Review Article

Stimuli Responsive Wormlike Micelles in Biomedicine

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Abstract

Amphiphilic molecules have ability to self-assemble above their critical aggregation concentration in aqueous solution, transforming a variety of microstructure or nanostructure. The worm like micelles is one of them having peculiar rod-like or thread-like structure with excellent viscoelastic properties and unique rheological responses. The morphologies and characteristics of such nanostructures depend on the molecular structure of amphiphiles or surfactants and related conditions. The present review concentrates on the stimuli responsive rheological control of wormlike micelles and their applications in biomedicines.

Key words : worm like micelles, drug loading, nanomedicine.

Introduction

Every amphiphilic molecules or compounds like surfactants are composed of a water-loving (hydrophilic) head group and a water-hating (hydrophobic) tail group.[1,2] These molecules spontaneously self-assemble to form micellar structures when dissolved in water.[3-6] Israelachvili et al., have introduced a concept of 'critical packing parameter' (P) for the prediction of micellar shape in their equation P=v/al where, v is the volume the hydrophobic part, a is the optimal surface area occupied by the surfactant head group at the micelle-water interface and l is the critical length of the hydrophobic tail.[7] The P values determined the self-assembling morphologies of aqueous amphiphilic molecules. P<1/3 represents spherical or spheroidal micelles, 1/3<P<1/2 denotes rod like or wormlike micelles (WLM), 1/2<P<1 for vesicles, P~1 for bilayers and P>1 represents reverse micelles. When micelles grow into rod-shaped or worms, they gain long cylindrical shape and flexibility which is similar to polymers. Polymers have a stable structure but WLMs exists in solution maintaining a dynamic equilibrium between constant braking and reformation. Due to this dynamicity to maintain the equilibrium, wormlike micelles are known as equilibrium polymers or living polymers. The excellent rheological properties with viscoelasticity make WLMs more potential agent in oil industry and are used to make home care products.[8]

Formation of wormlike micelles mainly takes place when aqueous solution of surfactants (mainly cationic surfactants) mixed with a hydrotrope with low molecular weight.[9] These hydrotropes are sometimes called as primers and they screen the electrostatic repulsions between the two adjacent charged head-groups of surfactant molecules (Figure 1).[10] The WLMs can be also prepared from non-ionic or zwitter ionic surfactants in the absence of hydrotopes.[11,12] The viscoelastic properties and rheological changes of these soft matters can be controlled varying the system conditions.

Stimuli - responsive micelles

Stimuli- responsiveness is the change that occurs in physicochemical properties due to variations in the external environment. Smart worm-like micelles (SWMs) are sensible to changes in the environmental changes such as light, electric current, temperature and pH. Micellar structures and its rheological response can be tuned by activating the triggers. This stimuli responsive behaviour of the WLMs has to lead to an active area of multidisciplinary research with potential applications in areas such as microfluidics, tissue engineering, drug delivery, and clean fracturing fluids.[13]

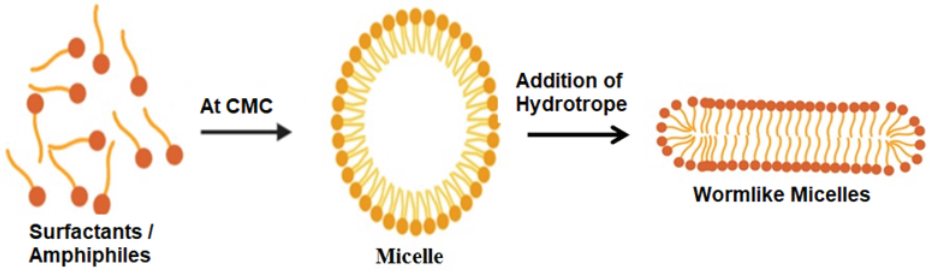

Figure 1: Formation of wormlike micelles after addition of hydrotrope to the micelles

Redox-responsive WLMs

Electro-rheological (ER) fluids are colloidal dispersions with tunable viscosities mediated by the application of electric potential.[14] These fluids are considered as important materials for the fabrication of smart structures and machines. ER fluids are synthesized by the dispersion of the solid particles in liquids. However requirement of higher particle concentrations along with high voltage is a limiting factor that hampers the use of ER fluids in industrial applications. These liquids also suffer from poor solubility. Similar drawbacks were addressed by using 'redox-switchable' cationic surfactants. These cationic surfactants in the presence of sodium salicylate (NaSal) self-assemble into electro-reversible WLMs. Further, by varying the entanglement length and degree, the viscoelasticity of the WLMs can be tuned by redox reactions.[15]

Light-responsive WLMs

Application of ultraviolet or visible light as an external stimulus is considered as an efficient technique as it is non-invasive and can avoid any changes in the composition. Light-responsive WLMs are formulated using two broad strategies. In a first approach photosensitive functional moieties are added to the surfactants and in another approach the surfactant structure is covalently bound to the photosensitive functional moiety. Light can also be directed towards a specific spatial location hence it is widely used in nanoscale devices such as lab-on-a-chip and micro-patternable biomaterials.[16,17]

