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Strategies to improve micelle stability for drug delivery

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Abstract

Micelles have been studied as drug delivery carriers for decades. Their use can potentially result in high drug accumulation at the target site through the enhanced permeability and retention effect. Nevertheless, the lack of stability of micelles in the physiological environment limits their efficacy as a drug carrier. In particular, micelles tend to disassociate and prematurely release the encapsulated drugs, lowering delivery efficacy and creating toxicity concerns. Many efforts to enhance the stability of micelles have focused mainly on decreasing the critical micelle forming concentration and improving blood circulation. Herein, we review different strategies including crosslinking and non-crosslinking approaches designed to stabilize micelles and offer perspectives on future research directions.

Summary

Different strategies to improve micelle stability were reviewed in this work. Specific examples with improved drug delivery efficacy owing to enhanced micelle stability were illustrated.

Keywords

Micelle; stability; crosslinking; critical micelle concentration (CMC); drug delivery

1. Introduction

Many different drug carriers have been developed for controlled drug delivery in recent decades, including micelles, liposomes, polymer or protein-drug conjugates, polymeric nanoparticles, and pathogens [1–13]. Among these drug carriers, micelles have a number of attractive features. Micelles are self-assembled microstructures formed by surfactants in an aqueous system and are usually < 50 nm in diameter [14]. Polymeric micelles are defined as organized auto-assemblies formed in a liquid, which are composed of amphiphilic macromolecules, in general amphiphilic di- or tri-block copolymers made of solvophilic and solvophobic blocks [15]. Polymeric micelles can exceed 100 nm in size and can still be regarded as micelles [16]. These self-assembled micelle structures can protect insoluble hydrophobic drugs, which mimic aspects of biological transport systems in terms of structure and function [17]. Micelles have been widely used as drug delivery carriers for a

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series of different molecules, including low molecular mass hydrophobic drugs, proteins, and genes [18–22].

Compared with other drug delivery strategies, micelles have two unmatched advantages. The first is their relatively small size. The hydrodynamic sizes of a micelle is usually less than 50 nm [23]. Considering the dimensions of physiological pores in the body's vasculatures (e.g., pores of kidney glomeruli, inter-endothelial junctions for healthy tissues, tumors, cancerous tissues, etc.), nanomedicine utilizing smaller particle sizes (e.g., < 100 nm) is favored for blood circulation, tissue penetration, and cellular uptake [24–30]. Recent evidence has indicated that a sub-50 nm drug formulation is desirable to achieve the collective outcome of deeper tumor tissue penetration and more efficient cancer cell internalization, as well as the cellular response [31, 32]. Therefore, small micelles can markedly improve the *in vivo* performance of encapsulated drugs, leading to high accumulation at the target site (e.g., tumor tissue) due to the enhanced permeability and retention (EPR) effect [33–35].

The second advantage of micelles is their feasibility of large-scale manufacture. A micelle is the simplest assembled entity, with well-defined molecular structures and assembly behaviors. This enables simple drug formulation and ease of manufacturing. These attributes are vital; other advanced particle systems are complicated to prepare and have inherent problems that hinder their large-scale production in a stable and consistent manner. For example, periodic shortages due to difficulty in obtaining manufacture approval have resulted in limited availability of DOXIL® (Jassen Products, LP. Titusville, NJ), a polyethylene glycol (PEG)ylated liposome with encapsulated doxorubicin [36]. In contrast, a micelle formulation is simple to manufacture at a large scale, such as Taxotere® or Taxol®, which contain only the drug (docetaxel), the micelle (polysorbate 80), and the solvent (alcohol) [37]. The two advantages of micelles have spurred their acceptance as a first-line drug formulation technology[18] .

Despite the advantages, a fundamental limitation of micelles as drug delivery carriers is their low stability when encountering environmental changes. Once the concentration is below the critical micelle forming concentration (CMC), micelles can disassociate. This is typical when micelle formulations are injected into the blood. Disintegration of micelles due to their dilution in blood and other factors that include protein binding may result in a burst release of previously encapsulated drugs into the bloodstream. Such premature drug release can negate the potential benefits of a carefully optimized drug carrier, which include high drug loading, prolonged blood circulation due to the EPR, and targeting capability. The result can be an unfavorable drug biodistribution and a therapeutic outcome that is similar to that of an unprotected (non-encapsulated) drug [38]. For example, the micellar drug Taxotere® is quickly removed from the blood circulation once intravenously (i.v.) injected [39]. This can reduce the therapeutic performance of the encapsulated drug and raise concerns about toxicity [18, 40]. Therefore, how to stabilize micelles, especially in the physiological condition, is a significant challenge for their drug delivery applications.

In this review, we explore several factors that can potentially influence the stability of micelles and discuss different strategies to stabilize micelles. The current and potential

therapeutic uses of micelles are considered with specific examples provided of the benefits of enhanced micelle stability on drug biodistribution and therapeutic outcome.

2. Micelle stability and evaluation methods

When a micelle solution is diluted to a very low concentration (typically $< 10^{-3}$ mM), the surfactant content is not sufficient to drive the self-assembly of micelles. Instead, they tend to distribute at the air-water or aqueous-organic solvent interface which leads to the disintegration of the micelles. Thus, a minimal concentration of surfactant, the CMC, is required to maintain the structure of micelles [18]. CMC is determined by the micelle inherent properties and is critical to evaluate the stability of micelles at diluted concentration.

