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Extended Abstract

Nanomedicine & Drug Delivery : Unimolecular nanoparticles for targeted drug delivery- Shaoqin Sarah Gong- University of Wisconsin-Madison, USA

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Abstract

Drug nanocarriers have received increased attention because they can greatly enhance the therapeutic efficacies of drug payloads. Conventional polymer micelles, formed by the self-assembly of multiple linear block copolymers, are one of the most widely studied drug nanocarriers. However, one major concern with these conventional polymer micelles is their poor in vivo stability due to the dynamic nature of the self-assembly process. Premature rupture of these drug nanocarriers during circulation can cause a burst release of payloads into the bloodstream, which can lead to potential systemic toxicity and surrender their targeting and/or imaging abilities, thereby largely limiting their in vivo applications. Unimolecular micelles formed by single/individual multi-arm star amphiphilic block copolymers have been investigated to overcome this drawback. Because of their covalent nature and unique chemical structure, properly engineered unimolecular micelles can possess excellent in vivo stability. Moreover, due to their excellent chemical versatility, these unique unimolecular micelles can be tailored with different targeting ligands (e.g., small molecules, peptides, antibodies, nanobodies or aptamers) and/or imaging probes (e.g., fluorophores, radioisotopes or MRI contrast agents) to achieve multifunctionality. We have successfully developed a series of multifunctional unimolecular micelle platforms for targeted cancer (e.g., breast cancer and neuroendocrine cancer) theranostics. We have also engineered unique unimolecular micelles to treat glaucoma as well as vascular diseases (e.g., intimal hyperplasia attenuation) in a targeted manner. Moreover, other than small drug molecules, siRNA, peptides and small proteins have also been successfully delivered via unimolecular nanoparticles through electrostatic interactions. In summary, unimolecular nanoparticles are a promising drug nanocarrier that warrants further investigation for a broader range of potential applications.

Polymeric nanoparticle (NP)-based delivery systems have been extensively investigated to improve the diagnostic and treatment efficacy of a wide range of diseases, ranging from cancer and cardiovascular diseases , to bacterial and viral infections . Polymeric NPs are attractive for drug delivery applications because many polymers are biocompatible and biodegradable. Polymer chemistry is also very versatile, thereby making it possible to precisely control the molecular structure, NP morphology, and surface characteristics (e.g., zeta potential and ligand conjugation) of polymeric NPs. The design of polymeric NPs can drastically impact the safety, pharmacokinetics, pharmacodynamics, and ultimate in vivo fate of their payloads

Certain types of polymers can form NPs with a core–shell structure in aqueous media owing to the various types of inter/intra-molecular interactions, including electrostatic interactions, hydrophobic interactions, and hydrogen bonding. A broad spectrum of payloads for therapeutic and diagnostic purposes have been delivered by polymeric NPs. The stability of the NPs, or the ability to control NP stability, is of great importance for in vivo/human applications. However, conventional polymeric NP systems, which mostly rely on relatively weak interactions as previously mentioned, often exhibit insufficient in vivo stability in terms of nanostructures . Specifically, it is well-documented that dilution in the bloodstream, flow stress, environmental factors (e.g., pH and ionic strength), and interactions with serum proteins can lead to the disruption of the polymeric NPs before functioning . For instance, a recent report attributed poor micelle stability to the failure of NK-911, a self-assembled polymeric micelle, at the early clinical stage as it bursts too rapidly after i.v. injection Moreover, a recent study also found that more than 80% of the se
lf-assembled PEG-polyester micelles dissociated within 1 h after intravenous administration .

Among all of the strategies that can be applied to address this instability issue, unimolecular NPs have received increasing attention because they are stable regardless of their concentration or the microenvironment. The concept of unimolecular NPs was introduced in the 1990s. Thereafter, development of the polymeric unimolecular NPs has been accelerated owing to their desirable characteristics as drug nanocarriers as well as versatile polymer chemistry. In particular, polymeric unimolecular NPs formed by a single multi-arm polymer molecule containing only covalent bonds and exhibiting a core–shell structure are especially valuable for biomedical applications. Polymeric unimolecular NPs can be made from a variety of polymers. One way to classify

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unimolecular NPs is based on their chemical composition, which can be divided into two main categories: water-dispersible unimolecular micelles and water-soluble unimolecular NPs (Figure 1). Water-dispersible unimolecular micelles are typically formed by single/individual dendritic multi-arm amphiphilic block copolymers, conferring excellent in vitro and in vivo stabilities . Their unique hydrophobic core is of particular interest in delivering hydrophobic therapeutics or imaging probes. Hydrophobic agents can be loaded into the hydrophobic core of the unimolecular micelles through hydrophobic interactions, hydrogen bonding, or covalent conjugation. Water-soluble unimolecular NPs are typically formed by single/individual dendritic multi-arm water-soluble block copolymers. The cores of the water-soluble unimolecular NPs are usually polyelectrolytes (e.g., cationic or anionic polymers), which can be used to encapsulate hydrophilic payloads (e.g., nucleic acids, peptides, small proteins, metal-based drugs, etc.) via electrostatic interaction, hydrogen bonding, chelation, and/or ion–dipole interactions . For biomedical applications, the shells of the unimolecular NPs are commonly formed by poly(ethylene glycol) (PEG) or other types of hydrophilic polymers (e.g., polyzwitterions) to provide good water dispersity, reduce opsonization during circulation in the bloodstream, and improve biocompatibility . Both nanoplatforms have diverse applications.

