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Micelles based on HPMA copolymers ☆

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ABSTRACT

Polymeric micelles have been under extensive investigation during the past years as drug delivery systems, particularly for anticancer drugs. They are formed by the self-assembly of amphiphilic block copolymers in aqueous solutions and have a spherical shape and a size in the nano-range (<200 nm). Tumor accumulation of polymeric micelles upon intravenous administration can occur as a result of the leaky vasculature of tumor tissue (called the enhanced permeation and retention (EPR) effect).To benefit from the EPR effect, polymeric micelles need to have prolonged circulation times as well as high and stable drug loadings. Poly[N-(2-hydroxypropyl) methacrylamide] (pHPMA) is a hydrophilic polymer currently under investigation for its use in polymer–drug conjugates. Its biocompatibility, non-immunogenicity and the possibility for functionalization are properties that resulted in broad pharmaceutical and biomedical applications, also in the micelle technology research. Being hydrophilic, it can serve as a micellar stealth corona, while it can also be modified with hydrophobic moieties to serve as a micellar core in which hydrophobic drugs can be solubilized and retained. HPMA-based polymeric micelles have been showing very promising *in vitro* and *in vivo* results. This review summarizes the applications of pHPMA in the field of polymeric micelles, either serving as a micellar stealth corona, or, if hydrophobically rendered by derivatization, as a micellar core.

Contents

1. Introduction

Polymeric micelles are colloidal nano-assemblies which are spontaneously formed above a certain concentration (CMC, critical micelle concentration) from amphiphilic block or graft copolymers [1–3]. The formation of polymeric micelles in selective solvents (e.g. acetone) was first observed in the mid 1950s by Merret [4], for natural rubber grafted with poly(methyl methacrylate). Later, pioneering work was reported by Molau [5], who studied the colloidal behavior of micelles formed from block copolymers. The fundamental background as well as a broad variety of applications of polymeric micelles has since then been extensively described in literature [3,5–8]. A schematic representation of polymeric micelle formation from an amphiphilic polymer is given in Fig. 1. In aqueous solution, amphiphilic block copolymers consisting of a hydrophobic and a hydrophilic block self-assemble into nanoaggregates composed of a hydrophobic core and a hydrophilic shell. Their inner core serves as a depot for hydrophobic bioactive compounds, which are either physically entrapped or chemically attached, while the hydrophilic shell is responsible for the colloidal stability of polymeric micelles and protects them against protein adsorption and opsonization during circulation, resulting in long circulation times. In addition, the small size of polymeric micelles (size ranges from 10 to 200 nm) and their long circulation times, allows for accumulation in pathological sites with leaky vasculature (e.g. tumors), through the enhanced permeation and

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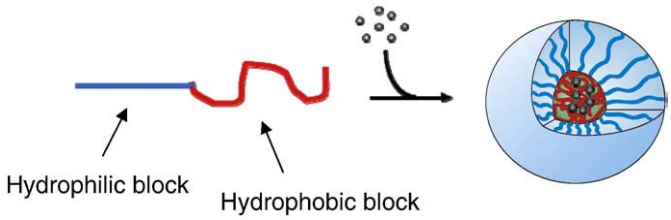

Fig. 1. Formation and drug loading of polymeric micelles by self-assembly of amphiphilic block copolymers in water.

retention (EPR) effect [9] (Fig. 2). Therefore, polymeric micelles have been recognized as an important and attractive class of drug carriers, especially for the intravenous administration of hydrophobic drugs [10–12], and several formulations based on micelles are presently under evaluation in clinical trials [13].

The physicochemical characteristics of the building blocks influence the physical and biological properties of the micellar nanocarriers [15]. The chemical nature and molecular weight of the hydrophilic block that will form the micellar corona strongly affect the stealth properties and accordingly the circulation kinetics of the micellar assembly. Poly (ethylene glycol) (PEG) is most commonly used as the hydrophilic shell-forming block, providing good stealth properties [16,17], while poly (N-vinyl-2-pyrrolidone) (PVP) is a frequently used PEG alternative [18]. The chemical nature and molecular weight of the core-forming block are important factors for determining the stability, drug loading capacity and drug release profile of polymeric micelles [19]. A great variety of core-forming blocks have been studied, such as poly (propylene oxide) (PPO) [20], hydrophobic poly(amino acids) [21], poly(lactic acid) (PLA) [22], copolymers of lactic acid and glycolic acids [23,24], and poly(ε-caprolactone) [25,26]. Besides hydrophobic interactions, micelles can also be formed by electrostatic interactions, using charged block copolymers of oppositely charged macromolecules, resulting in the formation of polyion complex (PIC) micelles [12,27–29]. In addition, there have been also reports in literature of polymeric micelles formed by complexation via hydrogen bonding [30–32], as well as metal–ligand coordination interactions [33,34], both referred to as non-covalently connected micelles.