In addition to dilution, the structural stability of micelles is influenced by the complicated physiological environment, such as salt concentration, solvents, temperature, and pH. For example, after injection/infusion into the bloodstream, micelles may undergo several environmental changes, including significant dilution, exposure to pH changes, and contact with numerous proteins, lipids, and cells. The hydrophilic and hydrophobic domains of certain micelles are linked via ester, amide and other functional groups. The micelle structure may potentially be disrupted due to the hydrolysis of linkers when facing significant pH changes. Other disruptors include protein absorption through non-specific binding or electrostatic interaction. The resulting premature release of the encapsulated therapeutic content may lead to the accumulation of the drug in healthy tissues or organs, which could cause severe side effects and a further decrease of the pharmaceutical activity of the drug [41]. The fundamental strategy to improve the stability of micelles is to enhance intra-micellar interactions, which are often reflected by a decreased CMC. Therefore, measuring the CMC value can directly evaluate the efficacy of these strategies.

The classical method to measure CMC is based on the observation of the concentration-mediated change in physical properties of micelles by measuring electrical conductivity [42], surface tension [43], chemical shifts detected by nuclear magnetic resonance (NMR) [43], absorption [42], determination of self-diffusion coefficients [43], and fluorescence intensity [42]). Transmission electron microscopy (TEM) and dynamic light scattering (DLS) are commonly used to show the overall morphology and size of micelles. The determination of aggregation number, which is the number of small molecules or polymer chains assembled to form a micelle, is another way to evaluate the assembly behavior [44]. The micelle aggregation number can be determined by isothermal titration calorimetry [45, 46] or calculated from an apparent molecular mass of self-assembled micelle in a solvent obtained by static light scattering. In addition, fluorescence resonance energy transfer (FRET), which is sensitive to small changes in the distance between molecular groups, can be used to measure the integrity of micelles in solvents [47–49]. Typically, fluorescent energy donors and acceptors are encapsulated in the micelle hydrophobic domain, and the emission wavelength of the acceptors can be detected. Once a micelle dissociates upon dilution or other environmental changes, the resulting increased distance between donor and acceptor pair will lead to a decrease of the previous acceptor emission and an intensified emission of the donor.

3. Covalent crosslinking strategies to stabilize micelles

As previously discussed, enhanced stability of a micelle could be reflected by the decrease of its CMC. In general, polymeric micelles have a significantly lower CMC (10^{-6} - 10^{-7} M) than conventional small molecule micelles (10^{-3} - 10^{-4} M) [23, 50–52]. The low CMC is attributed to the long hydrophobic block of the amphiphilic copolymers, the presence of which, however, significantly increases the size of polymer micelles or spheres (typically from 100 nm to the μm scale). An increase in size generally lowers the *in vivo* performance of the encapsulated medicine [30–32]. In addition, the assembly of these long hydrophobic chains can barely achieve a thermodynamic equilibrium and is highly dependent on the specific method used to formulate the assembly [50]. As a consequence, the size and quality of the assembled polymeric micelles or spheres are sensitive to almost every formulating parameter, such as the polymer and drug concentration, stirring style and speed, and solvents [53–55].

It is highly desirable to develop micelles with further lowered CMC and increased stability with the goal of obtaining more efficient drug delivery carriers. Attempts have been made to co-inject empty micelles to increase the micelle concentration in the body to avoid micelle burst and drug loss [40, 56]. The effectiveness of this strategy remains questionable and is not yet well accepted as a stabilization method. Currently, the most popular and effective method, among many others, is crosslinking to decrease the CMC and stabilize micelles. In this section, different covalent crosslinking strategies to lower the CMC are introduced in 3.1 and specific crosslinking methods are discussed in 3.2.

3.1 Covalent crosslinking strategies

The dominant driving force for micelle formation is the reduction of free energy through the removal of hydrophobic fragments from the incompatible aqueous environment. Micelle formation is reversible and highly dependent on weak intermolecular interactions within the micelles. The most popular covalent crosslinking strategy involves the formation of covalent bonds/crosslinking within specific domains of the micelle, such as the shell and core domains. This reinforces the weak intermolecular interactions and thus stabilizes the micelles.

3.1.1 Shell crosslinked micelles—Shell crosslinking is a recognized way to stabilize polymeric micelles assembled from the copolymers. Early studies [57] focused on micelles derived from AB-type diblock copolymers, which possess a hydrophobic core (A) and hydrophilic shell (B). In these systems, crosslinking has to be controlled within the hydrophilic domains (shell) rather than between individual micelles to avoid the formation of large covalently bound aggregates. For this purpose, dilute concentration (0.1-0.5% solids) can effectively prevent extensive inter-micellar crosslinking [58]. Nevertheless, the diluted concentration can drastically limit the crosslinking efficiency. To circumvent this issue, ABC triblock copolymers have been studied. They have a significant advantage over AB diblock copolymers when preparing shell crosslinked micelles [58]. In addition to the A and B constituents, ABC triblock copolymers have an outer domain (C) termed the corona, which can bestow different functions on micelle systems. For micelles derived from ABC

triblock copolymers, crosslinking is possible at a much higher concentration (e.g., 10% solids), since the additional outer C domain can effectively eliminate the chances for inter-micellar crosslinking and also provide potential sites for conjugating ligands for various functions. (Figure 1) Nevertheless, micelles based on ABC triblock copolymer with a crosslinked shell are relatively complicated and require sophisticated designs.

3.1.2 Core crosslinked micelles—Shell crosslinking is effective in stabilizing micelles but may modify the surface chemistry and the hydrophilicity of the shell region. This could potentially affect the blood circulation performance of the micelles, which is very dependent on the stealth property of polymer materials in the hydrophilic shell. To prevent the undesirable changes to the micelle surface characteristics, core crosslinking has been adopted as an alternative way to stabilize micelles. Core crosslinking is typically done after micelle formation. The reactive groups for core crosslinking are either already present in the core region or are added later. The groups do not interfere with the micelle formation process. Typical crosslinking methods include polymerization of radicals, addition of bifunctional crosslinkers, or click chemistry. Potential crosslinkers added following micelle formation must permeate the micelle's hydrophobic domain before reacting with the substrate within the inner core of the micelle. This can be difficult to achieve, raising potential transport concerns. Although crosslinking of the shell or core region can efficiently improve the stability of the polymeric micelles, it does not influence the release of the encapsulated drugs, which are still released in a non-controllable manner[41]. Covalently entrapping drugs has been combined with core crosslinking to achieve proper drug retention within the micelles, such as during blood circulation. The encapsulated drugs can be released in a predefined manner via the cleavage of a specific linker in response to environmental stimuli, such as a pH-sensitive linker[59].

