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Polymeric micelles for nano-scale drug delivery

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ABSTRACT

This review describes the design of polymeric micelles from block copolymers and their performances as nano-scale drug delivery systems, with emphasis on our recent work. The basic drug delivery system platform developed by our group consists of polymeric micelles comprising a core–shell structure with a versatile drug-loading hydrophobic core and biocompatible hydrophilic shell, and are several tens to one hundred nanometer in size. These characteristics are preferable to bypass both renal clearance and entrapment by the reticuloendothelial system, thus allowing subsequent accumulation within tumor tissues by the enhanced permeability and retention effect. Furthermore, polymeric micelles may be designed for enhanced biological performance by modification of the block copolymers to contain chemistries that can sense a specific biological environment. These "smart" micelles allow for target site-triggered drug release by reversible stabilization of the micelle structure and controlled intracellular trafficking (efficient endosomal release). Smart micelles designed with responsive features have demonstrated the utility in many cases compared to controls lacking such functionality. Additionally, the ability to control the size of polymeric micelles in the range of several tens to hundreds of nanometer significantly affects their longevity in the blood stream and efficiency of tumor tissue accumulation and penetration. In hypovascular tumor tissues, smaller polymeric micelles are more effective for tissue accumulation/penetration, bringing about stronger anti-tumor activity. All together, fine-tuning the structure of block copolymers enables preparation of polymeric micelles with versatile functions for treatment of many diseases including intractable cancer.

1. Introduction

Since application of polymeric micelles as nano-scale drug delivery systems (nano-DDS) in the late 1980s [1], numerous polymer self-assemblies have been extensively developed aimed to deliver various drugs including; low molecular weight anti-cancer drugs, contrast/imaging agents, proteins, plasmid DNA, antisense DNA, and more recently short interfering RNA (siRNA) [2–5]. Currently, several promising candidates are in clinical trials, e.g., doxorubicin (DXR)-encapsulated poly(ethylene glycol) (PEG)–poly(propylene oxide) (PPO)–PEG (Pluronic) micelle (SP1049C) in phase III [6], paclitaxel (PTX)-encapsulated PEG–polyaspartate block copolymer micelle (NK105) in phase II [7,8], PTX-encapsulated PEG–polylactide (PLA) block copolymer micelle (Genexol-PM) in phase II [9], SN-38 (the active form of irinotecan hydrochloride)-encapsulated PEG–polyglutamate block copolymer micelle (NK012) in phase II [7,10], and cisplatin-incorporated PEG–polyglutamate block copolymer micelle (NC-6004) in phase II [7,11]. Those studies have proven the practical utility of polymer self-assemblies as injectable nano-DDS through both experimental and clinical results, which has generated much excitement while also providing a strong foundation for further developments in the nano-DDS field. Additionally, it should be noted that findings in the field of biology have also facilitated the development of nano-DDS. One of the most important findings was made by Matsumura and Maeda, where they identified key differences between the vascular found in cancerous and normal tissues. They showed that the rapidly forming vasculature in solid tumors is "leaky" with impaired lymphatic drainage, which leads to enhanced accumulation of macromolecules/macromolecular drugs within tumors [12]. This phenomenon, termed the enhanced permeability and retention (EPR) effect, has been now widely accepted as a general concept for "passive" tumor targeting with nano-DDS.

Polymeric micelles were one of the first polymer self-assemblies reported as a nano-DDS [13], and are composed of distinct two domains, a drug-loading core and a hydrophilic shell (Fig. 1). Amphiphilic block copolymers, containing a hydrophilic block and a hydrophobic block, are firstly revealed to construct those distinct domains in a micelle structure through spontaneous self-assembly as a result of hydrophobic interactions in aqueous

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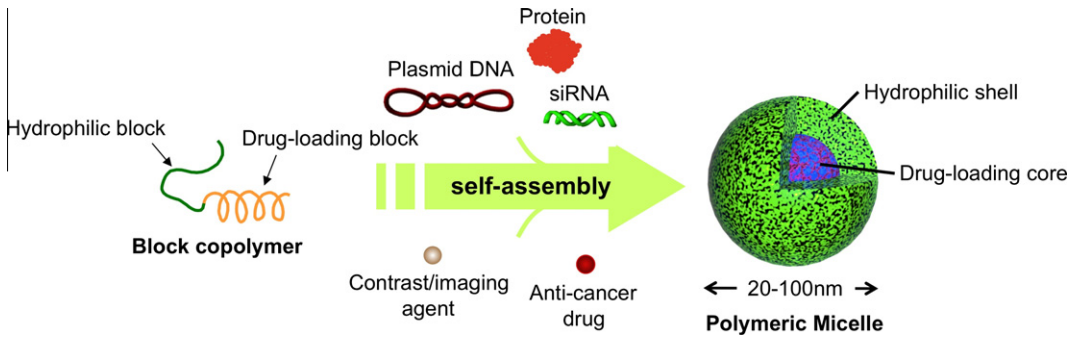

