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Review

Nanoscale Self-Assemblies from Amphiphilic Block Copolymers as Proficient Templates in Drug Delivery

Dhruvi Patel [1,2], Ketan Kuperkar [2,*], Shin-ichi Yusa [3] and Pratap Bahadur [4]

[1] School of Civil and Environmental Engineering, Cornell University, Ithaca, NY 14850, USA; dhruvi.svnit.32@gmail.com
[2] Department of Chemistry, Sardar Vallabhbhai National Institute of Technology (SVNIT), Ichchhanath, Surat 395007, India
[3] Department of Applied Chemistry, Graduate School of Engineering, University of Hyogo (UH), 2167 Shosha, Himeji 671-2280, Japan; yusa@eng.u-hyogo.ac.jp
[4] Department of Chemistry, Veer Narmad South Gujarat University (VNSGU), Surat 395007, India; pbahadur2002@yahoo.com
* Correspondence: ketankuperkar@gmail.com

Abstract: This review article emphasizes the current *enlargements* in the formation and properties of the various nanostructured aggregates resulting from the self-assembly of a variety of block copolymers (BCPs) in an aqueous solution. The development of the different polymerization techniques which produce polymers with a desired predetermined molecular weight and low polydispersity is investigated with regard to their technological and biomedical applications; in particular, their applications as vehicles for drug delivery systems are considered. The solution behavior of amphiphilic BCPs and double-hydrophilic block copolymers (DHBCs), with one or both blocks being responsive to any stimulus, is discussed. Polyion complex micelles (PICMs)/polymersomes obtained from the electrostatic interaction of a polyelectrolyte-neutral BCP with oppositely charged species are also detailed. Lastly, polymerization-induced self-assembly (PISA), which forms nanoscale micellar aggregates with controlled size/shape/surface functionality, and the crystallization-driven self-assembly of semicrystalline BCPs facilitated when one block of the BCP is crystallizable, are also revealed. The scalability of the copolymeric micelles in the drug delivery systems and pharmaceutical formations that are currently being used in clinical trials, research, or preclinical testing is emphasized as these micelles could be used in the future to create novel nanomedicines. The updated literature and the future perspectives of BCP self-assembly are considered.

Keywords: self-assembly; block copolymers (BCPs); polymeric micelles (PMs); polymersomes; polymerization-induced self-assembly (PISA); drug delivery

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1. Introduction

As with surface-active agents, which possess dual moieties that behave differently in water and thus adsorb onto interfaces and self-assemble to form nanoscale micelles of different sizes and shapes, block and graft copolymers contain incompatible polymer-size moieties that behave differently in selective solvents and form core–shell micelles and polymersomes. Depending on the polymeric blocks, which have a varied structure and chemical composition and a wide range of polar and non-polar entities linked together, these block copolymers (BCPs) impart unique solid-state and solution properties [1,2].

Self-assembly can be induced in molecularly dissolved polymers with different hydrophilic groups that have one block that is responsive to a stimulus which transforms it and makes it hydrophobic. Furthermore, such copolymers with a hydrophilic polyelectrolyte block may also assemble into ion complex micelles in the presence of an oppositely charged polymer. Also, self-assembly can take place during polymerization. This review focuses on the polymeric nanostructures formed from the self-assembled BCPs that serve

as efficient and effective drug carrier candidates and have become an emerging area of research interest from the perspective of drug delivery applications. Unlike polyblends, which are used in the recycling of modified plastics, nanocomposites, and interpenetrating polymer networks and are physical mixtures of two incompatible polymers that undergo a phase separation at the macroscopic scale, these BCPs undergo only a micro-heterogeneous separation due to the covalent bonding that connects the different blocks [3,4]. The varieties of microdomains formed by BCPs in a solid state are highly useful as thermoplastic elastomers and have acquired relevant industrial importance (not discussed in this review) [5]. In addition, the BCPs in a liquid state show unique solution characteristics, which make them versatile candidates in pharmaceutical formulations, catalysis, polyblends, detergency, et cetera [6,7].

The most common BCPs, which have been commercially available for several decades, are ethylene oxide (EO)-propylene oxide (PO)-*based* BCPs. These have been sold under their BASF trade names as linear triblock copolymers (Pluronics®) and star-block copolymers (Tetronics®). These nano-ionic amphiphilic BCPs are available with varying molecular characteristics and demonstrate superior surface activity and micelle formation and are analogous to poly(ethylene oxide) (PEO, also called polyoxyethylene and poly(ethylene glycol)) condensate-type conventional nonionic surfactants with different nonpolar (lipophilic) parts, such as commercial Triton®, Brij®, Tween®, Soluplus®, Solutol® HS15, Cremophor® EL, Gelucire®, Akypo®, et cetera [8,9].

Recently, polymeric-*based* nanomaterials have exhibited wonderful properties due to their fabrication ability using various technologies. These have been of immense interest as nanocarriers in the design of pharmaceuticals and in the refining of drug delivery systems; therefore, they offer a suitable tool for the release of hydrophobic drugs and bioactive agents. Polymeric nanocarriers for drug delivery applications include nanogels, nanocapsules, and polymer-coated liposomes (and inorganic nanoparticles); self-assemblies from amphiphilic macromolecules include hydrophobically modified polymers (particularly polysaccharides) and graft/block copolymers. Among these nanocarriers, polymer micelles (PMs) and polymersomes from BCP self-assembly have been of the highest interest due to the ease of fabrication into the desired size/shape/charge, complete characterization, and the tunable properties for drug delivery applications [10,11]. Consequently, in the past few years, BCPs have significantly influenced the drug encapsulation capability and delivery efficacy; so, they are very important in the sustained delivery of drugs due to the core–shell morphology of the aggregates, the excellent thermo-reversible rheological behavior, and the bio-adhesive properties that demonstrate a noteworthy scope [12,13]. There have been several reviews on biomedically important PMs in the literature, but the majority of them focus on their potential applications as nano-vehicles for cancer therapy [14–16]. However, less attention is paid to presenting the different aspects of the polymer and colloid chemistry. Therefore, the current review attempts to emphasize the new advances and developments in PMs from a variety of strategies, using different amphiphilic multiphase systems and using blocks from different monomers with varying molecular characteristics and structural features. In giving an account in this direction, the present review, unlike the other reported works, focuses on the self-assembly of amphiphilic BCPs, double-hydrophilic block copolymers (DHBCs) with various stimuli applied, polyion complex micelles (PICMs), polymerization-induced self-assembly (PISA), and crystallization-driven self-assembly (CDSA) in an aqueous solution under one single roof; this will offer an insight into the significance of the copolymeric micellar entities for the desired potential applications.

1.1. Structural Design

Due to the presence of distinct moieties, BCPs display a multiphase system that has been vitally important for a few decades and has aroused considerable research interest among chemists, physicists, biologists, and chemical engineers [17,18]. Figure 1 illustrates the different structures of such smart BCPs, which consist of at least two or more polymeric

blocks that are often incompatibly arranged in particular architectures, such as those with a linear, cyclic, or star-like structure, et cetera [19,20].

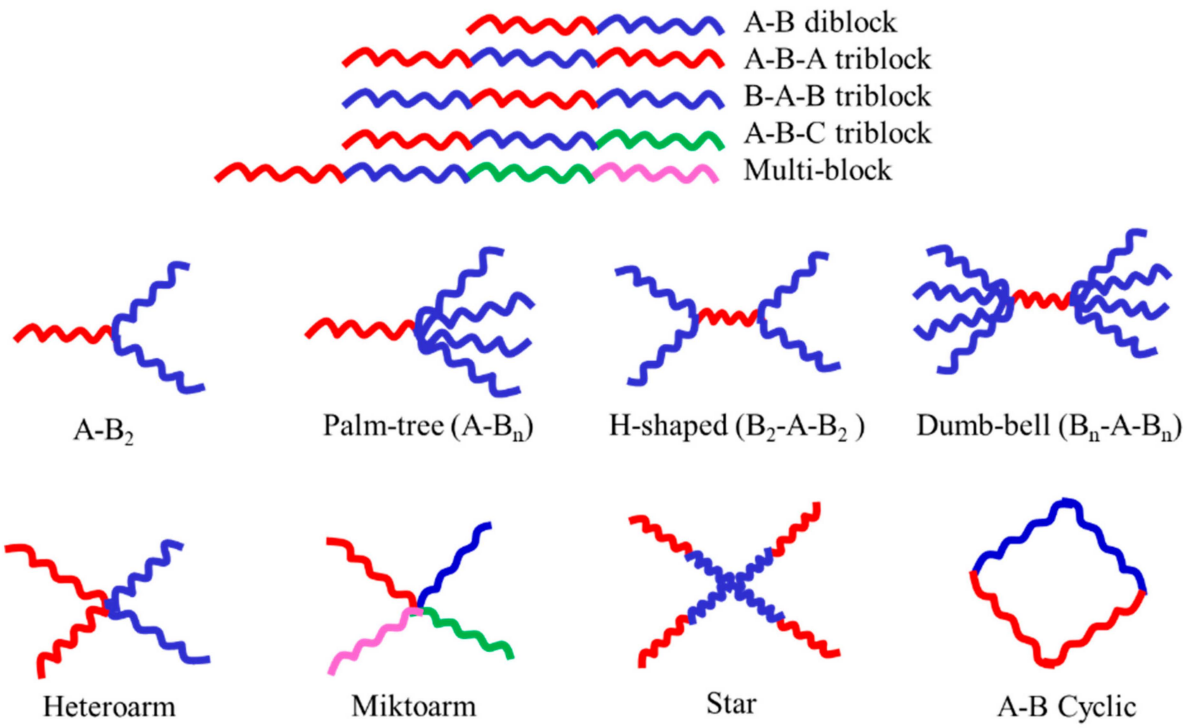

Figure 1. Schematic representation of some block copolymer structures.