3.2 Covalent crosslinking methods

3.2.1 Photo/ultraviolet-induced dimerization—Compared with other crosslinking methods, photoinduced dimerization is advantageous because no additional crosslinking agents are required and no byproducts are formed during the reaction [60]. Furthermore, the size and shape of micelles are maintained [61]. The cross-linking density can be easily controlled by tuning the light wavelength or intensity. Radiation-induced dimerization was reported as early as 1998 by Liu [62], who obtained a crosslinked poly(2-cinnamoylethyl methacrylate) shell by photolysis of sample with ultraviolet (UV) light. The UV-induced dimerization of a cinnamic acid and its derivatives have been well explored [63, 64]. Typically, UV-irradiation at 365 nm induces dimerization of coumarin or cinnamoyl groups in aqueous media [61, 65]. This reaction is attractive because the crosslinking process is reversible. The newly formed bonds can be cleaved upon UV-irradiation at 254 nm [61, 66]. This potentially enables a controllable drug release at a special UV condition. However, the strategy is limited by its low tissue penetration ability and potential toxicity [67]. In addition to UV, visible light has also been used to induce micelle crosslinking involving di-selenide bonds, where the crosslinked micelles displayed excellent physiological stability and could encapsulate antitumor drugs [68, 69]. In addition, di-selenide bonds are sensitive to the redox environment, which makes controllable degradation and drug release at the targeted location feasible. In a tumor-bearing mouse model, diselenide-crosslinked micelles delivered

significantly more drugs to tumors (1.69-fold higher) compared with non-crosslinked micelles [68].

3.2.2 Di-functional crosslinkers—The first reported crosslinker used to prepare shell-crosslinked micelles was p-(chloromethyl) styrene [57]. This di-functional crosslinker was used to form quaternary amines on the pyridine groups of the hydrophilic domain of a block copolymer of polystyrene and poly(4-vinyl pyridine), followed by a radical polymerization of the styrenyl side chains of the crosslinker at the micelle shell region [57]. Further efforts have included a series of di-functional crosslinkers taking advantage of the condensation reaction, conjugation, quaternization, and others to obtain shell crosslinking. For example, a diamine crosslinker can react with two carboxylic acid groups of poly(acrylic) acid in aqueous medium through a carbodiimide catalyzed condensation reaction to stabilize the shell layer of micelles [70, 71]. In a similar way, cystamine, a diamine crosslinker that contains a cleavable disulfide bond, can be used to stabilize micelles, which can be subsequently destabilized in a reducing environment [72]. Glutaraldehyde is a commonly used crosslinking agent, which can also react with primary amines, such as the poly(lysine) block of a micelle [73]. Through quaternization, the 1,2-bis(2-iodoethoxy)ethane (BIEE) crosslinker has been reacted with N,N-dimethyl aminoethyl methacrylate in aqueous solution to obtain shell crosslinking [74]. The Michael Addition reaction has been exploited in the use of a divinyl sulfone to crosslink hydroxylated blocks of a micelle in a basic condition [75]. Similar to the strategy of crosslinking hydrophilic shells, a di-functional crosslinker is also effective to crosslink the hydrophobic core of a micelle. Examples are the use of diamines [76–78], di-activated esters [79], and di-benzophenone [80].

3.2.3 Click crosslinking method—A click chemistry based crosslinking method was reported, in which acetylene groups in the shell of poly(acrylic acid)-poly(styrene) diblock copolymer micelles were crosslinked with azide-functionalized dendrimers [81]. The unreacted azide groups are also able to conjugate with a fluorescent label, which is essential for *in vivo* tracking and imaging, and other biologically active ligands. Such an azide-alkyne cycloaddition reaction was studied as a shell crosslinking strategy [23, 82, 83] and has also been applied to core crosslinking micelle systems [84, 85]. These crosslinked micelles have enhanced stability, improved drug loading capacity, and *in vitro* release profile [83], or low toxicity when incubating with cells [84]. Whether drug delivery is improved remains unclear.

3.2.4 Silicon chemistry method—A condensation reaction that produces the formation of siloxanes was reported as a method to crosslink micelle cores [86]. Siloxane bonds were formed upon the addition of triethylamine into precursor (trimethoxysilyl) propyl methacrylate (TMSP-MA), which induced the hydrolysis of the methoxy silane groups and the formation of crosslinked Si–O–Si linkage [87]. In a similar way, the poly ((triethoxysilyl) propyl methacrylate) block in a micelle system could form a crosslinked core through water-triggered hydrolysis and siloxane formation [88]. Another type of silicon chemistry-based method involves ring-opening polymerization of silacyclobutanes to crosslink micelle cores [89]. This reaction was reportedly catalyzed by hexachloroplatinic

acid (H_2PtCl_6), and other series of similar crosslinker derivatives based on silacyclobutane have been reported [90].

3.2.5 Reversible boronate ester bond—Boronate ester bonds are formed between a boronic acid and an alcohol, diol, or molecule with multi-hydroxyl groups, such as glucose. The boronate ester bonds are reversible and sensitive to pH or competing substrates. The reversible boronate ester has been used to crosslink micelles to enhance stability and improve the release kinetics with external stimuli. For example, boronic acid containing polymers and catechol containing polymers were reported to form crosslinked micelles as drug delivery carriers [91, 92]. Using FRET technology to evaluate micelle integrity, such crosslinked micelles showed prolonged blood circulation. When triggered by the low pH in a typical tumor environment, the resulting micelles could quickly release their drug payload. The preferential accumulation of the drug in tumors was observed by imaging of harvested organs [91]. Nevertheless, the sensitivity of the boronate system to oxidative conditions, such as hydroxyl peroxide [93], is a concern with respect to toxicity because hydroxyl peroxide is necessary in the redox signaling pathway of normally-functioning cells [94].

