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Research review paper

# Polymeric micelles in mucosal drug delivery: Challenges towards clinical translation

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ABSTRACT

Polymeric micelles are nanostructures formed by the self-aggregation of copolymeric amphiphiles above the critical micellar concentration. Due to the flexibility to tailor different molecular features, they have been exploited to encapsulate motley poorly-water soluble therapeutic agents. Moreover, the possibility to combine different amphiphiles in one single aggregate and produce mixed micelles that capitalize on the features of the different components substantially expands the therapeutic potential of these nanocarriers. Despite their proven versatility, polymeric micelles remain elusive to the market and only a few products are currently undergoing advanced clinical trials or reached clinical application, all of them for the therapy of different types of cancer and administration by the intravenous route. At the same time, they emerge as a nanotechnology platform with great potential for non-parenteral mucosal administration. However, for this, the interaction of polymeric micelles with mucus needs to be strengthened. The present review describes the different attempts to develop mucoadhesive polymeric micelles and discusses the challenges faced in the near future for a successful bench-to-bedside translation.



**Contents**



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## 1. Main challenges in pharmaceutical development

A diversity of biopharmaceutical drawbacks (*e.g.*, low aqueous solubility, physicochemical instability, poor bioavailability, fast clearance, high toxicity) challenges the formulation, administration, delivery and targeting of approved drugs and the development of new chemical entities (NCEs). For example, poor aqueous solubility, a characteristic of 50–70% of the therapeutic agents, represents the most remarkable hurdle to ensure the bioavailability of drugs administered by non-parenteral routes (Stegemann et al., 2007). This motivated the investigation of novel metallic, lipidic, polymeric and hybrid nanomaterials that improve the performance of drugs and NCEs both *in vitro* and *in vivo* (Deshpande et al., 2013; Park et al., 2012; Singh et al., 2013; Sosnik et al., 2008). In this welter and effervescent intellectual milieu, polymeric micelles (PMs) have emerged as one of the most versatile, scalable, cost-viable and clinically promising technology platforms (Kataoka et al., 2001; Sosnik, 2013a).

## 2. Polymeric micelles for drug delivery

### 2.1. Composition of polymeric micelles

PMs are nanostructures formed by the self-aggregation of copolymeric amphiphiles above the critical micellar concentration (CMC). The most commonly used copolymers comprise A–B diblocks and A–B–A triblocks where A and B represent the hydrophilic and the hydrophobic blocks, respectively. Depending on the block arrangement along the copolymer backbone and the chemical nature of the blocks, different synthetic pathways have been employed to produce these amphiphiles. Independent of the synthesis, hydrophilic blocks accommodate at the interface between the inner hydrophobic domain composed of the hydrophobic segments and known as core and the external medium, forming the micellar corona (Fig. 1). The corona not only stabilizes the system by steric means but can also control the release of the drug payload that mainly takes place by simple diffusion (Lee et al., 2007a,b; Owen et al., 2012). Due to the flexibility to tailor different molecular features (*e.g.*, molecular weight, hydrophilic–lipophilic balance (HLB), size of the micelle and of each domain, architecture, surface chemistry, shape), PMs have been exploited to encapsulate motley poorly-water soluble therapeutic agents (Chiappetta and Sosnik, 2007; Falamarzian et al., 2012; Jhaveri and Torchilin, 2014; Moretton et al., 2014).

Moreover, the possibility to combine amphiphiles displaying different functionalities in one single aggregate and produce mixed micelles that capitalize on the features of each component, substantially expands the therapeutic potential of these nanocarriers (Chiappetta et al., 2011a, b; Ribeiro et al., 2012).