1.2. Updated Synthesis Route

As the incompatible macromolecular blocks show a variety of microphase domains in solid-state and core–shell micelles and polymersomes in selective solvents (a solvent which is good for one of the blocks), BCPs with the desired structure and molecular characteristics (mol. wt. and % blocks in low polydispersity) can be synthesized using advanced polymerization techniques.

Free radical polymerization is a commonly used synthesis approach. However, owing to the uncontrolled polymerization mechanism, the manufactured polymers are extremely polydispersive, with uncontrolled molecular weight. The living anionic polymerization route first discovered by Szwarc in the 1950s is often followed for a *well-established* BCP synthesis with a narrow molecular weight distribution or low polydispersity [21]. Thus, several BCPs were prepared, and their self-assembly was investigated in aqueous and non-aqueous solvents. However, this too can be difficult due to the limitation of the fact that only a few monomers can undergo copolymerization to obtain the desired BCPs.

The controlled radical polymerization (CRP) technique has proven to be highly beneficial for the convenient preparation of BCPs from a wide variety of hydrophilic (charged or neutral) and hydrophobic monomers with definite architecture and predetermined molecular weight with very low polydispersity (~1). The commonly known strategies for CRP are atom transfer radical polymerization (ATRP), reversible addition–fragmentation chain transfer polymerization (RAFT) and nitroxide-mediated polymerization (NMP). The RAFT method produces a polymer with a fine molecular weight distribution [22], while ATRP produces the BCPs within an inclusive temperature series [23,24]. NMP uses a nitroxide initiator to produce BCPs with low polydispersity and well-controlled stereochemistry [25,26]. Thus, the literature studies have reviewed multiple synthesis routes, such as tuning polymerization by macroinitiators or 'living' free radical polymerization, to produce BCPs [25,27]. Such advances in polymerization synthesis have made BCPs technologically important materials as dispersants and solubilizers for hydrophobic dyes/drugs/pesticides/perfumes; in the fabrication of mesoporous materials; as compati-

bilizers for two polymers; in the synthesis of nanoparticles and reservoirs for drug delivery systems; and so on. However, the selection of the above-mentioned synthesis technique depends on the structure of the desired copolymer, e.g., diblock, triblock, multiblock, star-shaped, et cetera. The updates on the different controlled polymerization techniques are detailed in several reviews [28].

2. Types of BCPs

2.1. Hydrophilic BCPs

Hydrophilic polymers are easily dissolved in water and cannot form micelles easily due to a water-loving tendency. Double-hydrophilic block copolymers (DHBCs) represent a new class of switchable water-soluble amphiphiles and have been of great interest due to their propensity to undergo self-assembly into varied micellar morphologies when one of the blocks is switched from hydrophobic to hydrophilic because of stimuli such as temperature, pH, or the presence of some additives [29,30]. DHBCs are made of neutral–neutral, neutral–polyelectrolyte, or polyelectrolyte–polyelectrolyte blocks and remain molecularly dissolved in aqueous media. This enables them to provide a new scope of applications in drug carrier systems, gene therapy, crystal growth, colloid synthesis, and desalination membranes [31–33].

A few examples of hydrophilic blocks based on several water-soluble polymers, both neutral and charged and from natural sources or synthetically produced, are mentioned below (Figure 2a). (i) The naturally sourced blocks are, for example, hydroxypropyl cellulose, chitosan, alginate, sulfated polysaccharides, and poly(amino acids) (or polypeptides), such as poly(L-glutamic acid), poly(L-aspartic acid), poly(L-lysine), and poly(L-histidine). (ii) The synthetic neutral polymers are poly(ethylene oxide), polyvinylpyrrolidone, polyvinyl alcohol, poly(*N*-isopropylacrylamide), polyvinylcaprolactam, and various polyelectrolytes (anionic, cationic or zwitterionic), such as polyacrylates, poly(vinylpyridinium chloride), poly(diallyldimethylammonium chloride), poly(styrene sulfonate), et cetera.

2.2. Hydrophobic BCPs

Hydrophobic polymers, being nonpolar, are a bit too rigid to dissolve in the aqueous medium. They form micelles at a very low temperature and have a tendency to undergo phase separation [12,34–36]. A few examples of hydrophobic blocks are poly(propylene oxide) (PPO), poly(butylene oxide) (PBO), poly(lactic acid) (PAA), poly(caprolactone) (PCL), poly(butadiene) (PB), poly(styrene) (PS), poly(methylacrylate) (PMA), poly(dimethyl siloxane), poly(vinyl pyridine), et cetera (Figure 2b).

The DHBCs with two distinct hydrophilic blocks remain molecularly dissolved in water. Conversely, if one of the blocks is responsive to any external stimulus, then that block becomes hydrophobic in nature and the DHBC turns to amphiphilic BCP, which would then self-assemble to form core–shell polymer micelles. Such DHBCs can form "stimuli-responsive" or "smart" schizophrenic copolymeric micelles (with a reverse core and shell arrangement), based on which the two blocks in the BCPs have to be hydrophobic (incompatible with water or a given solvent), as demonstrated in Figure 3. Schizophrenic micelles form a water-soluble diblock polymer. Their ability to self-assemble into different structures in response to the applied external stimuli makes them ideal precursors in sensors, actuators, and other thermo-optical devices [33–36].

Thus, in diluted aqueous solution, AB type DHBC molecules can self-assemble to form two different micelles, one with a core of the hydrophobized A block and a shell of the hydrophilic B block, and the other with a core of the hydrophobized B block and a shell of the hydrophilic A block. The schizophrenic micelles can be switched from conventional to the reverse and vice versa by changing the temperature, solution pH, ionic strength, or solvent composition or in the presence of additives. This type of self-assembly leads to schizophrenic morphological features, as illustrated in Figure 3. Prof. Armes and colleagues, as well as a few others, have reported on extensive investigations of water-soluble diblock copolymers that exhibit so-called "schizophrenic" characteristics [33–35]. Mohammad et al.

developed the schizophrenic behavior of a water-soluble diblock polymer poly(methacrylic acid-block-N-isopropyl acrylamide) to fabricate a thermo-optical device [36].

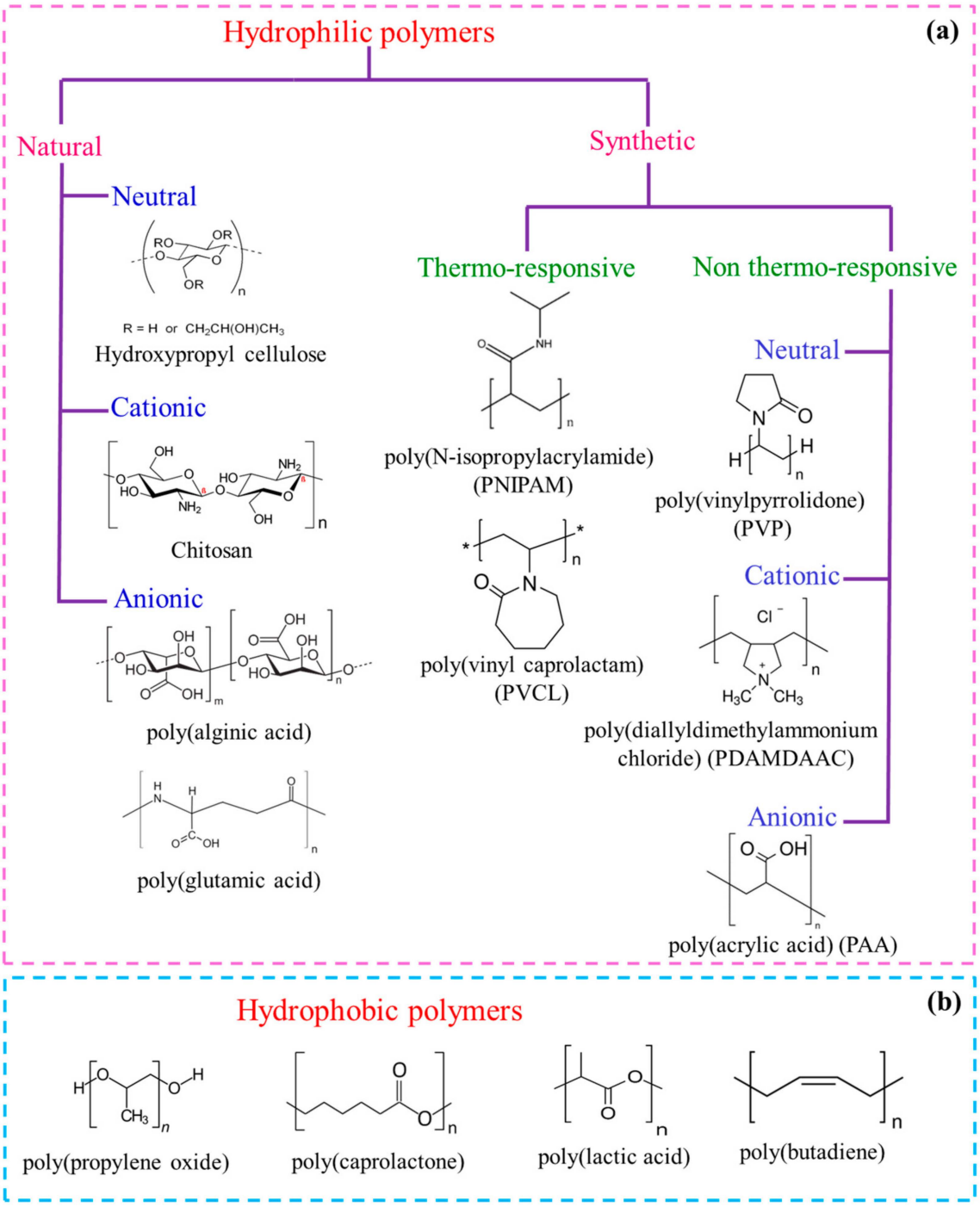

Figure 2. Examples of some (**a**) water–soluble homopolymers from natural or synthetic origin (charged or uncharged), and (**b**) hydrophobic polymers that may undergo polymerization to form BCPs.