In a pioneering study by Wolff et al., stimuli-responsive WLMs were prepared using the classic cationic surfactant CTAB and 9-methylanthracene as the hydrotrope to induce the formation of WLMs. Initially the monomers were irradiated at 300 nm and then at 249 nm to avoid the reduction in viscosity by dimerization of monomers.[18] Following this the work was extended to several non-polar derivatives of anthracene.[19]

Thermo-responsive WLMs

Thermo-responsive WLMs are prepared by incorporating thermal stimulating moieties in the surfactants. Polyethylene glycol (PEG) is a widely used thermal stimulating moiety to impart thermo responsive properties to WLMs.[20] The effect of the PEG length on the thermo responsiveness of the WLMs were investigated by Ahmed et al.[21] It was observed that long PEG chains reduced the thermo sensitivity of the WLMs. Non-ionic WLMs containing PEG groups display thermo-viscosifying properties as the micellar growth is favoured by thermal trigger.

Studies performed without the addition of additives showed that the viscosity of the WLMs initially increased with the temperature and decreased after a maximum. The temperature ranges for this reaction was recorded from 0°C to 40°C.[22] The thermo-viscosifying characteristics were also found to depend on the concentration of the surfactants used for the preparation of WLMs. WLMs based on thermo-viscosifying effects were also prepared from mixtures of CTAB and 5-methyl salicylic acid. This mixture displayed a bluish low viscosity liquid around 48°C which changed to colorless, viscous fluid at 54°C. Viscosity measurements showed that the transition of micellar structures from vesicles to worms was mediated by the temperature changes. It was also observed that this transition is temperature switchable i.e., the disrupted vesicles can transform into worms upon heating and then reform into vesicles when cooled.[23]

pH-responsive WLMs

Like temperature, pH has also been used widely to control the molecular assemblies and bulk properties of the solutions. Generally pH-responsive WLMs are developed based on the available cationic CTAB and zwitterionic alkyl dimethlyamine oxide (CnDMAO) in the presence of hydrotropes. Another strategy to develop pH-responsive WLMs is by the design of new surfactant architecture. The typical property of no display of net charge in the neutral pH by the zwitterionic surfactants leads to weak repulsions among the surfactant head groups. This helps in the formation of long flexible WLMs without the addition of any additives. However zwitterionic surfactants become positively charged when the pH level is below the isoelectric point. Hence pH plays a

significant role in the assembly of WLMs and also offers the possibility to manipulate the architecture of micelles and hence their properties.[24,25]

pH-responsive WLMs were also fabricated by using acid hydrotrope and cationic surfactant solution. Huang et al.,strategized a simple method to prepare pH-responsive WLMs using CTAB and potassium phthalic acid. This study showed that by varying the pH from 3.90 to 5.35 the nature of the fluid can be reversed between gel-like and water-like states. The pH responsiveness of the WLMs was confirmed using nuclear magnetic resonance, UV/Vis and fluorescence anisotropy. The pH responsive behaviour was attributed to the decrease in the binding ability of the hydrotrope. The authors also concluded that the same strategy can be applied to other cationic surfactants.[26-28] Anionic surfactant based pH-responsive WLMs were mostly prepared using carboxylic acid as it is highly sensitive to pH. Most of the reported WLMs were prepared using carboxylate-containing surfactants.[29]

Biomedical applications of WLMs

WLMs are being increasingly used for biomedical applications as they are biodegradable and closely resemble the properties of polymer solutions.[30] WLMs based nanodrug carriers are reported to prolong the circulation time and improve the bioavailability of the drugs.[31] WLMs has also demonstrated higher accumulation in the tumour sites via enhancing permeation and retention (EPR) effect.[32]

The self-assembled nature of the WLMs possess a hydrophobic core which helps to improve the solubility of poorly soluble drugs.[33] The stimuli responsive nature of the WLMs makes them an attractive candidate for the targeted delivery of drugs especially in cancer therapy. Anticancer drugs can cause severe toxicity to the surrounding healthy tissues. Hence it is of vital importance to design drug carriers that can selectively deliver the drugs. Thus the stimuli-responsive nature of WLMs has been used in several studies to deliver the drugs in the tumour site. Triggers such as temperature, redox potential and pH are closely related to the biomedical field as they are often found in the sites of pathology.[34] For example, the pH level of tumour microenvironment is more acidic than the normal tissues.[35] Temperature is also a "biology relevant" trigger and it is mostly used to trigger the process of gelation in "injectable" scaffolds.[36] Nanoparticles have been incorporated in polymeric micelles to improve the solubility of hydrophobic drugs and imaging agents. pH-responsive polymers prepared from diblock copolymer and poly (ethylene glycol)-block-poly (2-diisopropylaminoethyl methacrylate) (PEG-b-PDPA) were used to target the delivery of hydrophobic drugs to the endosomes.[37]