4. Non-covalent crosslinking strategies

In addition to the majority of crosslinking methods that involve covalent bond formation, there are other crosslinking methods based on non-covalent molecular interactions. These include static electric interaction and hydrogen bonding, and have been applied to enhance the intra-micelle interaction and micelle stability [95].

4.1 Complexation of micelle cores

Diblock copolymers containing two hydrophilic blocks in which one of the blocks is ionic can self-assemble upon interaction with an oppositely charged species to form the so-called polyion core micelles [96] (Figure 2a). A typical example is the polyion micelle that can be assembled from the block copolymer poly(ethylene) glycol-*b*-poly(lysine) and poly(ethylene) glycol-*b*-poly(aspartic acid) [97]. The obtained polyion complexes do not significantly increase the hydrophobicity within the core, but do enhance micelle stability through electrostatic ionic interactions [97–99]. Compared with other crosslinking methods, polyion micelles are markedly less toxic because no small molecule crosslinker is used in the crosslinking process. In addition, polyion micelles typically display a high loading capacity for hydrophilic drugs [100] and can be used for DNA or RNA condensation [101, 102]. Furthermore, the stability of the formed complexes can be further enhanced through external crosslinking. For example, poly (ethylene oxide)-*b*-polymethacrylate anions (PEO-*b*-PMA) and divalent metal cations have been used to prepare core-complexed micelles [103]. In this process, PEO-*b*-PMA copolymers were self-assembled into block complexes in the presence of divalent ions, such as Ca^{2+} and Ba^{2+}, followed by a second covalent crosslinking of available carboxylate groups in the micelle core region using diamine crosslinkers (Figure 2b). The second crosslinking maintained the core-shell morphology of the micelle and further increased core stability.

In addition to static electric interaction, other complexation methods can be used to enhance the stability of micelle without compromising drug loading capacity. For example, π-π

stacking of aromatic groups, as introduced by N-(2-benzoyloxypropyl methacrylamide (HPMAm-Bz) or the corresponding naphthoyl analog (HPMAm-Nt), was reported to strengthen the hydrophobic core and enhance the overall micelle stability [104]. The occurrence of π-π stacking in micelles was confirmed by solid-state NMR [104]. Using a particular polymeric micelle based on methoxy poly(ethylene glycol)-b-(N-(2-benzoyloxypropyl) methacrylamide) (mPEG-*b*-p(HPMAm-Bz)) block copolymers, paclitaxel was loaded with excellent capacity and strong drug retention without the need for chemical crosslinking and covalent drug attachment [105]. Substantially increased paclitaxel accumulation was observed compared with the unstable micellar formulations used as the control. This led to the reported complete tumor regression in xenograft models by the π-π stacking stabilized micelles.

As an additional example, hydrogen bond formation between urea-functional groups in a PEG and polycarbonate copolymer was reported to strengthen the micelle cores [106]. The formation of hydrogen bond decreased the CMC of the micelle and improved micelle stability in the presence of destabilizing agents. By introducing both acid and urea-functional groups to the PEG and polycarbonate copolymer, the ratio of acid/urea groups could be further adjusted and optimized to achieve the desired micelle stability through the hydrogen bond formation between urea-urea and acid-urea [107].

4.2 Other complexation methods

Additional non-covalent complexation methods include macrocyclic host-guest complexation, which is an interaction used to bind two chemical entities. The goal of the approach is to design the structure of polymeric micelles [108], such as the interaction between β-cyclodextrin (β-CD) and adamantyl (ADA) [109]. Furthermore, the altered topology of the hydrophobic core was reported to enhance the stability of micelle and decrease the CMC [110]. In particular, PEGylated polymeric micelles with both flattened and curved corannulene core regions were prepared; only micelles with the curved corannulene displayed decreased CMC (Figure 3). The observations highlight the significance of topology in manipulating the stability of micelles. In the curved corannulene, the curvature-induced electron delocalization can create dipole-dipole interactions, which facilitate intermolecular electrostatic interactions that stabilize micelles.

5. Strategies to stabilize micelles without crosslinking

Since CMC is an inherent property of micelles, manipulating the structure of micelles to modify their micelle forming behavior has been frequently attempted without additional crosslinking. These efforts include altering hydrophilic/hydrophobic block ratios of the micelles [111], increase of the crystallinity of hydrophobic segments [112], and other non-crosslinking strategies. Typically, CMC decreases with increasing chain length of the hydrophobic block, which is explained by the enhanced hydrophobic interaction within the cores [113]. Furthermore, decoration of micelle cores with various fatty acids reportedly decreased the CMC of the modified micelles due to the introduction of hydrophobic segments by the fatty carbon chains to the micelle cores [114, 115]. Similarly, benzyl groups have been introduced to PEO–PCL copolymers. The resulting micelles displayed lowered

CMC due to the increased rigidity and hydrophobicity of the micelle core [116]. Nevertheless, this design may significantly increase the size of polymer spheres (typically from 100 nm to the μm scale), which was reported to severely decrease the potential targeted delivery efficacy and lower the *in vivo* performance of the nanomedicine [30, 32, 117]. By changing the crystallinity of the hydrophobic segment, micelles with semi-crystalline core structures could be obtained. These displayed much lower CMC values than micelles with amorphous core structures [112]. A possible explanation is that the crystallization process itself may be an additional driving force for the micelle assembly, resulting in a lower CMC value.