Due to their structural fragility, the practical applicability of such micelles is virtually never acknowledged. By utilizing a bifunctional cross-linker and the reactive functional groups of polymer chains, the micellar core and corona are cross-linked to increase their stability. This modulation is represented well in Figure 4.

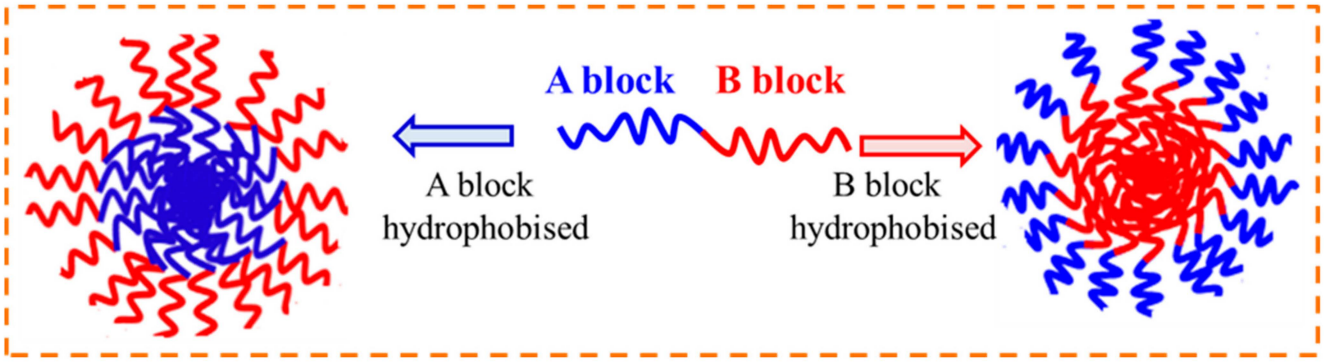

Figure 3. Formation of schizophrenic micelles in AB type DHBC.

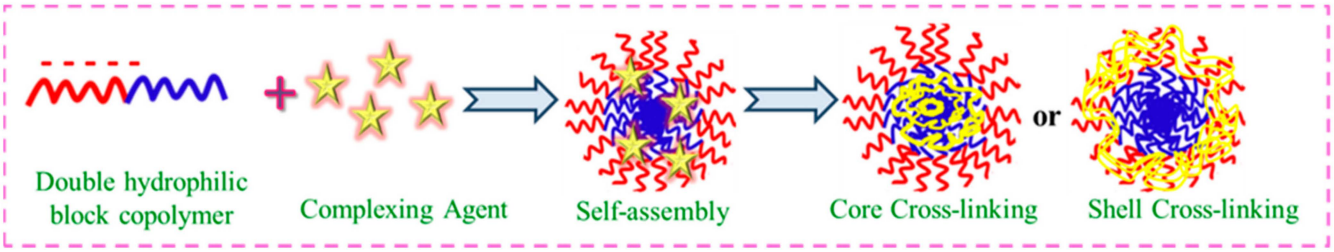

Figure 4. Self-assembly of core–shell cross-linking using DHBC.

Additionally, PMs may be produced by electrostatically interacting oppositely charged polymers into a polyelectrolyte block to make it hydrophobic. These are referred to as polyion complex micelles (PICMs) or PIC polymersomes and are discussed later.

2.3. Stimuli-Responsive Block Copolymers (SRPs)

"Stimuli-responsive", "smart", or "intelligent" polymers are water-soluble smart macromolecules that respond to varied stimuli, such as (i) physical, viz., temperature, solvents, light, magnet, and ultrasound; (ii) chemical, viz., reactants, redox conditions, and pH; and (iii) biological, viz., enzymes and glucose (Figure 5). These are of immense interest in biomedical applications such as drug delivery, biosensors, tissue engineering, and self-heating materials [37,38].

Investigations of SRPs have advanced in the past two decades [39–41]. These polymers can undergo phase transitions or exhibit configurational tuning in response to external stimuli such as pH, temperature, light, electric field, chemicals, magnetism, ionic strength, et cetera. These can cause certain physical or chemical changes in these polymers, which can modify their solubility, surface properties, sol–gel transition, and other properties. Noncovalent forces like electrostatic interactions, hydrophobicity, or hydrogen bonding are frequently implicated in the characteristics of solutions. Such responsive polymers are extensively used in separation science, water treatment, water-borne coatings, recyclable catalysis, and oil recovery. In the case of BCPs, one or more blocks is responsive to any of the stimuli and can behave either hydrophilically or hydrophobically. Several studies have presented the use of such stimuli-responsive polymeric micelles for nano-cargos in drug delivery. Additionally, reports have shown the significance of the dual responsiveness or even the multi-responsiveness of BCPs [37–43].

(i) Temperature responsiveness

Thermo-responsive BCPs are the most extensively deliberated responsive polymers due to their distinctive temperature-dependent sol–gel transition properties. Furthermore, these can be tuned to display the sol–gel transition at a desired temperature in the presence of various additives or in the presence of a trace amount of another monomer. A number of literature studies have demonstrated the synthesis and self-assembly behavior of

temperature-responsive BCPs in an aqueous solution environment for prospective biomedical applications [4,5,44–47]. A few thermo-responsive homopolymers with their lower critical solution temperature (LCST) values are shown in Figure 6.

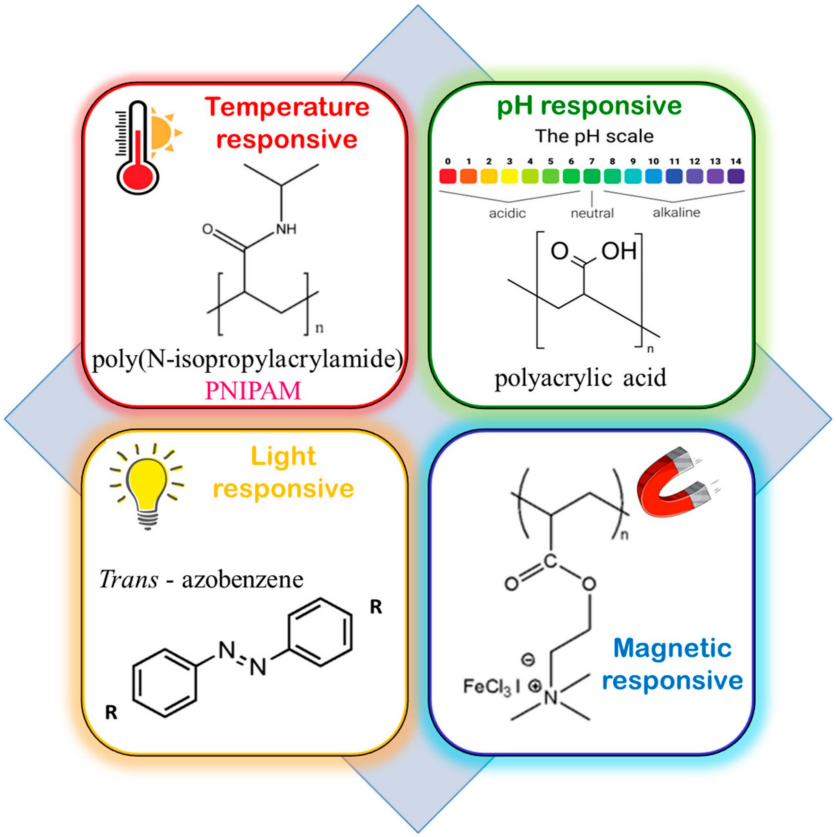

Figure 5. Some common examples of stimuli-responsive blocks in BCPs.

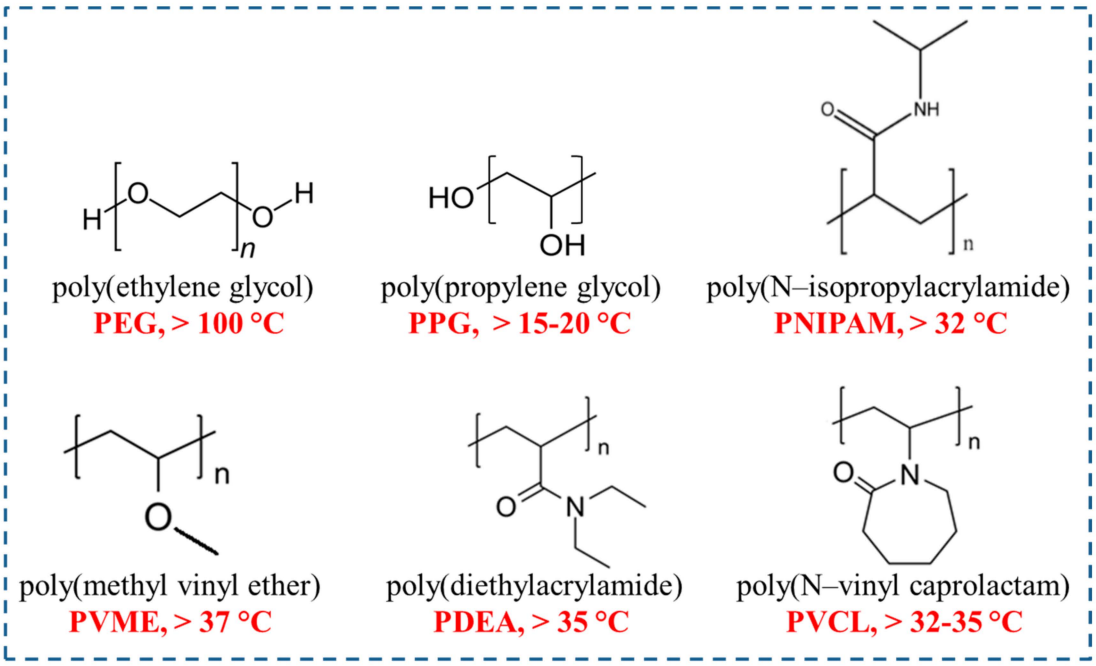

Figure 6. Some thermo–responsive polymers with their respective LCST values.

