Journal of drug delivery, 2013, (2013), 340315.

[46] Jiang,L., Yan, Y., and Huang, J., Advances in colloid and interface science, 169, (2011), 13-25.

[47] Tungala, K., Kumar, K., Sonker, E., and Krishnamoorthi, S., Reactive and functional polymers, 157, (2020), 104771.

[48] Shuai, X., Ai, H., Nasongkla, N., Kim, S., and Gao, J., Journal of controlled release, 98, (2004), 415-442.

[49] Ree, J.B., Lee, J., Satoh, Y., Kwon, K., Isono, T., Satoh, T., and Ree, M., Polymers, 10, (2018), 1347.

[50] Schuch, H., Klinger, J., Rossmanirh, P., Frechen, T., Gerst, M., Feldthusen, J., and Muller, E.H. A., Macromolecules, 33, (2000), 1734-1740.

[51] Kuei, B., and Gomez, D.E., Nature Communication, 12, (2021), 153.

[52] Kulshrestha, R., Singh, A., Kumar, A., Mishra, A., and Dinda, A., Indian journal of biochemistry and biophysics, 58, (2021), 321-333

[53] Khandpur, K.A., Forster, S., Bates, S.F., Hamley, W.I., Ryan, J.A., Bras, W., Almdal, K., and Mortsensen, K., Macromolecules, 28, (1995), 8796-8806.

[54] Chatterjee, J., Jain, S., and Bates, S.F., Macromolecules, 40, (2007), 2882-2896.

[55] Aziz, A.B.A.Z., Ahmad, A., Setapar, M.H.S., Hassan, H., Lokhat, D., Kamal, A.M., and Ashraf, M.G., Current drug metabolism, 17, (2016), 16-29.

[56] Owen, C.S., Chan, Y.P.D., and Shoichet, S.M., Nano today, 7, (2012), 53-65.

[57] Liu, J., Lee, H., and Allen, C., Current pharmaceutical design, 12, (2006), 4685-4701.

[58] Yang, F., Cao, Z., and Wang, G., Polymer chemistry, 6, (2015), 7995-8002.

[59] Zhou, Z., Li, G., Wang, N., Guo, F., Guo, L., and Liu, X., Colloids surfaces B Biointerfaces, 172, (2018), 136-142.

[60] Wei, H., Cheng, X.X., Zhang, Z.X., and Zhuo, X.R., Progress in polymer science, 34, (2009) 893-910.

[61] Song, X., Zhu, L. J., Wen, Y., Zhao, F., Zhang, X.Z., and Li, J., Journal of colloid and interfaces science, 490, (2017), 372-379.

[62] Kim, N.K., Oh, S. K., Shim, J., Schlaepfer, R.I., Karam, D. S., and Lee, J. J., Polymers, 13, (2021), 377.

[63] Nalluri, M.K.S., and Ravoo, J.B., Angewandte chemie international edition, 49, (2010), 5372-5374.

[64] Wang, Y., Ma, N., Wang, Z., and Zhang, X., Angewandte chemie international edition, 46, (2007), 2823-2826.

[65] Wang, S., Shen, Q., Nawaz., and Zhang, W., Polymer chemistry, 4, (20133), 2151-2157.

[66] Huo, M., Yuan, J., Tao, L., and Wie, Y., Polymer chemistry, 5, (2014), 1519-1528.

[67] Gu, H., Mu, S., Qiu, G., Liu, X., Zhang, Li., Yuan, Y., and Astruc, D., Coordination chemistry Reviews, (2018), 51-85.

[68] Zuo, C., Dai, X., Zhao, S., Liu, X., Ding, S., Ma, L., Liu, M., and Wei, H., Macro letters, 7, (2016), 873-878.

[69] Zhang, Z., Lv, Q., Gao, X., Chen, L., Cao, Y., Yu, S., He, C., and Chen, X., Applied materials and interfaces, 7, (2015), 8404-8411.

[70] Li, F., Xie, C., Cheng, Z., and Xia, H., Ultrasonics sonochemistry, 3o, (2016), 9-17.

[71] Wang, J., Pelletier, M., Zhang,H., Xia, H., and Zhao,Y., Longmuir, 25, (2009), 13201-13205.

[72] Liang, B., Wang, Z., and Xia, H., Ultrasonics Sonochemistry, 68, (2020), 105217.

[73] Dai, Y., Chen, X., and Zhang, X., Polymer chemistry, 10, (2019), 34-44.

[74] Harnoy, J.A., Rosenbaum, I., Tirosh, E., Ebenstein, Y., Shaharabani, R., Beck, R., and Amir, J. R., Journal of the American chemical society, 136, (2014), 7531-7534.