As a notable non-crosslinking strategy to achieve stable micelles, the unimolecular micelle is unique in that the micelles literally contain only one molecule, and so do not require additional crosslinking for stabilization. Unimolecular micelles are formed by individual multi-arm star amphiphilic block copolymers or telodendrimer (e.g., linear-dendritic block copolymers [118]) and have been utilized as drug delivery carriers. One study explored engineered unimolecular micelles for targeted breast cancer therapies [119]. Unimolecular micelles were formed by esterification between the dendrimer core of poly(amidoamine)-poly(lactide)-OH (PAMAM-PLA-OH) and the hydrophilic domain of OCH_3-PEG-COOH. The micelles displayed excellent *in vitro* and *in vivo* stability with high drug loading capacity. Significant tumor inhibition and high intratumoral drug concentration were also reported in the study. Other dendrimers, such as the commercially available hyperbranched Boltron® H40 polymer can also be used as the cores of unimolecular micelles (Figure 4). Furthermore, using a dendrimer as the core of the micelle system also enables the combination with covalently crosslinking to facilitate the drug release at the targeted site. For example, the cross-linkable telodendrimer pair, PEG-catechol-cholic acid were prepared and crosslinked via formation of a boronate ester [91]. This ester might hydrolyze in response to the acidic pH of the tumor environment, leading to a burst release of the encapsulated drugs. Biodistribution results confirmed the high drug accumulation in the tumor as the result of a quick drug release at the target site.

Recently, a zwitterionic polymer micelle with sharp polarity contrast between the hydrophilic zwitterionic domain and hydrophobic lipid domain was reported to show an undetectable ultra-low CMC below 10^{-6} mM, which was orders of magnitude lower than CMC ($>10^{-3}$ mM) of common micelle systems [121] (Figure 5). Without chemical crosslinking or other decoration methods, which potentially complicate the micelle preparation and increase the micelle size, this particular zwitterionic micelle system did not disassociate and protected encapsulated drugs/nanoparticles at extremely dilute concentrations. The mechanism of ultra-stability of the zwitterionic micelles appeared to be due to the superhydrophilicity of the zwitterionic moieties promoting the hydrophobic-hydrophobic interaction within the micelle core. Even when the zwitterionic moiety or polymer alone was added to a micelle solution without chemical modification of the micelles, the existing micelles in the modified solution were stabilized at a concentration below their inherent CMC. A docetaxel formulation has been prepared using this zwitterionic polymer micelle system. The new formulation displayed significantly improved stability in serum and high drug retention upon dilution, and substantially enhanced drug

delivery to the tumor region and an increased overall therapeutic outcome, compared with conventional micelles.

6. Perspectives

Numerous polymeric micelle systems have been developed to increase micelle stability with the goal of improving drug delivery. Nevertheless, various issues remained that prevented these strategies from being utilized in a clinical setting. Firstly, many current efforts involve sophisticated structure designs and/or complicated preparation procedures. Micelles are a simple and easy means of drug formulating. Increasing the complexity would pose a potential hurdle for consistent and large-scale manufacturing, which is a prerequisite for regulatory approval for clinical trials. The complexity further increases the difficulty to characterize micellar drug formulations and to repeat the results of the formulations and potential advantageous therapeutic outcomes. Challenges remain in enhancing the stability of micelles and their formulations through simple strategies without comprising the feasibility for large-scale manufacturing. Secondly, despite many studies concerning modification of micelle structure and their stability or correlation with CMC, more fundamental data are needed on how these potential modifications impact the micelle stability. For example, it is recognized that micelles in water will not disassociate at a concentration above the particular CMC. However, when these micelles are exposed to serum proteins, the majority of the micelle molecules will bind the proteins at this concentration rather than remaining as a micelle assembly. Potential theories or knowledge supporting and explaining similar observations will be beneficial for future design of micelles with ultra-stability. Lastly, despite the potential of many new materials in drug formulations, including the zwitterionic polymer materials [122–124], the consensus is still to use PEG almost exclusively as the hydrophilic component of micelles or nanoparticle systems, since PEG is approved by FDA for similar injection use. More research is needed to facilitate the translation of new material platforms to expand the list of approved materials for formulation scientists to develop more efficient medicines.

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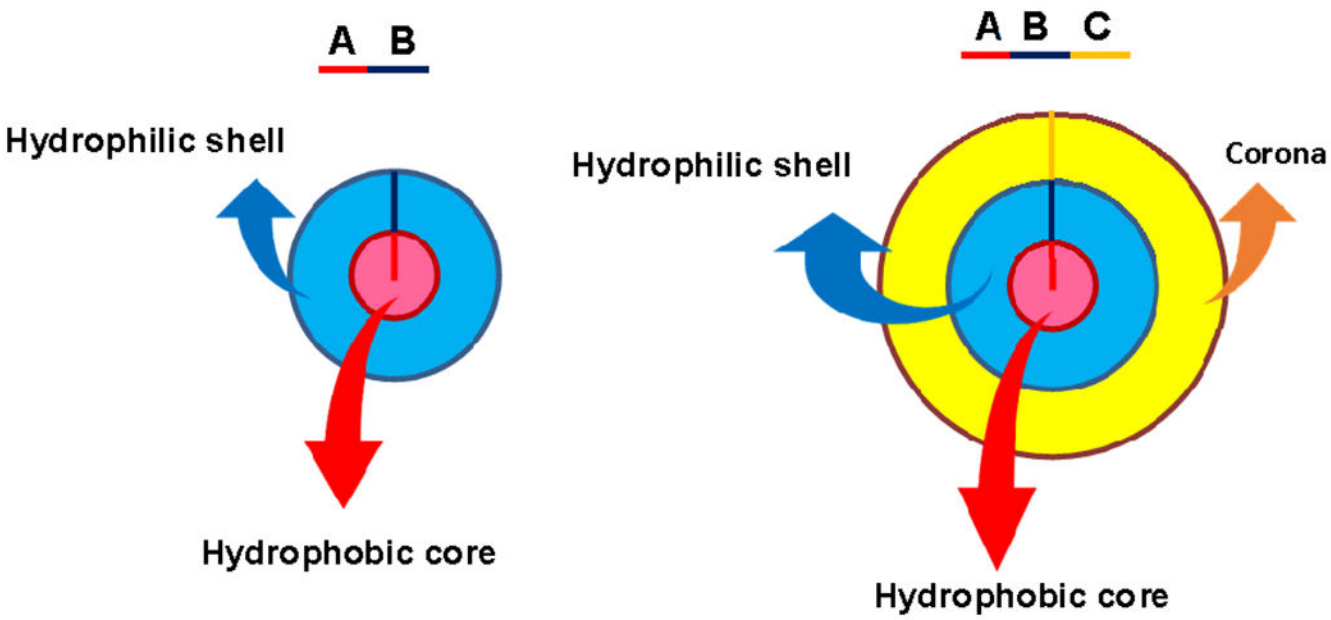