Pluronics® and Tetronics® BCPs have shown remarkable thermo-responsive micellization and gelation in aqueous solutions. Several copolymers with varied molecular characteristics as single or mixed surfactants have been extensively studied for their micellization and their rich phase behavior; several distinct liquid crystalline phases with the features of soft and hard gels have been shown; micellization and micellar growth/shape transitions have been investigated by theoretical modelling and a range of experimental methodologies [38–40]. The self-assembly of the PEO-containing hydrophilic block and different hydrophobic blocks, such as polybutylene oxide, polystyrene oxide, polybutadiene, polycaprolactone, polydimethylsiloxane, in an aqueous solution have been investigated [2]. The other extensively examined thermo-responsive block copolymer with hydrophilic moiety is the PNIPAM block with different hydrophilic blocks. These studies report on the phase behavior and micelle formation and the micro-/nanogels using a variety of instrumental techniques. The development of PNIPAM-*based* thermally triggered BCP micelles as cargo for the sustainable release of drugs was scrutinized worldwide and PNIPAM-*based* BCP micelles as perspective candidates for drug delivery; i.e., PNIPAM-*based* BCP micelles form a hydrophilic shell below the LCST and a hydrophobic core above the LCST. (PChM-PNIPAM), constructed with poly(cholesteryl 6-methacryloyloxy hexanoate) (PChM), and PNIPAM blocks were designed as the hydrophobic core and hydrophilic shell of the micelles, respectively, with increasing temperature [48–51].

(ii) pH responsiveness

pH-responsive BCPs bring about changes in the unique density, chain conformation, solubility, and configuration due to the presence of functional groups in the polymer that can be ionized upon a slight variation in the changing solution pH [45–47]. These polymers are enclosed by acidic or basic groups along the chain or at the end of the chain. The charges produced are assumed to induce the electrostatic repulsion among the polymer chains, leading to the alteration in hydrodynamic volume, which is capable of producing the flocculation, chain collapse–extension, and precipitation of the homopolymers. It has proven possible to create random pH-responsive copolymers using traditional free radical polymerization. The pH-responsive BCPs are of significance as their pH-directed self-assembly can act as a suitable vehicle for drug delivery systems. Figure 7 shows the types and examples of a few well-known pH-responsive homopolymers.

Interestingly, block copolymers with one pH-responsive block can self-organize into varied micelle shapes in a solution with subtle changes in pH and are being considered for numerous potential applications. Any alterations in the pH may lead to the protonation or deprotonation of functional groups existing in the polymers, leading to the various morphologies, like spherical micelles, vesicles, microgels, et cetera.

(iii) Light responsiveness

Light has been recognized as a smart external stimulus for creating responsive drug delivery systems. An enormous assortment of such photo-responsive systems, operating at a particular wavelength to accomplish on-demand drug release, has been reported. In particular, light-responsive BCPs have been of particular interest because of the specific interval and site controls that make them useful for prospective applications in controlled drug delivery systems and in forming self-healing, reversible wettability materials [48–51]. Also, such BCP-*based* nanocarriers are considered for the design of non-toxic treatment regimens that *deal* with spatiotemporal control beyond the release of captured therapeutic cargoes. There are two main types of light-responsive polymers: (i) reversible light-responsive polymers that are usually polymers with photochromic entities with reversible structural change, i.e., structural isomerization, e.g., organic dyes, such as azobenzene and spiropyran and (ii) irreversible light-responsive polymers that are usually polymers with photochromic units and irreversible chemical bond breakage, e.g., *o*-nitrobenzyl groups, pyrene groups, and coumarin groups (Figure 8). The UV irradiation leads to the cleavage of the photochromic moieties and converts the hydrophobic block to a hydrophilic block. Such apparent structural changes in the light-responsive BCPs may disrupt the self-assembled

micelles and release the encapsulated hydrophobic cargo from the micellar core. In order to control the delivery of the hypoxia-activated bio-reductive prodrug tirapazamine for the treatment of metastatic breast cancer using hypoxia-boosted phototherapies, Yuanyuan et al. established near-infrared (NIR) light-decomposable nanomicelles made of PEGylated cypate and mPEG-polylactic acid (mPEG2k-PLA2k) [52,53].

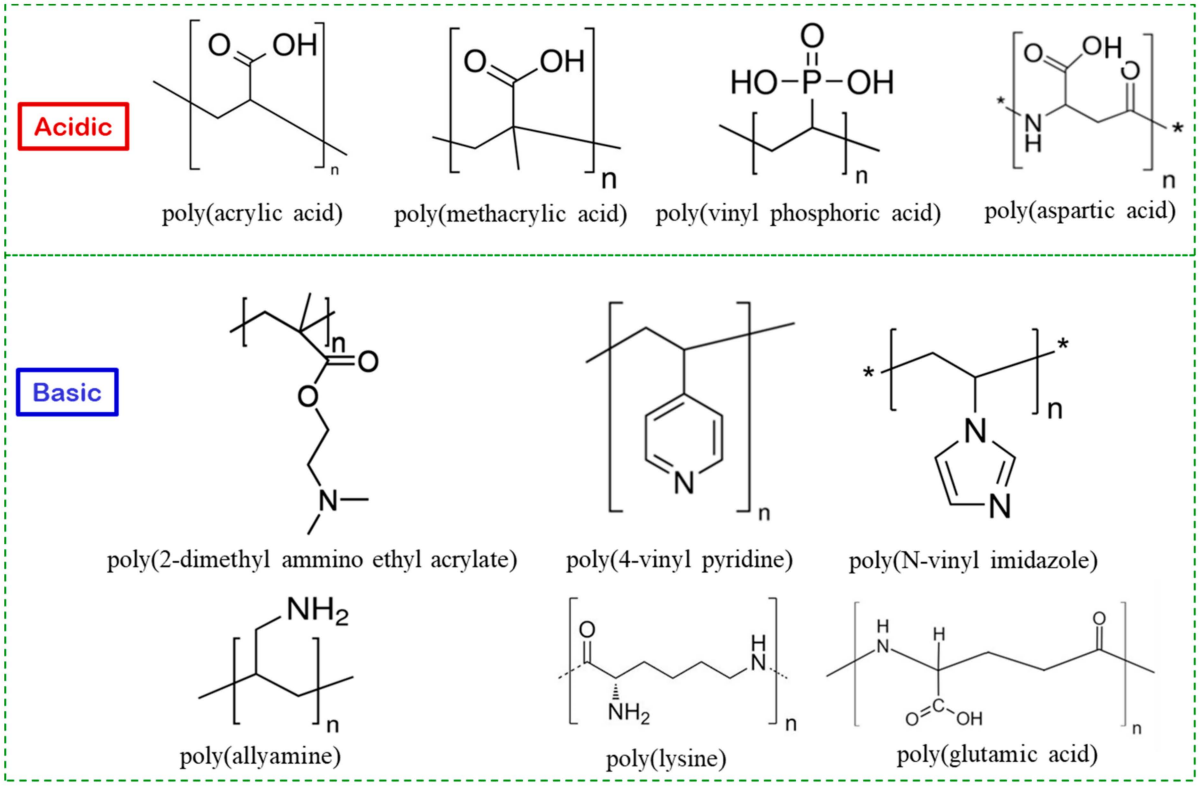

Figure 7. Some examples of pH-responsive polymers.

(iv) Magnetic responsiveness

Among the varied inorganic nanomaterials that are *reactive* towards the *exterior* magnetic field, iron oxide (Fe_3O_4) nanoparticles have gained keen interest in the field of biomedical applications owing to their high surface area to volume, biocompatibility, low toxicity, and easy synthesis [54,55]. The BCPs functionalize the Fe_3O_4 nanoparticles to encouragingly improve the dispersibility of the nanoparticles in the blood circulation duration [56].

(v) Multi-responsiveness

Recently, multi-responsive BCPs have also gained considerable attention as they respond to more than one stimulus (temperature, pH, redox, light, and magnetic field) concurrently and thereby exhibit formed micellar morphologies [38,45,57]. These multi-responsive BCPs are made by fusing two or more distinct monomers, each of which has a unique reaction to stimuli. For example, the poly[(2-dimethylaminoethyl) methacrylate] (PDMA) and poly(2-*N*-morpholinoethyl) methacrylate (PMEMA) polymers are both temperature- and pH-responsive. Multi-stimuli-responsive BCPs are expedient in their ability to release drugs according to their precise biological microenvironment, such as the composition of cells, extracellular matrix (ECM) components, soluble factors, physical forces (e.g., fluid flow and mechanical stress), et cetera [43,58].