Fig. 1. Polymeric micelles prepared by self-assembly of block copolymers and drugs.

solutions [1]. Thus, hydrophobic drugs can be entrapped into the micelle core non-specifically through hydrophobic interactions or specifically by covalent bonding with the block comprising the hydrophobic domain. In contrast, hydrophilic charged macromolecules including peptides, proteins, and nucleic acids, can be loaded into the micelle core by using oppositely charged blocks to form polyion complex (PIC) cores through electrostatic interactions and charge neutralization [2,14]. For use as the shell-forming block, several hydrophilic and non-ionic polymers, such as PEG, poly(N-vinyl pyrrolidone) (PVP), poly(N-isopropyl acrylamide) (PNIPAM), and poly(hydroxypropyl methacrylamide) (PHPMA), have been reported. Among them, PEG is the most frequently used hydrophilic block for several reasons, including; PEG retains excellent solubility in aqueous media and several organic solvents allowing for flexibility in preparation procedures, PEG is non-toxic and exhibits low immunogenicity, and finally, PEG generally does not interact with biological components, thus simplifying its biodistribution upon administration. In addition, it is important to note from a practical standpoint that PEG has served as an injectable material since the late 1960s [15] and also several PEG–protein conjugates, such as PEG–adenosine deaminase (Adagen) became available for clinical use since 1990 [16].

Polymeric micelles possess several basic properties desirable for a nano-DDS [1,2]; (1) a hydrophilic coating around a drug-loading core which allows for solubilization of water insoluble drugs and protection of incorporated proteins or nucleic acids from their degradation at off-target sites, (2) suitable size (several tens nanometer) with a narrow distribution to avoid rapid renal excretion thus allowing accumulation into tumor tissues via the EPR effect following intravenous injection, (3) a biocompatible polymer shell to suppress non-specific interactions with biological components including entrapment by the reticuloendothelial system (RES), thereby leading to prolonged blood circulation of micelles. This "stealth" property to minimize non-specific interactions is also essential for tumor accumulation of macromolecular drugs via EPR effect. Additionally, the synthetic materials used for micelle formation allows for fine-tuning of the chemistries contained in the polymeric materials, which can dramatically improve the functional outcomes of polymeric micelles as necessary for their intended use, and such effects are reviewed extensively [1–5, 17–20], e.g., longevity in blood circulation, tissue accumulation and penetration, controlled intracellular trafficking, spatial and temporal controlled release, and reduced inherent toxicity. The fact that slight chemical modifications are amplified to result in substantial improvement in biological performance has directed many chemists and engineers towards the nano-DDS field. In the following sections, we describe the general design concept of DDS and polymeric micelles by highlighting recent advances in micelles prepared from PEG-based block copolymers.

2. General concept for the design of DDS

DDS have been developed to control the time-dependent drug distribution in the body (biodistribution) for improved therapeutic benefits and also reduced adverse effects. For instance, low molecular weight anti-cancer drugs are known to distribute not only to tumor tissues but also to undesired healthy organs/tissues, resulting in the severe side effects. Accordingly, if a drug carrier enables an anti-cancer drug to accumulate only within tumor tissue, it would be the ideal formulation for cancer treatment without marked side effects. Biodistribution controlled with DDS is considered to consist of three main stages (Fig. 2); the first is organ/tissue accumulation, the second is tissue penetration, and the third is intracellular trafficking. Which stage is focused on in a drug carrier design strongly depends on the type of drugs delivered and their target diseases (or organs/tissues). In the case of clinically available anti-cancer drugs, the controlled organ/tissue accumulation is the

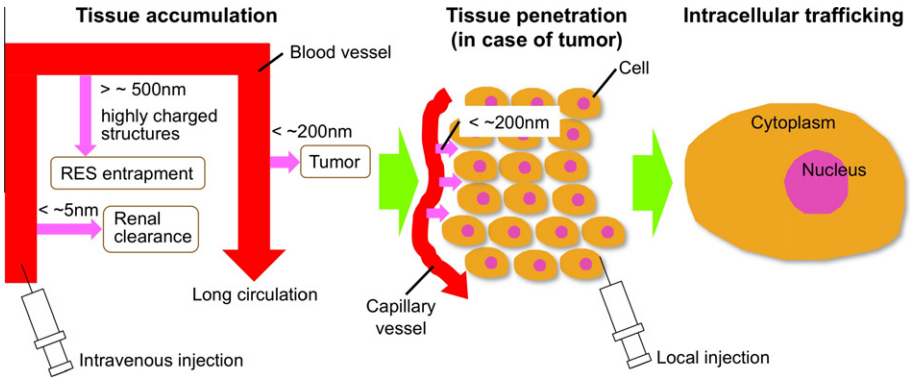

Fig. 2. Three stages in biodistribution of drugs.