Figure 1.
Illustration of micelles assembled from AB diblock copolymers and ABC triblock copolymers

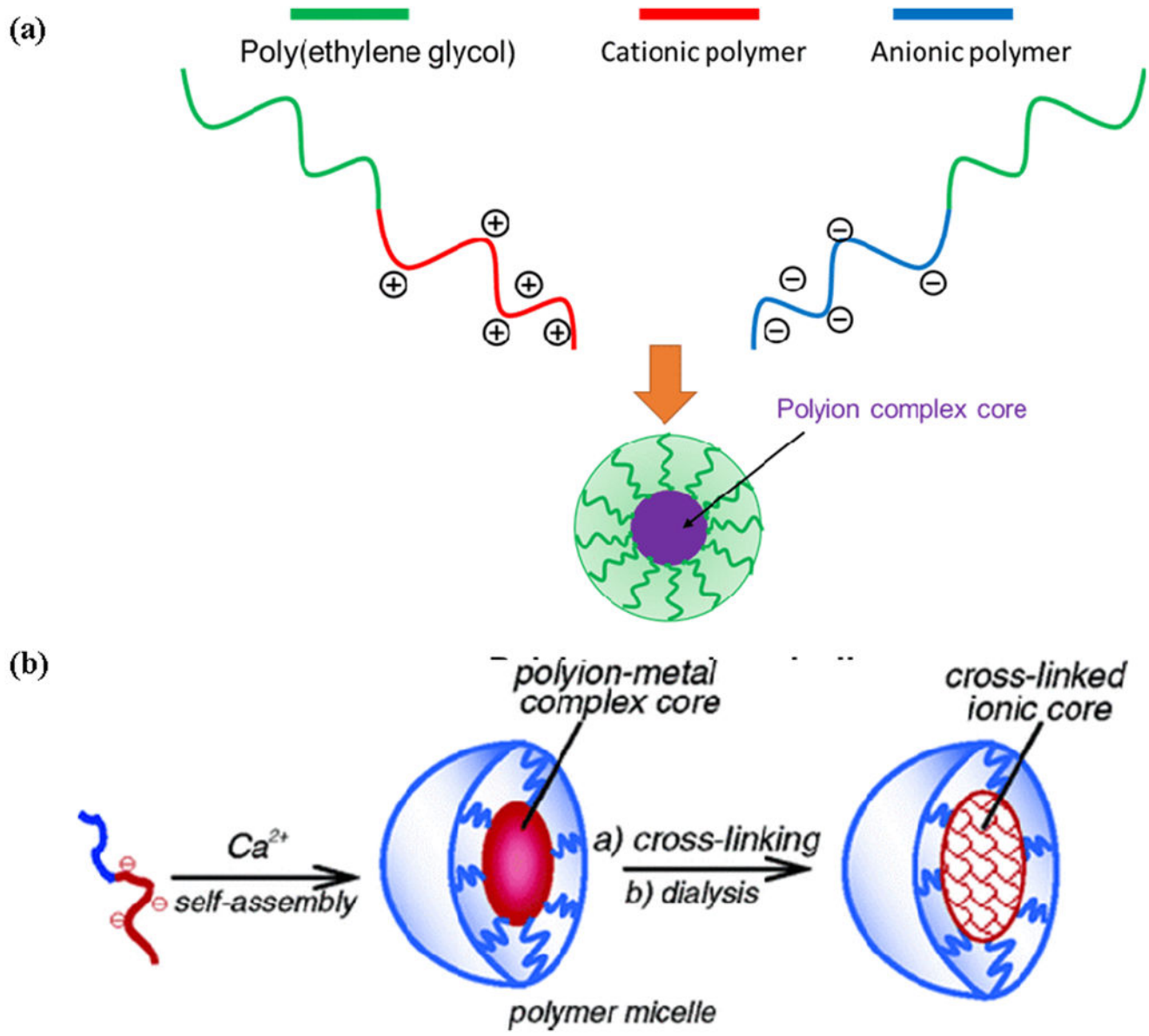

Figure 2.

Formation of polyion micelles (a) Polyion complex micelle formation from diblock copolymers. (b) Scheme of polymeric micelle with crosslinked ionic cores. Copyright © 2005 American Chemical Society[103].

