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The perspectives of using unimolecular micelles in nanodrug formulation

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“Together with the advantages of ease in functionalization, biodegradability and biocompatibility, unimolecular micelles could be interesting for drug delivery, bio-imaging and theranostic platform designs.”

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Nanotechnology plays important roles in improving druggability of small molecules with therapeutic potentials. Typically, polymeric micelles, as one of the most widely applied drug nanocarriers, are widely applied to overcome drugs' poor aqueous solubility or low bioavailability, as well as undesired pharmacokinetic dynamics or side effects [1–3]. It is worth mentioning that traditional polymeric micelles, self-assembled by thermodynamic aggregates, are not stable upon dilution or at concentrations below the critical micelle concentration [4,5]. Furthermore, they are also sensitive to environmental changes in case of temperature, pH or ions, which greatly hinder their usage in the pharmaceutical industry [6,7].

In order to overcome these limitations, recent endeavors have focused on the design of novel micelle formulations without thermodynamically unstable self-assembly process. Unimolecular micelles are defined as a class of single-molecule micelles with a distinct core and shell that are covalently bound together [8,9]. The unique property of unimolecular micelles lies with its uniform size and high stability, without considering dosing dilutions or environmental changes. Thanks to these excellent physicochemical features, biodegradable and biocompatible unimolecular micelles are popular for therapeutic applications, especially as nanodrug formulations [10].

From a materials design aspect, typical unimolecular micelles are made of highly branched macromolecules with core-shell structure. For core building blocks, Boltorn polymer H40, cyclodextrins, dendrimer or dendrimer-like polymer, or polyhedral oligomeric silsesquioxane (POSS) are popular choices [11]. On the other hand, hydrophilic poly(ethylene glycol) (PEG), poly(amidoamine) (PAMAM), or poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA), as well as hydrophobic poly(ϵ -caprolactone) (PCL) or poly(L-lactide) (PLA), and temperature sensitive poly(N-isopropylacrylamide) (PNIPAM) might serve as shell materials to render multi-functionality of obtained micelles. The introduction of functional shell segments in unimolecular micelles would endow them with new strengths such as stimuli responsiveness, targeting ability, which greatly broaden their therapeutic applications.

Biomedical utilizations of unimolecular micelles

Drug delivery

By careful designs of building segments, unimolecular micelles could be with high biocompatibility, biodegradability and thermodynamic stability, which form a strong basis as drug delivery carriers. For typical drug delivery formulations, therapeutics could be encapsulated in unimolecular micelles in form of physical trapping or covalent conjugation. In the case of physical encapsulation, usually a hydrophobic drug is chosen to be loaded in unimolecular micelles with hydrophobic building segments by utilizing the hydrophobic–hydrophobic interactions, with the purpose of improving the drug's water solubility, stability and circulation time. As an interesting example, Zhang

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et al. utilized Boltorn polymer H40 as core and hydrophobic poly(ϵ -caprolactone) (PCL) as well as hydrophilic poly(ethylene glycol) (PEG) as shell segments to design a highly branched unimolecular micelle, with the ability to physically load doxorubicin or ketoprofen in nanomicelles with narrow size distribution and high stability [12]. Although physical encapsulation is one of the most extensively explored drug loading approaches, it is worth mentioning that the connection between the drug and unimolecular micelle is not tight enough, resulting in the early release of drugs before reaching therapeutic site. Alternatively, covalent conjugation, in which drugs are linked with unimolecular micelle backbone by chemical bond, might solve the problem of early or undesired drug leakage. As a typical example, doxorubicin was chemically connected to poly(L-lactide) (PLA) segments on H40-PLA-PEG star-shaped unimolecular micelles by pH-sensitive hydrazine group, which could achieve controllable release at only low pH environment [13]. However, it is still worth mentioning that it might also require a careful design of chemical conjugation process to avoid the decrease of drug efficiency.

