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Review article

Polymeric mixed micelles as nanomedicines: Achievements and perspectives

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ABSTRACT

During the past few decades, polymeric micelles have raised special attention as novel nano-sized drug delivery systems for optimizing the treatment and diagnosis of numerous diseases. These nanocarriers exhibit several *in vitro* and *in vivo* advantages as well as increased stability and solubility to hydrophobic drugs. An interesting approach for optimizing these properties and overcoming some of their disadvantages is the combination of two or more polymers in order to assemble polymeric mixed micelles. This review article gives an overview on the current state of the art of several mixed micellar formulations as nanocarriers for drugs and imaging probes, evaluating their ongoing status (preclinical or clinical stage), with special emphasis on type of copolymers, physicochemical properties, *in vivo* progress achieved so far and toxicity profiles. Besides, the present article presents relevant research outcomes about polymeric mixed micelles as better drug delivery systems, when compared to polymeric pristine micelles. The reported data clearly illustrates the promise of these nanovehicles reaching clinical stages in the near future.

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1. Introduction

In recent years, one of the most studied nanocarriers in diagnosis and pharmacotherapy of numerous diseases are polymeric micelles (PMs). These interesting vehicles are composed of amphiphilic polymers that self-assemble into nanostructures with sizes ranging between 20 and 200 nm [1–4]. This thermodynamically driven process occurs above a copolymer determined concentration, commonly known as critical micellar concentration (CMC) [5,6]. PMs are formed by an inner hydrophobic core, in which poorly-water soluble-drugs can be entrapped and by an outer hydrophilic shell which insolates the encapsulated drug from the external medium [1–3]. This outer hydrophilic corona can be functionalized with different moieties, such as folate (FOL), monoclonal antibodies (mAb) and monosaccharides (mannose, glucose, fructose), among others, as an attempt to achieve active targeting and/or pH/temperature responsive nanocarriers [7–9].

Over the past few years, PMs have raised special interest as nano-sized drug delivery systems, not only because they provide increased solubility and stability of hydrophobic drugs [10–13], but also due to their *in vivo* exhibited advantages *versus* the free drug [14]. As a consequence of their size, they are large enough to prevent premature elimination via glomerular filtration and sufficiently small to pass through certain blood vessels [4]. Furthermore, they are capable of both (i) improving cellular uptake of drug-loaded micelles and (ii) granting an alternative way of internalization (endosomes). This is of vital importance in several pathologies, where the pharmacotherapy is affected by drug reflux mechanisms related to multi-drug resistance (MDR) [15]. All these advantages are translated in altered pharmacokinetics: longer mean residence time (MRT) of the drug in the bloodstream [14–17]; increased bioavailability [18]; reduced administered dose and possible diminished of non-specific organ toxicity as a result of more precise drug delivery to target tissues [14].

The appropriate application of PMs as nanocarriers for drug delivery requires taking into account several parameters, such as micelle stability, micellar size distribution, drug loading capacity and presence of functionalities [19–22]. Micellar stability mainly depends on the copolymer self-aggregation tendency (CMC value). The CMC of the amphiphilic polymers is influenced by the hydrophilic-lipophilic balance (HLB) of the polymer [21]. In general, maintaining the hydrophilic portion, the longer the hydrophobic chain, the lower the CMC. Micelles-based in copolymers that present low CMC value may resist in a greater extent the dilution suffered when administered intravenously since PMs as dynamic systems. If the micelles disassemble, the drug is rapidly released and toxic effects might appear. On the other hand, micelle stability is also governed by the physical state of its hydrophobic core, the interactions between the lipophilic fractions and their molecular weight [19,22]. This point has been thoroughly detailed by several reviews that provide vast information on the stability of the micelles [10,23,24].

Furthermore, the affinity between the loaded drug and the polymer is one of the most relevant factors that determines the drug loading capacity [6,19], whereas the size and its distribution are affected by the molecular weight of the polymer, the proportion and length of both the lipophilic and hydrophilic segments, the drug loading capacity and the micelle aggregation number [6].

An interesting approach for optimizing these properties and overcoming some of the disadvantages of single micelles, as the dissociation suffered upon dilution [25], is the combination of two or more distinct amphiphilic polymers in order to assemble mixed micelles (Fig. 1) [14]. Ideally, their CMC may be calculated from the CMC values and molar fractions of their components [8]. In comparison to single PMs, the mixed micellar systems exhibit the following advantages: improvements in the thermodynamic (lower CMC) [26] and kinetic stabilities [27] (25), enhanced drug loading capacity [28], more accurate size control [29] and easier ways to incorporate different modifications [30]. In this review, several mixed micellar formulations will be fully analysed, with emphasis on type of copolymers, physicochemical properties, *in vivo* progress achieved so far, as better pharmacokinetic parameters and improved biodistribution and toxicity profiles.

2. Commonly used amphiphilic macromolecules

Among mixed micellar systems, there exist various block copolymers employed as drug delivery vehicles, with distinctive characteristics, which can be classified in different families. Fig. 2 shows the chemical structure of several copolymers and some surfactants that are used for the preparation of mixed micelles.

One of the most studied amphiphilic materials to prepare polymeric mixed micelles are derivatives of poly(ethylene oxide)–poly (propylene oxide)-poly(ethylene oxide) (PEO–PPO–PEO) block copolymers [31]. Among them, there are two commercially available families: (i) the linear and bifunctional PEO–PPO–PEO triblocks or poloxamers (Pluronic®) (Fig. 2A) and (ii) their branched 4-arm counterparts named poloxamine (Tetronic®) (Fig. 2B). The latter presents two tertiary amine groups in the center of the molecule, which contributes to the thermal stability and, more importantly, confers both temperature and pH sensitiveness to the copolymer [32]. Both families are available in a wide range of molecular weights and ethylene oxide/propylene oxide EO/PO ratios. Also, their advantages include low toxicity, suitable biocompatibility and appropriate availability [10]. In contrast, these block copolymers usually exhibit high CMC, making the formulation less stable, as the micelles tend to dissociate easier when diluted upon the bloodstream [33].

Other relevant amphiphilic macromolecules used to self-assemble into polymeric micelles are the ones formed by biodegradable hydrophobic blocks of polyesters covalently bonded to hydrophilic blocks, mainly of polyethylene glycol (PEG). Moreover, these hydrophobic polyesters such as poly(lactic acid)