### 2.2. Production of polymeric micelles

Techniques for the production of PMs could be direct or indirect and depend on the nature of the copolymer and the intended cargo (Gaucher et al., 2005). The former methods comprise the direct solubilization of the amphiphile in aqueous medium and the subsequent encapsulation of the drug. Conversely, the latter relies on the use of water-miscible organic solvents (*e.g.*, acetone, dimethylacetamide) that co-solubilize the copolymer and the drug and that are eliminated later on by evaporation (Gaucher et al., 2005) or dialysis (Yasugi et al., 1999). In addition, towards scale-up under an industrial setting, the process could be optimized in terms of encapsulation efficiency, final drug payload and production yield. The arrangement of blocks along the polymer backbone is an additional tailorable parameter that affects the micellar structure, the self-aggregation behavior and the drug release kinetics (Venkataraman et al., 2011). For example, to undergo self-assembly, the terminal hydrophobic blocks of B–A–B amphiphilic triblocks fold on themselves, giving place to the so-called "flower-like" PMs (Fig. 2). These copolymers are usually synthesized by the ring-opening polymerization (ROP) of lactones such as lactide and epsilon-caprolactone with hydroxyl-terminated bifunctional poly(ethylene glycol) (PEG) precursors. Due to this different arrangement and steric constraints, these aggregates display substantially larger core and greater encapsulation capacity that fit bulkier molecules (*e.g.*, paclitaxel, rifampicin and doxorubicin free base) than the A–B and A–B–A counterparts (Lee et al., 2007a,b; Moretton et al., 2010; Oh et al., 2009; Zhang et al., 2012). On the other hand, depending on the nature of the hydrophobic block, these PMs often require production methods employing water-miscible organic solvents and a final drying step to increase their physical stability, and prevent secondary aggregation (or micellar fusion) and phase separation (Moretton et al., 2012; Venkataraman et al., 2011). This phenomenon is very common in PMs containing poly(epsilon-caprolactone) as the hydrophobic component.

More complex multiblock $(A–B)_n$ block arrangements have been also synthesized and the micellization characterized (Cohn and Sosnik, 2003; Cohn et al., 2003; Sosnik and Cohn, 2005). These aggregates displayed larger size and lower CMC than derivatives with similar HLB and lower molecular weight. Regardless of the greater molecular weight, the amorphous nature of the hydrophobic poly(propylene oxide) blocks enabled the direct solubilization in aqueous medium.

### 2.3. Morphology of polymeric micelles

The morphology of the micelles is usually spherical for amphiphiles that combine relatively long hydrophilic blocks with short hydrophobic ones (Gonzalez-Lopez et al., 2008). Conversely, the progressive increase of the relative copolymer hydrophobicity favors the formation of rod-

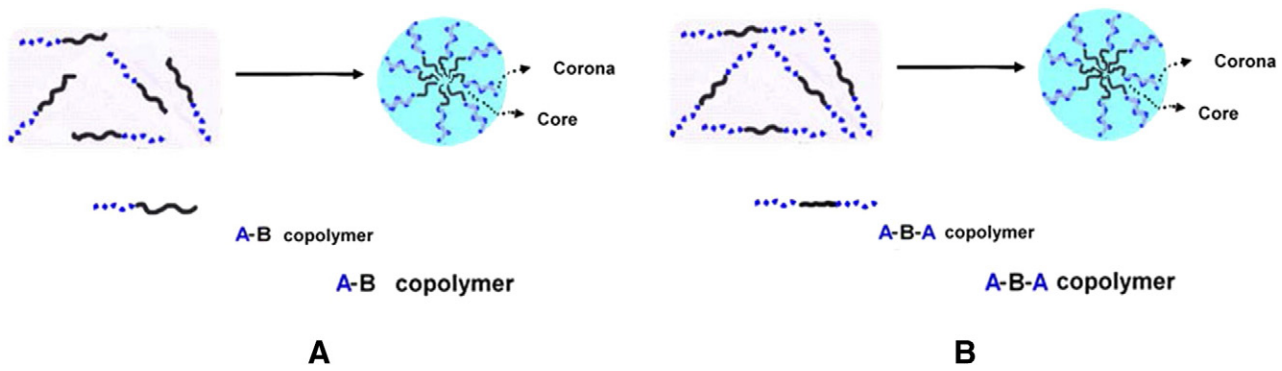


**Fig. 1.** Schematic structure of polymeric micelles generated from (A) A–B diblock and (B) A–B–A triblock copolymers. A and B represent the hydrophilic and the hydrophobic blocks, respectively.