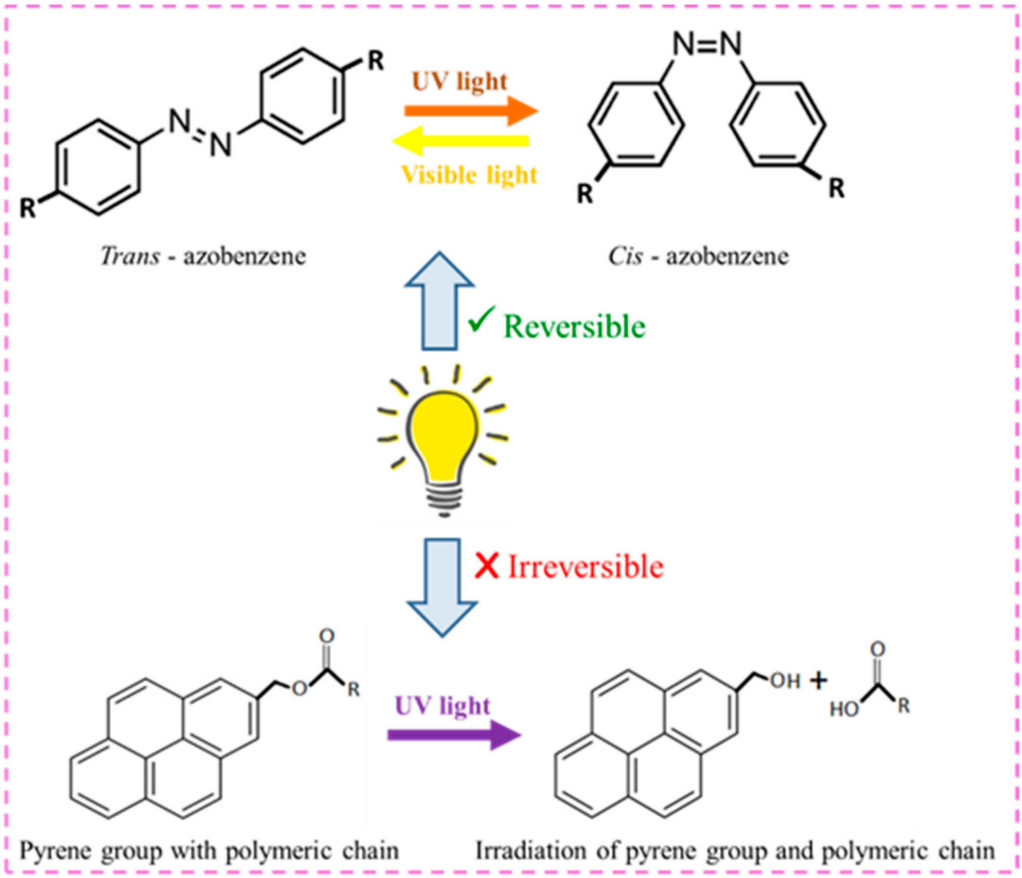

Figure 8. Light-responsive polymers with reversible photochromic and irreversible photo-cleavable moieties.

3. Physicochemical Features of the Self-Assembly in BCPs

With the possibility to synthesize a variety of BCPs from several different kinds of monomers (neutral or ionic) that can lead to a material with well-defined features and tunable properties, researchers are actively engaged in optimizing self-assembled structures from non-toxic micellar aggregates with a great drug-loading capacity and a decent release profile in the optimized release rate at the targeted organ/tissue/cell. In the following section, we discuss the features of polymer self-assembly with regard to micelles and polymersomes. However, these nanoscale self-assemblies formed by BCPs depend on the structure, chemical nature, and molecular characteristics of the copolymers and the solution conditions.

In the following sections, we describe the self-assembled structures formed from (i) amphiphilic block/graft copolymers, (ii) responsive double-hydrophilic block copolymers, (iii) polyion complex assemblies from polyion-neutral BCPs and oppositely charged substances, and (iv) polymerization-induced self-assembly. The focus is on delivering a brief synopsis of all these aspects and their advances in recent years, along with their possible applications in drug delivery systems.

3.1. Polymeric Micelles (PMs)

Unlike classic conventional micelles, the critical micelle concentration (CMC) of BCPs is often very low (<10 mg/L) and not accurately determined. They form kinetically stable nanoscale core–shell architectures that exist in nanoscale sizes (~10–100 nm) and have a fairly narrow size distribution, which enables them to accommodate nonpolar/weakly polar bioactive substances. Furthermore, PMs are less expected to break down and expedite the efficient drug administration over a long period of time. As a consequence, PMs have grabbed

most of the research interest as potential cargo for therapeutic applications [20,59,60]. However, the solubilizate site relies on the chemical nature/structure of the solubilizate as well as that of the BCP and its micelle size/shape. As mentioned above, the core signifies the "cargo" for the encapsulation of various therapeutic reagents, where the hydrophilic shell confirms that the micelles remain in a discrete state, thereby minimizing the unwanted drug interactions with cells. Thus, PMs provide promising vectors for the carrying and delivery of drugs and allow the formation of multipurpose roles for the expansion of innovative therapies for incurable diseases [2,61,62].

Additionally, PMs can attain different features; with these features, they can be transformed into varied nanoparticles that remain undissociated in extreme dilutions via cross-linking of the core or shell, as shown in Figure 9. Cross-linking instigates covalent/non-covalent bonding and produces dynamic micellar systems [63–65]. Cross-linking raises the solubility by several orders of magnitude without diminishing the drug-loading capability. Furthermore, cross-linking has an effect on the permeability of the shell, which changes the pace at which the drug is released over time.

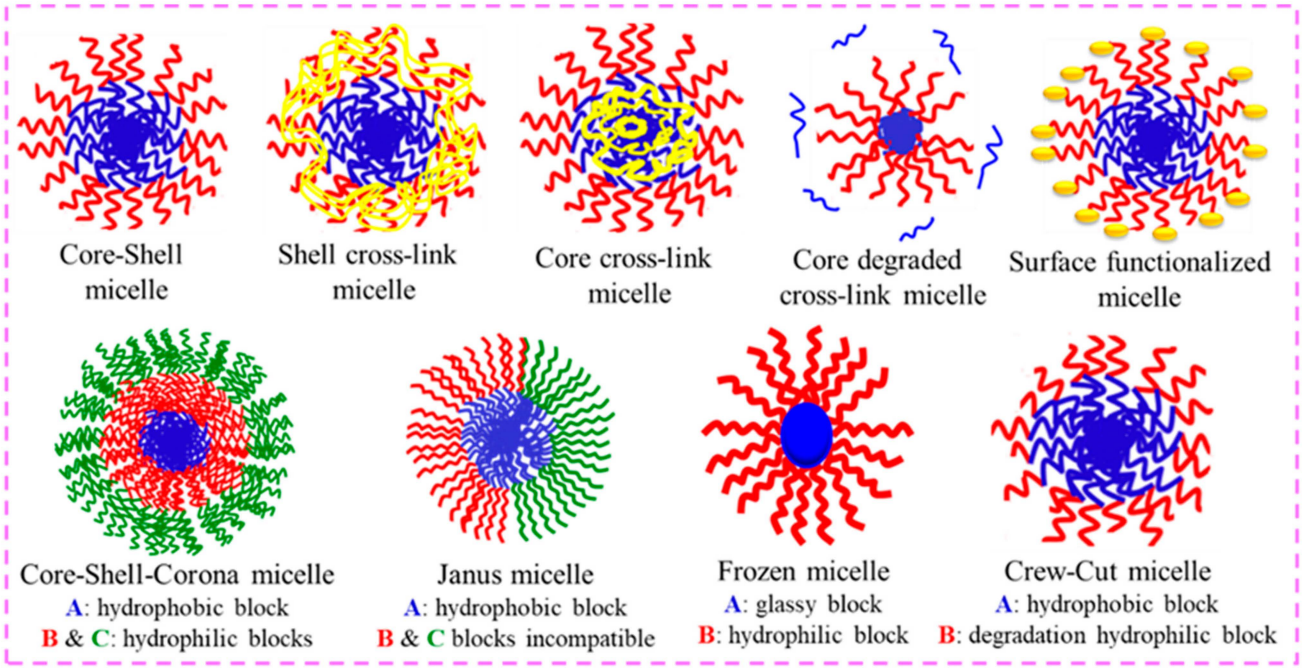

Figure 9. Alteration in the PMs via cross-linking of the core, shell, and surface functionalization. Also, other possible PMs structures, viz., core–shell–corona, Janus micelles, frozen micelles, and crew-cut micelles, are schematically shown.

An overall methodology aims to introduce some functional groups/substituents in the BCPs which ease the cross-linking of the core or shell. Also, the shell permeability can be tuned by changing the degree of cross-linking, which determines the drug loading and the release mechanism of the polymeric micelles. A study by Yilmaz et al. showed a strong influence upon the doxorubicin (DOX) release rate after the cross-linking of the core. It offered efficient trapping of DOX molecules, which later became discharged in a controlled manner. For pH-responsive drug transport, Jie et al. created core-cross-linked PMs which were tunable with BCP with imidazole [66]. For DOX-*based* drug delivery, Jong et al. produced cross-linked PM *based* on poly(ethylene oxide)-b-poly(methacrylic acid) (PEO-b-PMA) with ionic cores and divalent metal cations. Because of the carboxylic group protonation in the micelles' cores, the DOX-loaded polymer micelles displayed observable pH-sensitive action with faster relief of DOX in acidic environments. These micelles also revealed a significant cytotoxicity against human A2780 ovarian cancer cells [67]. PMs can be biocompatible and have the capability to accrue in tumors via enhanced permeability and

retention (EPR). Their functionalization through surface modification with specific ligands and the introduction of stimuli-sensitive groups allows specific targeting and release.