Poly [N-(2-hydroxypropyl) methacrylamide] (pHPMA) is a hydrophilic, non-immunogenic and biocompatible polymer [13,35,36]. pHPMA and its copolymers are among the most intensively studied polymeric drug carriers [13,35,37–42], and several anticancer drug–pHPMA conjugates have been clinically evaluated [36,43–48]; the progress in this field is reviewed in the other chapters of the present Advanced Drug Delivery Reviews (ADDR) issue.

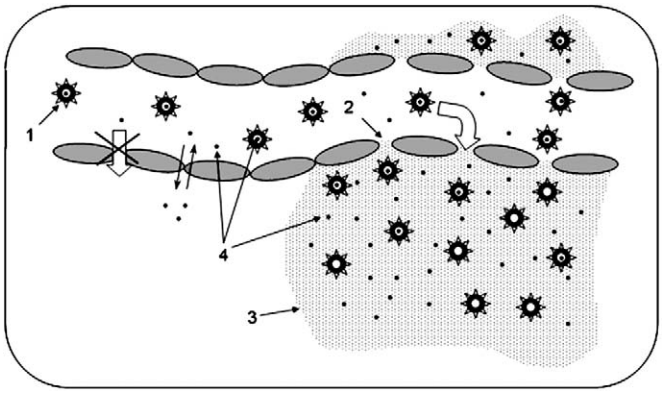

Fig. 2. Passive accumulation of small (<200 nm) drug carriers in pathological sites with leaky endothelium, through the enhanced permeation and retention (EPR) effect [14]. Reproduced with permission from Springer.

pHPMA has been investigated as a building block of polymeric micelles, either in the hydrophilic shell or in the form of a derivative as the hydrophobic core. Fig. 3 shows the chemical structures of HPMA and related compounds that have been studied as micelle-forming blocks. In this review, micellar systems, either with pHPMA as corona or with derivatized hydrophobic pHPMA as the micellar core are described and discussed.

2. HPMA as a building block of micelle-forming block copolymers

2.1. HPMA as the hydrophilic shell of polymeric micelles

PEG is the "golden standard" as hydrophilic coating of drug delivery systems. It has a low toxicity, provides steric stabilization of macromolecules and nanoparticles, and a variety of pegylated products has been approved by FDA [17]. However, it has been shown that PEG-liposomes are rapidly cleared at low lipid doses as well as upon repeated administration [49–52], a phenomenon referred to as the accelerated blood clearance (ABC) phenomenon. It was recently shown that anti-PEG IgM, induced by the first dose of PEGylated liposomes, is (at least in part) responsible for this finding [53], but the full mechanism responsible for the ABC phenomenon has not yet been elucidated. It is not clear whether it is specific for PEG or for any repetitive unit present on the surface of nanoparticles. It has also been reported that PEG can promote aggregation of nanoparticles after freeze drying [54]. Consequently there is need for hydrophilic blocks as alternatives for PEG that provide stealth properties. As an example, Romberg et al. showed that the pharmacokinetics of poly(amino acid)-coated liposomes were superior to those of PEG-coated liposomes at low doses and upon repeated administration [55].

pHPMA is an attractive candidate as the hydrophilic, shell-forming block of polymeric micelles. Besides its biocompatibility and its non-immunogenicity [35,56], an advantage of pHPMA over PEG is its multifunctionality, which allows multiple drug or targeting molecules to be conjugated to the same polymer chain. Konak et al. [57] studied the effect of hydrophobic side chains on the aqueous solubility of pHPMA copolymers, in order to covalently couple large amounts of hydrophobic drugs to the polymer. At high extents of derivatization, micelles were formed with the hydrophobic molecules oriented in the core and pHPMA forming the shell, while the micellization was dependent on the side-chain content, polymer concentration, temperature and pH. In a subsequent paper, the same group investigated block copolymers of pHPMA with poly(n-butyl acrylate) in aqueous solutions and observed formation of compact and small micelles (size <50 nm) with a pHPMA corona [58]. Similarly, Barz et al. [59] synthesized diblock copolymers of pHPMA with poly(lauryl methacrylate) and investigated their self-organization in aqueous solutions. They observed that micellar structures with diameters of 100–200 nm were formed which showed neither cell toxicity nor adverse effects up to concentration of 2 mg/ml, while their cellular uptake was also demonstrated (Fig. 4).

In the field of gene delivery, DNA-based polyelectrolyte complexes have been investigated as non-viral gene delivery systems [60–64]. However, these complexes showed limited stability in the presence of serum. Moreover, their positive charge results in non-specific interactions with plasma proteins and blood cells, thereby inducing a rapid elimination from the circulation after intravenous administration [65,66]. To increase the stability of polyplexes, block copolymers with a non-charged hydrophilic and a polycationic block were developed [27,28,67], which form polyion complex micelles with a polycation/DNA core. In these complexes, the hydrophilic block acts as a surface coating, increases the colloidal stability, and limits interactions with cells and plasma proteins [68,69]. Most frequently, PEG is used as the hydrophilic 'stealth' polymer of polyplexes [8,67,70]. Interestingly, also pHPMA has been used as a hydrophilic coating of these polyion complex micelles. Konak et al. [71], as well as Oupický et al. [72], synthesized diblock