Unimolecular micelles can be engineered using various types of organic NPs including dendritic polymers (e.g., hyperbranched polymers (HBPs) and dendrimers) and brush polymers as the initiating central core for the multi-arm amphiphilic block copolymers Although inorganic NPs (e.g., Au NP, quantum dots, CuS NPs, and upconversion NPs) have also been employed as the central core of unimolecular micelles, those are beyond the scope of this review.

Both HBPs and dendrimers are highly branched, three-dimensional dendritic macromolecules. Their globular and dendritic architectures endow them with unique properties including abundant functional groups, intramolecular cavities, non/low entanglement, and low viscosity. HBPs and dendrimers differ in that dendrimers have regular structures, while HBPs have irregular structures]. Dendrimers are synthesized step-by-step in an iterative fashion, while HBPs are typically synthesized via a one-step process. Both HBPs and dendrimers have been widely used to fabricate unimolecular micelles.

Hyperbranched polyesters are an attractive class of HBPs because they are biodegradable and biocompatible, which is extremely important if these molecules are to be used for drug delivery or other biological applications. Boltorn™ (e.g., H30 and H40) is one of the most studied hyperbranched polyesters, and its monomer unit is 2,2-bis(methylol) propionic acid. Because of its biodegradability, biocompatibility, globular architecture, and abundant functional groups, Boltorn hyperbranched polyesters have received a lot of attention in the design of nanoplatforms, including unimolecular NPs. Since H40 itself is hydrophobic, when conjugated directly with PEG, it can also be used to encapsulate hydrophobic drugs. However, due to the extremely small size (~3 nm) of H40, the drug (e.g., paclitaxel) loading level of H40-PEG unimolecular micelles is limited to less than 0.3 wt.%. To significantly enhance the drug loading content, we and others reported H40-based unimolecular micelles formed by multi-arm amphiphilic block copolymers H40-polyester (e.g., poly (l-lactide) (PLA) and polycaprolactone (PCL))-poly(ethylene glycol) in aqueous media. For example, H40 with –OH terminal groups was used as the macroinitiator to synthesize H40-PLA via ring-opening polymerization (ROP), followed by PEG conjugation via esterification. The H40-PLA formed a hydrophobic functional core for hydrophobic drug encapsulation, while the hydrophilic PEG shell provided the unimolecular micelles with good water dispersity. These core–shell structured unimolecular micelles can be a stable drug nanocarrier with a much higher drug loading level (for instance, ~12 wt.% for doxorubicin (Dox)] and ~33 wt.% for 5-fluorouracil (5-FU).

Delivery of nucleic acids is also of great interest to treat or prevent human diseases, such as genetic disorders and cancers. The polyplexes formed by the electrostatic interactions between cationic polymers and negatively charged genes have been widely explored to overcome the limitations associated with nucleic acids, such as limited cellular uptake due to their highly negatively charged nature, insufficient chemical stability, and short plasma half-life. However, as aforementioned, polyplexes also exhibit poor in vivo stability due to various factors, including interactions with serum proteins (e.g., albumin) and in vivo dilution The use of unimolecular NPs could not only address the limitations with naked nucleic acids, but also provide excellent in vivo stability.

In this review, we have surveyed recent progress on unimolecular NPs, including the architecture of water-dispersible unimolecular micelles and water-soluble unimolecular NPs, as well as their potential therapeutic and diagnostic applications. In contrast to multi-molecular self-assembled polymeric NPs, unimolecular NPs can offer excellent in vitro and in vivo stabilities due to their covalent nature. In addition, multifunctional unimolecular NPs can be conveniently fabricated due to their unique chemical structures and versatile chemistry. Unimolecular NPs, and in particular, unimolecular micelles, have been extensively investigated for targeted cancer therapy and, more recently, for targeted cancer theranostics. Unimolecular NPs have also been explored to treat a number of other diseases including vascular

and eye diseases, as well as genetic disorders. Their diverse polymer chemistry makes it possible to design numerous desirable unimolecular NP platforms for different applications.

Despite their promise, some challenges exist for clinical translation. First, the synthesis process for the multi-arm polymer molecules used to form the unimolecular NPs may be more complex than for linear polymers. Thus, more facial polymer synthesis and conjugation strategies to fabricate well-defined multi-arm polymers are highly desirable. Of note, once a well-controlled scale-up synthesis process for the multi-arm polymers is established, it is expected that the unimolecular NPs will exhibit better reproducibility and quality assurance than multi-molecular self-assembled polymeric NPs. The unimolecular NPs can readily form in an aqueous solution and stay as intact NPs during freezing drying and the re-dispersion process, while the formation of multi-molecular nanoplatforms requires the optimization of various parameters, including concentrations, temperatures, solvents, and processing parameters. The stability of multi-molecular nanoplatforms is also affected by a number of processes (e.g., freezing drying and re-dispersion) and various factors (e.g., concentration, flow stress, interaction with serum proteins, etc.). The second challenge is a lack of fundamental understanding of the interactions between unimolecular NPs and cells/tissues. In contrast to some of the well-investigated drug delivery systems (e.g., liposomes and multi-molecular polymer micelles), exploration of core-shell structured unimolecular nanoparticles is still largely limited to small animal (e.g., mouse) experiments. Thus, more in-depth understanding of the interactions between unimolecular NPs and cells/tissues, and more comprehensive investigation on their in vivo behaviors including pharmacokinetics, pharmacodynamics, and biosafety needs to be carried out before clinical translation.

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