The literature reports have shown the formation of various types of PMs that become cross-linked via –SS– linkages that aid the dual purpose: firstly, they avoid impulsive micelle detachment in the blood, and secondly, they allow the release of the entire drug. This is verified in the study of Li and co-workers, where the PMs demonstrated decent stability and a rapid release compared to extensive dilution [68]. Alternatively, the surface functionalization of BCPs can be accomplished using bio-responsive linkers. Such systems are proposed to tune the hydrophilic character of the functional groups into a hydrophobic one, or vice versa [69]. An FDA-approved polymer *m*PEG-*b*-PCL, with outstanding biodegradability and biocompatibility in the area of drug delivery, has been extensively used. Chemical modifications, like changing different groups, attaching drugs at the terminal end, and host–guest interaction, have evolved to increase drug loading efficacy and release. The drug loading amount of (DOX) by the transporter was enhanced as a result of the interaction, according to the experimental data from Yan et al.'s development of an amphiphilic poly(caprolactone) of pendant carbamic acid benzyl ester [70]. The BCP of Poly(caprolactone) modified with Phenylboronic acid (PBA), prepared by organocatalytic ring-opening polymerization by Wang et al., has a superior capacity to prevent cancer cell proliferation and the subsequent DOX encapsulation [71]. Runliang et al. prepared DOX-loaded micelles from a PBA-modified polymaleic anhydride-F127 polymer for tumor cell treatment [72].

Studies have confirmed the establishment of core–shell–corona micelles when there is a core-forming hydrophobic A block with an outer shell and corona from two incompatible hydrophilic blocks B and C. Such micellar constructs are referred to as '*onion*' micelles. By synthesizing Poly(styrene-b-acrylic acid-b-ethylene glycol) (PS-b-PAA-b-PEG), an asymmetric triblock copolymer, Bastakoti et al. created pH-triggered micelles with a core–shell–corona assembly with a PS as a hydrophobic core, PAA as an anionic shell, and PEG as a hydrophilic corona [73]. Schluter et al. described rod-like micelles with two diverse half coronas based on polydendrons. Additionally, PS and PEO macromonomers underwent progressive ring-opening metathesis polymerization to produce cylindrical *Janus* micelles. Amphiphilic BCPs with hydrophobic blocks with high glass transition temperatures form stable spherical and cylindrical micellar aggregates with "glassy" cores and vesicles with glassy wall interiors in aqueous dispersions. These varied nanoscale micellar geometries are of potential interest in drug delivery applications, where stable and mechanically robust micelles are anticipated. These equilibrium structures, however, do not include the interchange of monomers from micelles like those found in surfactants and BCPs [74,75]. Lyotropic liquid crystals exhibit a liquid crystalline phase in solution, where a liquid crystalline core is formed with a hydrophilic shell. Additionally, studies have shown the development of anionic polymerized crew-cut micelles, which feature enormous insoluble blocks as the core and small soluble blocks as the corona. These PMs can be functionalized through the chemical attachment of a ligand (a bioactive substance, drug, protein, et cetera) at the micelle surface. These polymers can show manifold morphologies, such as spheres, rods, vesicles, lamellae, hybrid micelles, and several other structures, with narrow size distribution, and high stability in water. However, these nanoaggregate morphologies depend on how incompatible the blocks are and what their chemical nature is and on the mol wt. and wt. percent of the blocks. They also depend on the copolymer type, such as AB (di-block), ABA, BAB, and ABC (tri-blocks), and can be roughly predicted by the Israelachvili packing parameter, as described in the published works [2,54]. However, the size of the micelles relies on the preparation method, which signifies the minimum intermicellar exchange in water [12,76,77]. All these varied micellar structures have potential as versatile carriers for drug delivery.

3.2. Polymersomes

Usually, amphiphilic BCPs aggregate to form core–shell micelles of different microstructural features (spheroidal, rod- or wormlike structures). In addition, they exhibit artificial analogues of liposomes (bi-layered vesicles from low molecular weight phospholipids), which are often referred to as polymersomes. [78,79] These soft nanoparticles comprise a spherical aqueous environment enclosed by a bilayer membrane that is composed of a hydrated hydrophilic inner corona and an outer shield made of the hydrophobic middle part. These entities are well known due to their excellent robustness, high stability, longer blood circulation time, structural design, chemical versatility, and ease of surface functionalization, which make them attractive candidates in pharmaceuticals and the medicinal field [80,81]. Drugs, enzymes, proteins, peptides, and fragments of nucleic acids can all be solubilized by polymersomes inside their aqueous core area or membrane region [82,83]. Because of this, polymersomes have been developed into highly intriguing materials that can be used as nano-reservoirs in drug delivery systems (Figure 10).

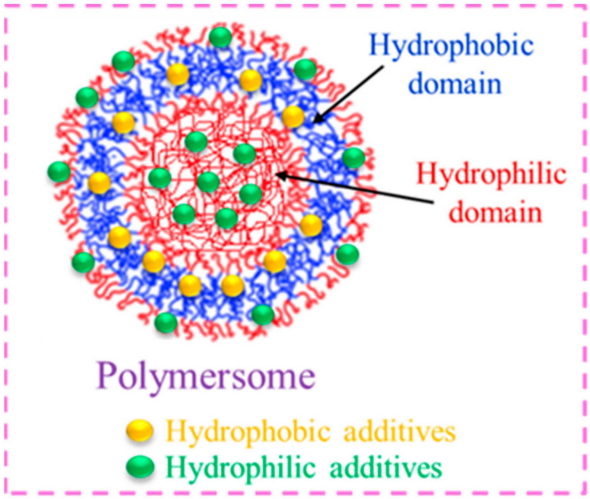

Figure 10. Hydrophobic/hydrophilic molecules entrapped in polymersomes.

Discher et al. initially noticed polymersomes in both theoretical and experimental investigations and explained various mechanisms for polymersome preparations [80,81]. Based on BCP chemistry, Letchford et al. presented a novel class of synthetic thin-shelled capsules with a water penetrability that was at least 10 times greater than that of conventional phospholipid bilayers [82]. Also, the polymersomes with thick and tough membranes are able to encapsulate hydrophilic and hydrophobic molecules and deliver higher in vitro and in vivo stability. Robertson et al. have examined the polymersomes which are responsive to pH, light, gas, glucose, enzyme, oxidation, reduction, and temperature, with various examples presented for different drug delivery and biological applications [83]. Pawar et al. developed various methodologies for the fabrication of polymersomes and explained how polymersomes can be applied in multipurpose biomedical research [84]. Mohammadi et al. described the biocompatibility of polymersomes for cancer theranostic with multifunctional nanomedicines [85].

3.3. Ethylene Oxide (EO)-Propylene Oxide (PO)-Based BCP Micelles

BCP has two or more different monomeric blocks in diverse structures and compositions, which give them distinctive solid-state and solution properties and allow them to show their usability in applications involving catalysis, detergency, dispersants, emulsifiers, pharmaceutical vehicles, et cetera. Among the amphiphilic BCPs, Pluronics® (poloxamers) and Tetronics® (poloxamines), the commercially available FDA-approved EO-PO block copolymers, have been extensively examined [86–88]. These polymeric surfactants are marketed as triblock and 4-armed branched structures with varying PPO mol wt and

%PEO. Pluronics® are poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO)-type amphiphilic triblock block copolymers, whereas Tetronics® are star-shaped poly(ethylene oxide) (EO)-poly(propylene oxide) (PO)-*based* amphiphilic block copolymers (BCPs); they have ethylene diamine as the central unit, to which four PO blocks are attached to nitrogen atoms, while the other end of the PO is linked to the EO block. Thus, their self-assembly leads to different sizes/shapes of core–shell micelles and polymersomes, liquid crystalline structures, and thermo-reversible gels, depending on their concentration. Furthermore, the self-assembly is strongly dependent on temperature and the presence of kosmotropic salts, ionic liquids, surfactants, and polar/nonpolar additives, which have been shown to have a profound effect on the formation properties and behavior of these nanoaggregates. Additionally, these copolymers can be functionalized at the end hydroxyl groups with drugs, bioimaging agents, and other functional polymers, which impart useful and stimuli-responsive properties. There have been several excellent reviews that describe the advances in aggregation and rheological aspects using a variety of experimental techniques, such as scattering and thermal techniques in particular, which detail the size/microstructures of the nanoaggregates and thermodynamics of their assemblies. Pluronics® and Tetronics® are chemically altered or functionalized to utilize various synthetic techniques, giving them improved and desirable qualities as vectors for delivery systems that enhance their properties. At the PEO chains of Pluronics® and Tetronics®, the covalent attachment of any small molecule, polymer block, ligand, or stimuli-responsive molecule changes the micellization, surface activity, solubilization power, and rheological behavior, which can be used to fine-tune the desired features in micelles. Medical diagnostics, imaging, and other applications have all taken advantage of these chemical changes in Pluronics® and Tetronics® [36,89–91]. The core–shell micelles with an outer hydrophilic and extremely polar and flexible PEO shell provide stability and stealth properties to these micelles and prevent aggregation and interactions with mononuclear phagocytic systems that lead to the removal of micelles from systemic circulation. These micelles show a high drug-loading capacity and possess superior thermodynamic/kinetic properties and stability, which can be easily tuned further using mixed systems of two copolymers in a suitably designed concentration/mixing ratio. Mixed Pluronic (L61/F127) micelles with loaded doxorubicin have already become the first Pluronic®-*based* micellar formulation to enter clinical trials as SP1049C (Supratek Pharma Inc., Dorval, QC, Canada). The therapeutic efficiency of these polymeric micelles relies on how these overcome biological barriers and deliver and release the drug at the target site [88–92].