Yu et al., imparted pH-responsiveness to the micelles by introducing hydroxyl pendant groups onto the PDPA block. The polymer was tagged with tetramethylrhodamine (TMR), which is a pH non-responsive fluorescence dye. When the pH was less than 6.3 there was no observable fluorescence signal from the micellar solution due to the aggregation of the dye molecules inside the micelle core. When the pH was increased above 6.3 the PDPA segment was protonated and the solubility was increased, This lead to the diassembly of the micellar aggregates and thus the fluorescence signal was restored.[38]

Lee et al., developed a worm like polymeric micelle from poly (L-lactic acid)-b-poly (ethylene glycol) (PLLA-b-PEG) block copolymers. The WLMs architecture was composed of a shell consisting of a short PEG block and a core made up of PLLA block. The surface of the WLMs were functionalized with folate receptors and cyclic arginine-glycine-aspartic (RGD) peptides to effectively target the breast cancer cells. This study showed that the micellar structures with the targeting ligands were able to get accumulated selectively in the tumour environment by receptor mediated targeting.[39]

Bioresorbable filomicelles were prepared from polylactide/polyethylene glycol (PLA/PEG) for the delivery of the anticancer drug paclitaxel by Jeloneket al. This study also investigated the importance of the stereochemistry of PLA block and the molar mass ratio of PEG for tailoring the micellar structures. It was observed that the selection of copolymer and the encapsulation method plays an essential role in the drug loading properties. Among the copolymers used mPEG5000 initiated copolymers showed better sustained drug release properties than that of mPEG2000 initiated copolymers.[40]

In yet another study WLMs and micelles were prepared from the amphiphilic diblock copolymer. The hydrophobic anticancer drug paclitaxel (TAX) was loaded into the core of the prepared WLMs and micelles. It was observed WLMs improved the solubility of the TAX as twice as that of the spherical micelles and the same trend was observed in drug loading. TAX loaded WLMs also demonstrated 5-fold higher cytotoxic effect than the spherical micelles. Thus the study highlighted that the WLMs can efficiently act as drug carriers with improved drug loading and solubilization properties.[41]

In a study by Lone et al., smart WLMs with pH stimuli sol-gel transition was prepared using Sodium Tetra Decanoyl Phenyl Alanine (STDPA) in the presence of NaCl. The prepared WLMs were pH responsive and showed excellent sol behaviour below pH 8.25 and transformed as a gel above pH 8.65. Even though the

pH range was very narrow the WLMs demonstrated excellent sensitivity to pH by undergoing reversibility. The rheological characteristics showed that at/above pH 8.65 the prepared WLMs showed viscoelastic properties due to the formation of WLMs and below the pH 8.25 the morphology of the micelles were spherical. Ibuprofen (IBU) was loaded into the WLMs and the drug release kinetics was performed in two different pH levels. It was observed that at pH 8.65 the drug was released in a sustained manner.[42]

WLMs can also efficiently load multiple drugs and thus can improve the therapeutic efficiency of the treatment. Xiaomeng et al designed a polymeric micelle system based on amphiphilic block copolymers. The WLMs were designed to improve the efficacy of etopside (ETO) and platinum drug combination ("EP/PE"). These drugs were used along alkylated cisplatin prodrug treat small cell lung cancer. The prepared WLMs demonstrated high amount of drug loading and sustained release. The multidrug carrier WLMs showed higher cytotoxic effect than the single drug micelles.[43]

Emad et al developed micelles using Pluronic/ phosphatidylcholine/ polysorbate 80 (PPPMM). These micelles was designed to improve the oral bioavailability of the nimodipine (NM) used to treat subarachnoid hemorrhage induced vasospasm. This drug formulation also suffers from short circulation time and extensive first pass metabolism. Hence NM was loaded into PPPMM. This formulation prolonged the circulation time of the drug and showed higher bioavailability. Thus WLMs shows promising features for improving the oral and parenteral delivery of drugs.[44]

WLMs also offers co-encapsulation of nanoparticles such as metals and quantum dots within them. This strategy was followed by Bae et al to develop multifunctional nanoparticles based on worm like micelles.[45]

WLMs were also used to incorporate magnetic nanomaterials for targeted tumour imaging.[46] Iron oxide nanoworms were synthesized with sizes similar to that spherical nanoparticles. It was observed that the spherical nanoparticles exhibited superparamagnetic property whereas the iron oxide nanoworms exhibited ferromagnetic property.[47]

Conclusion

WLMs have attracted considerable research interest over the years and several studies have successfully prepared WLMs for various applications. Stimuli-responsive WLMs are highly advantageous in the field of biomedical applications as they can selectively target the tumour environment thereby maximizing the therapeutic efficiency and minimiz ing the toxic side effects. WLMs have also been hybridized with polymers, nanoparticles and biomaterials to develop multifunctional materials. Overall WLMs offers a great platform to develop customized biomedical materials that cater to a specific need required. Upcoming studies may see an increasing trend in the development of multi-stimuli responsive WLMs.

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Conflict of Interest

The authors declare no conflict of interest.

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