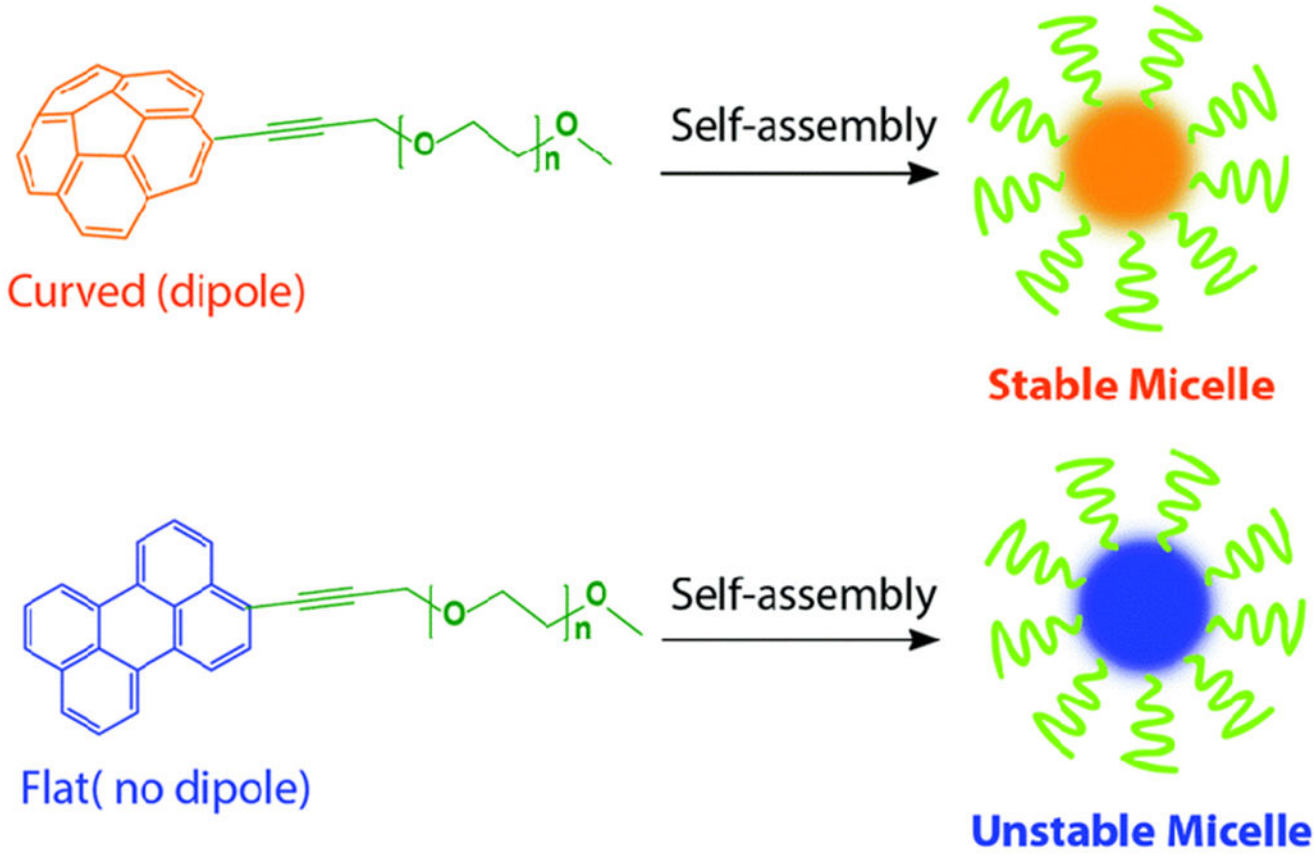

Figure 3.
Illustration of the topology effect on the stability of micelles.[110] Copyright © The Royal Society of Chemistry 2017