3.4. Polyion Complex Micelles (PICMs)

Polyion complex micelles (PICMs) form when aqueous solutions of two oppositely charged polyelectrolytes are mixed. In addition, strong electrostatic interaction increases entropy *because of the counter ion release* from the macroions; several other interactions, *like* hydrogen bonding and hydrophobic interactions, could also contribute. Additionally, stoichiometrically mixing two polyelectrolytes with opposing charges leads to the spontaneous formation of PICMs/polymersomes in water (insoluble in other solvents) due to electrostatic attraction. Due to the reciprocal neutralization of the two diametrically opposed charges, PICMs/polymersomes have no charge. Polyelectrolytes with opposing charges neutralize each other, which causes them to *drop* their colloidal stability and precipitate out of the solution. If polyelectrolytes can be connected to any hydrophilic and nonionic unit, the precipitation of PICMs/polymersomes can be prevented. The complexes can be water-soluble or insoluble (as coacervates or stable colloidal dispersions); their nature in terms of charged groups, molecular weight, flexibility, et cetera depends on the polyelectrolytes used and the stoichiometric mixing, *in addition to* the solution conditions (pH, temperature, and the presence of salt or other additives). The effects of ionic strength and pH are *significant* in the formation of PICs. Usually, low ionic strength *permits* the complex structure to display thermodynamic equilibrium, *whereas* high ionic strength shrinks it *because of* the shielding of the polyelectrolyte charges. The stable colloidal dis-

persions or insoluble coacervates can be examined by turbidimetric or light-scattering measurements. Smart PICMs/polymersomes have single- or multi-responsive properties against external stimuli. Using random copolymers with pendant quaternary ammonium and sulfonate groups, Shukanta et al. created PICMs using the RAFT technique to create anionic random copolymers from MPC and potassium 3-(methacryloyloxy) propane sulfonate and cationic random copolymers from 2-(methacryloyloxy)ethyl phosphorylcholine with methacroylcholine chloride. Thu et al. created PICMs by directly mixing the two opposing charges of PMPC-block-poly(sodium p-styrenesulfonate) and poly(2-(methacryloyloxy)ethylphosphorylcholine)-block-poly(vinylbenzyl trimethylammonium chloride) [93–99].

PICs have multiple applications in textiles, ink, and paper industries as binders, in coatings, and as flocculants for water purification, to name a few. In 1949, Fuoss et al. first reported that two oppositely charged polymers formed insoluble precipitates, but it was not until 1965 [100] that Michaels et al., after mixing two polyelectrolytes with opposing charges, studied stable nanosized spherical complexes by adjusting the solution pH, temperature, salt content, and other parameters. By successively adsorbing polyelectrolytes from solution onto a surface, layer-b-layer (LbL) films of interacting polyelectrolytes can be created [101–103]. The polyelectrolyte complexes formed in solution and multilayers on surfaces are extensively investigated using a variety of polyelectrolytes with several experimental techniques. A thorough theoretical justification describing counterion condensation on polyelectrolyte complexes has been provided [104–107].

A polyelectrolyte complex can self-assemble into PICMs when it becomes amphiphilic, which is similar to the way that amphiphilic BCPs behave. DHBCs made of a hydrophilic neutral block–polyelectrolyte block are molecularly dissolved in water. Nevertheless, if the solution of an oppositely charged polymer is added to it, self-assembly happens as a consequence of electrostatic attraction, where a core of complexed oppositely charged polymers is formed. The formation of micelles, viz., polyion complex micelles or polyion complex polymersomes and their morphological features, can be finely tuned based on the charge densities of complexing polyelectrolytes, their mixing composition, and their solution conditions, which enable them to be employed in drug and protein delivery [104–108]. The micelles formed with a complexed core and hydrated shells are PICMs (Figure 11).

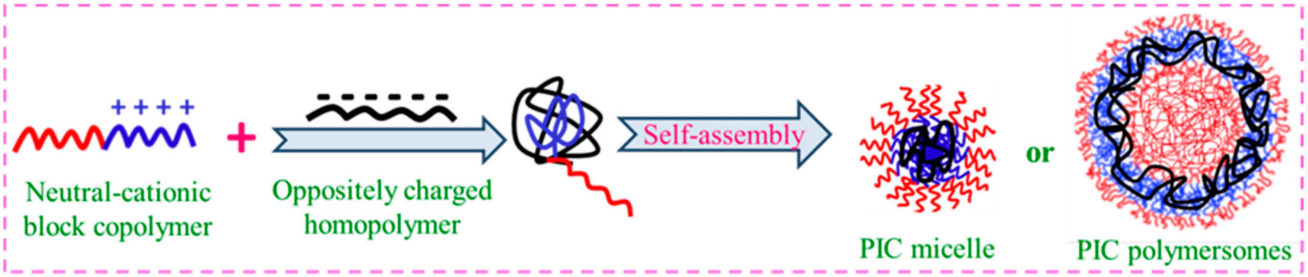

Figure 11. Polyion complex (PIC) micelles and polymersomes.

In an aqueous environment, a variety of synthetic and natural polyelectrolytes can interact with DHBCs to create PICMs or PIC polymersomes, which are extensively characterized by spectral, scattering, thermal, and microscopic methods. [104,105] Two DHBCs with oppositely charged polyelectrolyte blocks and the same or a different hydrophilic neutral block can interact to form interesting shapes. Additionally, these systems may be developed further by employing DHBCs that respond to inputs. Readers interested in learning more about PICMs might refer to several excellent review articles [106,107].

3.5. Polymerization-Induced Self-Assembly (PISA)

Polymerization-induced self-assembly (PISA) is a versatile approach that associates polymerization and self-assembly in a more concentrated solution for the rational production of concentrated BCP assemblies in a high yield using controlled/living polymerization

techniques. It is a straightforward one-pot process with convenient scalability and economic viability. [108–110] The synthesis of linear as well as nonlinear (e.g., star-shaped, or branched) BCPs can be performed by PISA. PISA mediated by RAFT using suitable chain transfer agents and a water-miscible monomer has become a powerful technique that provides BCP micelles with a defined morphology, a controlled size, and surface functionality [111–113]. In contrast to the conventional approach, PISA effectively produces a higher concentration of nano-assemblies without adding a non-solvent to induce micellization. The first polymeric block and the second monomer that are polymerized in PISA must both be soluble in the same solvent. When the second block is sufficiently lengthy, its solubility is reduced, allowing the resultant BCP to self-assemble in place and produce nanostructures. PISA involves the aqueous dispersion polymerization of a water-miscible monomer till a critical degree of polymerization (DP) transforms it into a water insoluble polymer, which then self-assembles into a core–shell micelle of different morphologies, depending on the molecular weight and nature/composition of the blocks (Figure 12). Here, the macroscopic precipitation is avoided by appropriately controlling the colloid stability through steric stabilization.

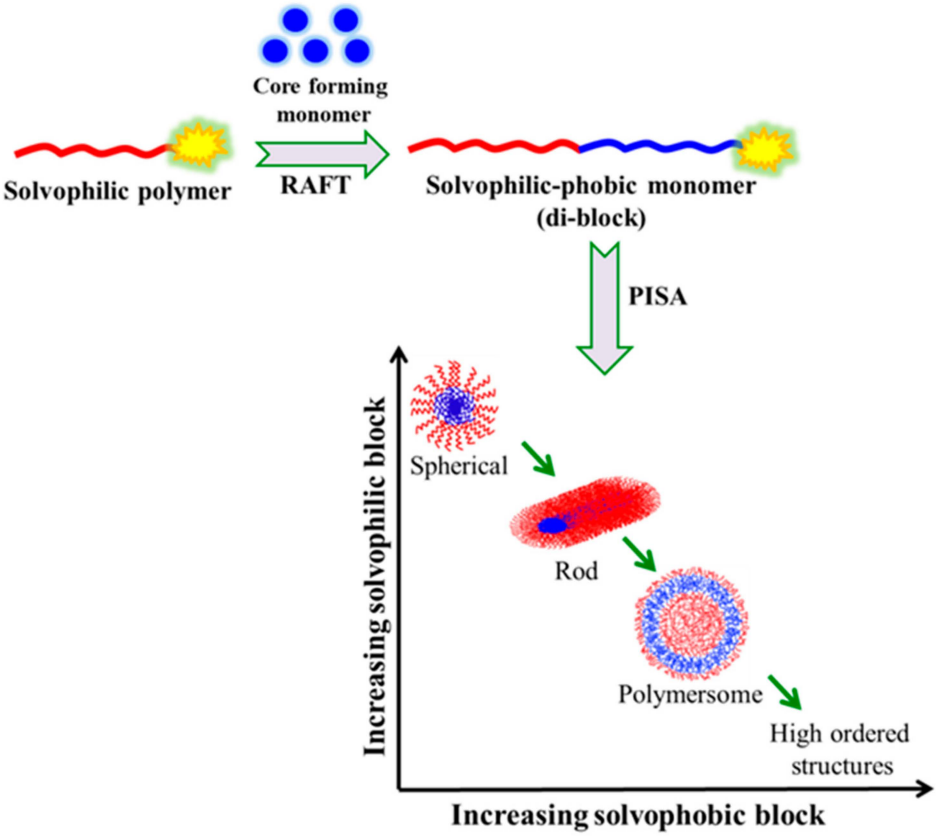

Figure 12. Schematic representation of PISA in solution.

