

## Polymeric Micelles and their Properties

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### Introduction

In recent years, polymeric micelles have attracted a lot of attention in terms of their specific delivery of hydrophobic cargo to the target site. Polymeric micelles are considered more stable than their surfactant counterparts and can prolong circulation times *in vivo* and their specific accumulation in the tumoral tissues [1]. They can effectively solubilize small hydrophobic drugs in their inner most hydrophobic core while their outer hydrophilic shell can afford protection against any kind of scavenging by the mononuclear phagocytic system [2]. Micelles often display a great resemblance in their comparison to viruses or lipoproteins as carriers of required payload, whether it is DNA for viruses or hydrophobic drugs for lipoproteins [3]. However, both lipoproteins and viruses have their own limitations in delivering their respective payloads to the target sites. Lipoproteins have a greater propensity of being recognized by healthy cells too apart from competing with natural lipoproteins on tumor sites [4]. Viral carriers can be recognized by immune systems, which in turn can elicit an immune response. In contrast, polymeric micelles do afford significant advantages over the above mentioned two carriers in terms of delivery of a hydrophobic payload. Physical stability and chemical stability in plasma, however, still remain the major concerns for polymeric micelles [5].

### Micellar Structure

Polymeric micelles are characterized by a robust core-shell structure. Diblock copolymers have been known to self-assemble into dynamic micellar structures, with a hydrophilic shell (representing one block) and a hydrophobic core (representing the other block) [6,7]. Similarly, tri or multi block copolymers with a poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) have been known to self-assemble into micelles with the polyethylene oxide (PEO) portion representing the hydrophilic shell and polypropylene oxide (PPO) portion representing the hydrophobic core [8,9]. These micelles are very dynamic in their assembly and are generally formed in water above a certain concentration, which is also known as the critical micellar concentration (CMC) [10].

### Applications

The important mechanisms that are generally employed to release the payload at the target sites are active and passive targeting. Passive targeting is reliant on the disease pathology and certain specific properties on the delivery system in order for preferential accumulation of the drug at the region of interest [11]. This process is famously described as the Enhanced Permeation and retention effect, as championed by Dr. Maeda et al [12,13]. Maeda and colleagues first described this EPR effect in murine solid tumor models. Later, this effect was corroborated by other scientists. Manifold higher concentrations of the drugs can be seen in the tumors when these drugs are administered as polymer-drug conjugates or when they are encapsulated in the polymer. This phenomenon can be extended to inflammation and infection too [14]. Some of the common

approaches for passive targeting involve stimuli-specific release of the drug at target sites. For example: the pH around the tumor region (hypoxic) is generally around 5. So if pH sensitive polymers are incorporated, then there will be a significant difference in the tumoral accumulation of drugs, as opposed to using a non pH-sensitive polymer [15,16]. Active targeting utilizes an approach, which involves surface modification of the nanocarrier systems, such as an attachment of a targeting ligand which is ultimately directed to certain receptors that will be over expressed in certain pathological systems [17]. One of the classic examples is the over expression of folate receptors in certain rapidly proliferating tumor cells. In such instances, the surface of nanocarrier is aptly modified with folic acid, which will serve as the targeting ligand in this case.

### Advantages and Disadvantages of Micellar Systems

Polymeric micelles can be safely used for parenteral administration than conventional solubilizing agents such as polyethoxylated Castor oil (Cremophor EL) or polysorbate 80 [18,19]. Being kinetically stable, polymeric micelles dissociate very slowly, thus prolonging the circulation times in blood. Their cores are typically larger than surfactant micelles thus improving their capacity to solubilize hydrophobic drugs [20]. When these polymeric micelles are coupled with Polyethylene glycol (PEG), they are conferred "Stealth" properties, thus reducing their uptake by the macrophages of the reticulo-endothelial (RES) system, and in turn, extending their *in vivo* circulation times. Some of the polymeric micelles are modulated to overcome the drug-efflux or resistance by inhibiting P-Glycoprotein (PGP) transport or Multi-Drug Resistance Protein 2 (MDRP 2) transport [21]. In spite of these, micellar delivery is prone to some short-comings too. Dilution of these micelles, when injected intravenously, may shift the equilibrium towards the unimer state, thus leading to their dissociation. This dissociation may be accelerated when these unimeric components bind to other constituents such as proteins [22]. This phenomenon can be overcome by cross-linking the micelles, either through covalent core cross-linking [23,24] or through shell cross-linking, thus affording rigidity to the micellar structure [25].

### Conclusion

Generally, more than 50% of the drugs possess, inherently, very limited water solubilities [21]. So, different nanotechnological methods have been generally employed to improve upon their

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solubility characteristics, which in turn can subsequently improve their bioavailabilities too. One of the most desired techniques is to load these extremely insoluble drugs into polymeric micelles or even conjugate these drugs to the polymers by covalent linking. These block copolymers have gained attention due to a number of favorable characteristics such as their easy commercial availability, varied compositions that can be further easily tailored, negligent or no side effects, proven compatibility with other excipients [26]. On the other hand, they also suffer from certain limitations such as their tendency to aggregate and their limited stability *in vivo*. Thus, these polymeric micelles are a subject of greater interest currently, and more investigative studies are being dedicated to have a better understanding of their overall characteristics [27].

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