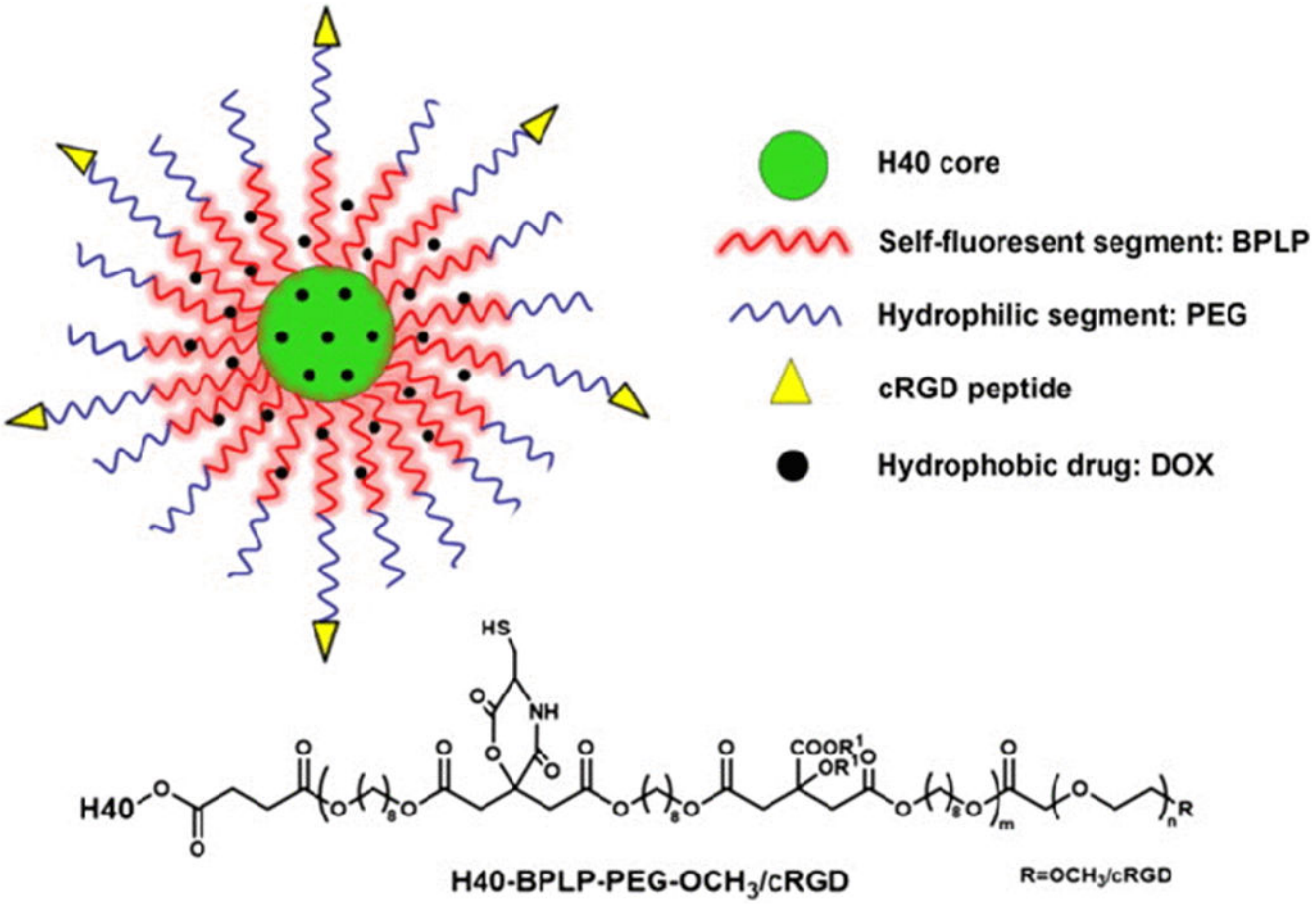

Figure 4.

A schematic illustration of a unimolecular micelle nanoparticle made of the multi-arm, hyperbranched, star amphiphilic block copolymer, H40-BPLP-PEG-cRGD[120] Copyright©, 2015 Elsevier Ltd.

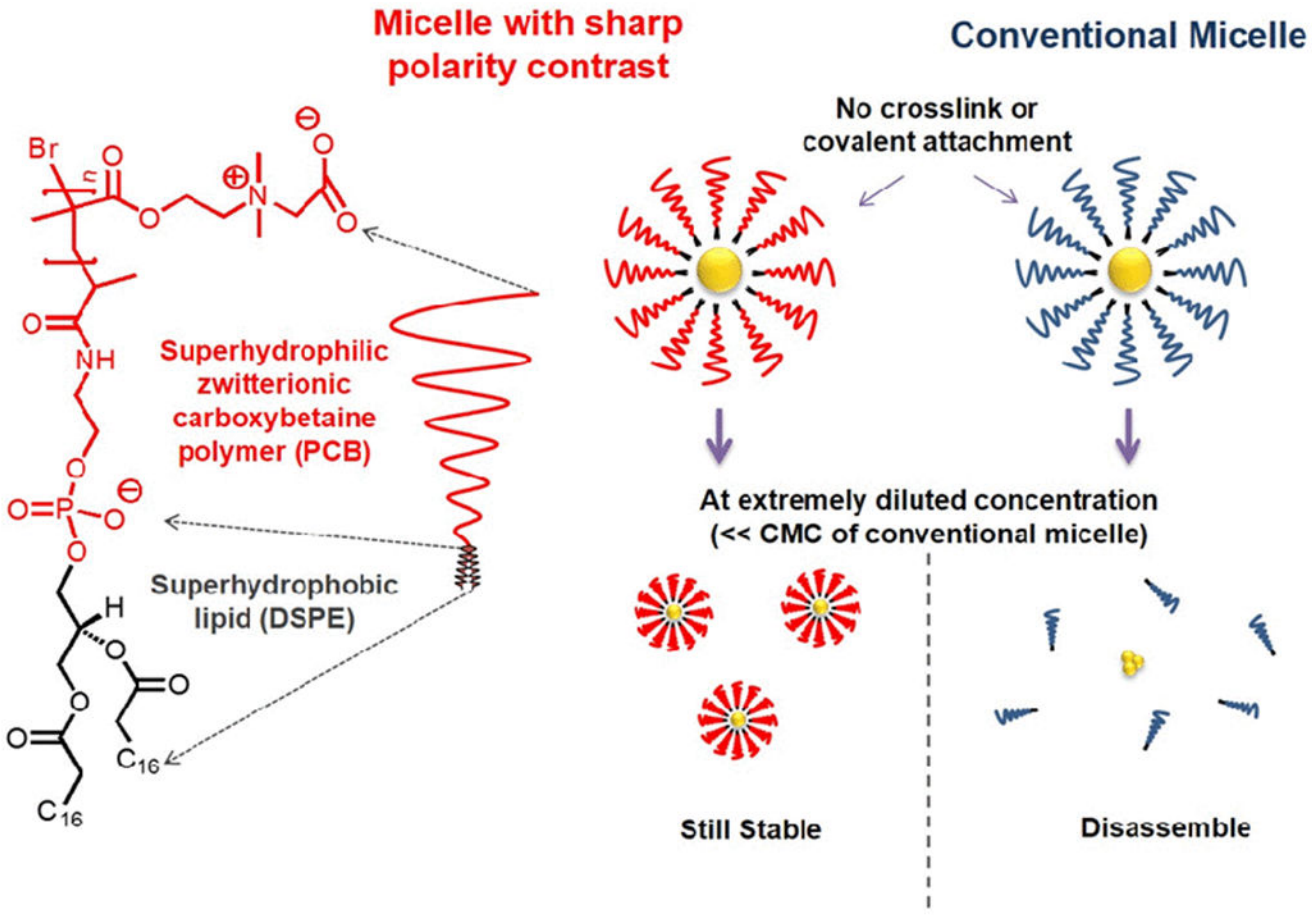

Figure 5.

Ultra-low-CMC micelles and their unusual ability to stabilize cargoes in extremely diluted conditions with micelle concentrations far below CMCs of common micelles [121] Conventional micelles dissociate at a concentration below CMC, and thus cannot stabilize a hydrophobic cargo at that concentration. Polar groups of conventional micelles were either non-ionic (e.g., Polysorbate 80, which is hydrophobic) or only contained one ionic group (e.g., sodium dodecyl sulfate). For zwitterionic micelles, as shown, the polar groups contained multiple zwitterionic moieties to form a polymer. Copyright © 2018, Springer Nature