PISA can be achieved with comparatively high solid contents (up to 50% wt) and can undergo very high monomer conversions within a short reaction time. Armes and co-workers have reviewed the polymer synthesis by PISA (RAFT) in polar or non-polar media (including supercritical CO_2 and ionic liquids) and non-aqueous media [114–116]. Thus, PISA enables the in situ production of self-assembled nano-objects with various morphologies ranging from sphere to rod to polymersome; finally, a precipitate is formed by modifying the solution conditions. It has become very important for nanocarriers in drug delivery and can achieve better cellular uptake, tracking, and enhanced bioavailability. The synthesis and in situ formation of nano-assemblies of diblock copolymers (PMPC-b-PPFPMA) can be achieved via PISA using RAFT in ethanol as a selective solvent.

3.6. Crystallization-Driven Self-Assembly (CDSA)

Crystallization-driven self-assembly (CDSA) represents a handy methodology for the production of 1D and 2D anisotropic nanostructures with a high level of dimensional control and a tunable core–shell micelle in solution. This approach has shown that semicrystalline BCPs are promising for the development of materials with complex architectures [117–119]. This propensity is caused by the core-forming block crystallizing after being heated over the glass transition temperature and cooled in a weak solvent. As a result, polymers that are easily accessible by coupled ring-opening and RAFT polymerizations can be used to create nanostructures with anisotropic morphologies and excellent solution stability. The self-assembly process is facilitated when one block of the BCP is crystallizable. For a copolymer with a crystallizable insoluble block, the crystal packing forces play an important role in determining the morphologies of the different core–shell micelles formed. A few recent reviews on such self-assembly of semicrystalline block copolymers have been published [120–125].

4. Applications of BCPs

The applications of BCP-derived nanopatterns in real-life technologies are of great significance in several areas. BCPs are extensively used in the advancing field of nanopatterning, including next-generation lithography for semiconductors. The capabilities constituting the BCP toolbox have grown over the ages and have delivered numerous extraordinary achievements. However, a few challenges remain to be overcome in ensuring its integrity in the development process. The nanoscale self-assembly of BCPs like micelles and vesicles has received great attention in the field of drug delivery applications due to its effective control of morphology, surface chemistry, and responsiveness [126–138]. Organic dyes are only partly water soluble, which is a major challenge for dye and paint industries. BCPs tend to solubilize such hydrophobic moieties in their micellar core in a manner which depends on the hydrophobicity of the BCPs. Several studies have reported the ease in which dye solubilization can be influenced in the presence of external stimuli or additives [139–142]. Due to their ideal drug loading and release features, lengthy shelf life, and low toxicity, smart BCPs are particularly successful in controlled drug delivery applications, as well as for treatment and diagnostics. In particular, polymersomes serve as successful carriers for drug delivery systems [143–146]. Consequently, due to their high functionality, these BCPs might be used in a variety of medical devices, including nanoreactors, "semi-artificial" enzymes, and biodevices with blood-compatible surface treatments [147–150].

Polymeric micelles have emerged as promising nanocarriers due to their ability to control the drug release profile and the release at the target site; they have enhanced permeability and retention and enhance the solubility of hydrophobic bioactive substances, particularly anticancer drugs. They can build up in the tumor microenvironment because of the increased permeability and retention impact of their nanoscale size. These micelles from biocompatible and nontoxic amphiphilic polymers are anticipated to be a fruitful treatment option for drug and gene delivery (DNA/siRNA) in various cancer therapeutic strategies, like the crossing of the blood–brain barrier, photothermal therapy, gene therapy, and immunotherapy. The majority of polymeric micelles are undergoing clinical trials for various cancer therapies. Here is a description of both the commercially available polymeric micelles and the micelles presently undergoing clinical trials. The paclitaxel (PTX)-loaded polymeric micelles (NK105) have improved clinical efficacy against ovarian, lung, neck, breast, and brain cancers. Clinical testing for breast, lung, and pancreatic cancer has been approved for the FDA-approved "Abraxane®" albumin nanoparticle. Long-circulating polymeric micelles with an amide linkage and a hydrophobic PEG-b-poly (aspartic acid) copolymer backbone make up NK105. PEG-PLA copolymer-*based* micelles were authorized in 2007 in the Republic of Korea. Genexol®-PM, a PM formulation containing paclitaxel, is offered by Samyang Co. in Seoul, Korea. Genexol®-PM has shown increased tumor tissue concentration and anticancer activity when compared to paclitaxel. Genexol®-PM has been

approved for use in the treatment of breast, lung, and ovarian cancer. It is commercially available in India under the name Nanoxel®, by Dabur Pharma Ltd., New Delhi, India. Doxorubicin (DOX)-containing micelles (NK911) have included the irreversible binding of DOX with a polymer, such as N-(2-hydroxypropyl) methacrylamide (HPMA), and an enzyme-sensitive spacer of glycyl-phenylalanyl-leucyl-glycine reached Phase-I clinical trials. Myocet and Doxil/Cealyx (PEGylated) were approved by the USFDA for ovarian and breast cancer. PEG-b-poly (α, β-aspartic acid) was verified by preclinical studies in cancer mouse models under the name NK911. SN-38-loaded polymeric micelles (NK012), which contain a micellar formulation comprising 7-ethyl-10-hydroxy-CPT (SN-38) attached through esterification via PEG-PLGA, have a greater half-life and superior bioactivity level at the tumor level in mouse models of brain cancer and renal, colon, pancreatic, and gastric cancer. In clinical studies for patients with esophageal and gastroesophageal cancer, the Kabanov research group and Supratek pharma developed SP1049C, Pluronic®-*based* DOX-loaded polymeric micelles. Pluronic® L16 and Pluronic® F127 (1:8 ratio) were combined to create SP1049C. For the formulation of platinum-*based* polymeric micelles used to treat diseases such as myeloma and lymphoma and testicular, ovarian, bladder, and lung cancer, cisplatin and oxaliplatin were widely used. In late 2004, the USFDA certified oxaliplatin (oxalato(trans-l-1,2-4 diaminocyclohexane) platinum (II)) as a main therapy for colorectal cancer when used in combination with 5-FU. Modifications were made to a formulation of oxaliplatin and platinum (II) (PtDACH), and a PEG-b-poly(glutamic acid) copolymer developed self-assembled polymeric micelles. Finally, clinical studies have begun for both formulations [151–160].

Pharmaceutical formulations are generally very complex and not completely understood. An enormous number of BCP-*based* drug delivery systems are widely explored to understand the drug release from the dosage, with the aim of developing the formulations that ensure safety and efficacy for patients [161–165]. Several different strategies have been *engaged to improve* the solubility and bioavailability of hydrophobic drugs. The nanoscale self-assemblies (polymer micelles and polymersomes) have been of great interest in recent years as these offer several advantages. The use of cosolvents, hydrotropes, micronization, and supramolecular complexes and the altering of the crystal structure have been adopted for the initial processes. Hydrogels, solid lipid nanoparticles, self-emulsifying dispersions, nano- and microemulsions, and liposomes have been developed over time. Several nanocarriers, such as inorganic metal/metal oxide nanoparticles, particularly AuNPs and magnetic NPs, and mesoporous silica; nanocarbons such as CNTs, graphene, and quantum dots; and organic nanocarriers such as dendrimers and NPs derived from polysaccharides, proteins, and biodegradable polymers have been found to be quite promising for drug encapsulation. Here, we provide the references of the review articles covering all such features [164–166].

The application of BCPs in the sensing field is also gaining momentum significantly. In an effort to create sensors with high sensitivity and selectivity, novel transduction methods and manufacturing techniques have been disclosed [167]. Metal oxides, non-oxide inorganics, and carbon-*based* ordered porous materials exhibit aligned structures and uniform cavities with micro- to meso- to macropore sizes, which lead to a very high surface area. Such features enable their utilization in energy conversion and storage, catalysis, gas capture, and water purification. Apart from the above-mentioned applications of these BCPs, their extensive use in separation and surface coating is anticipated [139–143].

5. Conclusions and Future Perspectives

This review presents a detailed description of different nano-assemblies from block copolymers obtained in tailor-made structures using a variety of hydrophilic/hydrophobic blocks, both charged and uncharged, and it highlights the evolution in the expansion of multifunctional nanoaggregates as vectors for delivery systems. Furthermore, it offers an insight into the nanoscale micellar aggregates formed from amphiphilic block copolymers (BCPs), stimuli-responsive double-hydrophilic block copolymers (DHBCs), and polyion complexes (PICs). Advanced polymerization synthesis techniques have been discussed;

these techniques enable us to craft the novel stimuli-responsive BCPs. The formation and characterizations of BCP micelles are explained. However, the drug transport throughout the body and to its targeted delivery site is among the modern challenges. The immediate challenge in BCPs is to design and formulate an effective micellar system that enhances their specific delivery to the targeted site along with an efficacious penetration ability that fights against the infected cells. Also, there are pressing challenges ahead, such as the expense of the regulatory approval for the commercialization of these aspirant BCP-*based* delivery systems. Accordingly, from the point of view of the industrial pharmaceutical trade, the customized BCPs are novelties. Thus, a judicious design of non-toxic probes in drug delivery systems will improve bioavailability, patient compliance, and therapeutic outcomes. Thus, this review will surely inspire the readers to consider all the BCP features, whose modes of operation can be tailor-made as per the desired needs and applications.

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