Furthermore, unimolecular micelles might be constructed with more functionalities by incorporations of functional units such as acetal linkers with pH responsiveness or targeting terminal groups to change the *in vivo* distribution of drugs. Taking advantage of these functional linkages or components, unimolecular micelle could be helpful in on demand drug delivery.

Bio-imaging

The delivery of imaging contrast agents to the disease site is key to achieving satisfactory bio-imaging. Fortunately, unimolecular micelles can also encapsulate imaging agents to increase their stability, compatibility and even biodegradability, which could greatly be beneficial for *in vitro* or *in vivo* bio-imaging.

As a typical example, gold nanoparticles (AuNPs) are widely utilized as computed tomography (CT) imaging contrast agents, but are greatly hindered by undesired instability [14,15]. Interestingly, rationally designed unimolecular micelle with reductive groups might help to achieve the *in situ* synthesis of AuNPs without the use of toxic reducing chemicals and greatly improve AuNP stability in blood circulation for increasing S/N ratios. Furthermore, the encapsulation of organic fluorophores could be helpful in fluorescence imaging [16,17]. Although they are a convenient and noninvasive contrast agent, organic fluorophores can easily experience quenching effects due to unsatisfied stability, which can lead to significant imaging failure. After trapping in unimolecular micelle, fluorescent dyes might be greatly inhibited from intermolecular interaction or aggregation due to the encapsulation within micelle structure, and could greatly promote imaging signal intensity or offer a more reliable platform for diagnosis [18]. For example, unimolecular micelle made of β -cyclodextrin core and poly(oligo(ethylene glycol)methacrylate) shell was utilized to reduce the aggregation of entrapped cyanine 5 and significantly led to tumor fluorescence signal increase in comparison with simple dye injection, indicating the strength of unimolecular design in bio-imaging [19].

Theranostics

The combination of therapy and diagnosis produces theranostics, which aims to achieve synergistic disease treatment and progress monitoring at the same time. Recent reports showed that, in unimolecular micelles, chemotherapeutics and bio-imaging reagents can exist with noninterfering ability and play their role separately to realize theranostics. Typically, Lin *et al.* reported that the co-delivery of AuNPs and anti-cancer drug doxorubicin by uniquely designed unimolecular micelles, made of β -cyclodextrin core and star-shaped shell consisting of PCL, poly(2-aminoethyl methacrylate) (PAEMA) and PEG units, resulted in satisfactory anti-tumor efficiency and CT imaging ability [20]. Furthermore, the unimolecular micelle could also be used as a smart theranostic platform with stimuli responsiveness. For example, prodrug camptothecin (CPT) and Gd complexes were encapsulated in hydrophobic and branched polyester cores of unimolecular micelle, while the shell made of oligo-(ethylene glycol) monomethyl ether methacrylate (OEGMA) and guanidine moiety guanidinopropyl methacrylamide (PGPMA) can keep them stable in the body circulation. The uptake of theranostic unimolecular micelles could easily convert the prodrug to an active form. In addition, the combined feature of quick release of the encapsulated agents and enhanced MRI imaging signals show high potential for precision medicine.

Conclusion & perspective

Different from traditional micelles from self-assembly of multicomponents with uncontrollable thermodynamic integrity, unimolecular micelles are stable regardless of environment changes or dilutions. Together with the advantages of ease in functionalization, biodegradability and biocompatibility, unimolecular micelles could be interesting for drug delivery, bio-imaging and theranostic platform designs.

It is also worth mentioning that the current developments of unimolecular micelles for biomedical applications might be still far from satisfying. For example, currently, the design, synthesis and purification of polyester unimolecular micelles is complicated with multiple steps and faces challenges in large scale production, however, they have a wide clinical application. Besides, physical encapsulation of drugs will likely result in drug leakage from micelles before reaching the disease site. Although covalent drug linkages might avoid this problem, the complexity of synthesis and the drug release process might increase. Hence, the further design of simple but more effective unimolecular micelles fabrication routes, as well as the design of unimolecular micelle with targeting ability or controllable release capacity, could be valuable and might shed the light on future nanodrug formulations.

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