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Polymeric micelle as a nanocarrier for delivery of therapeutic agents: A comprehensive review

Roshani D. Agrawal*, Amol A. Tatode, Nilesh R. Rarokar, Milind J. Umekar

Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur (M.S.) India

ABSTRACT

For selective and effective drug delivery of therapeutic agent nanocarriers are the most effective agents. Micelles are an aggregate of surfactant molecules that dispersed in a liquid colloid. Micelles have a variety of shapes such as spheres, rods, vesicles, tubules, and lamellae. The shape and size of a micelle are a function of the molecular geometry of its surfactant molecules and solution conditions such as surfactant concentration, temperature, pH, and ionic strength. Poly Ethylene Glycol (PEG) is the most commonly used hydrophilic segment of micelles for drug delivery. Besides PEG, other polymers including poly (N-vinyl pyrrolidone) (PVP) and poly (N-isopropyl acrylamide) (pNIPAM) have also been used as hydrophilic portion of micelles. In this review we all discus about the polymeric micelles (PMs) as a nanocarriers for delivery of therapeutic agents.

Keywords: Polymeric Micelles, Colloids, Nanocarriers, Drug Delivery, Poly Ethylene Glycol(PEG)

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***Address for Correspondence:**

Roshani D. Agrawal, Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur (M.S.) India

1. Introduction

A micelle is a colloid formed by a surfactant in equilibrium with the molecules or with the ions that contribute at micelle formation. In the past decades, nanocarriers have emerged as an attractive research field in cancer therapy, including liposomes, micelles and nanoparticles made of various materials. Polymeric micelles (PMs) are extensively studied carriers for the delivery of poorly water-soluble drugs [1]

Based on the type of intermolecular forces driving the micelle formation, block copolymer micelles can be divided into several categories including hydrophobically assembled amphiphilic micelles, polyion-complex micelles, and micelles stemming from metal complexation [2]. The hydrophobically assembled micelles usually consist of amphiphilic macromolecules that have distinct hydrophobic and hydrophilic domains, and the commonly used block segments of copolymers have been summarized [3]. Upon exposure to aqueous medium, the amphiphilic molecules are spontaneously self-assembled into supramolecular core/shell structures and water-insoluble drugs can be loaded into the hydrophobic cores [4, 5].

Micelles have demonstrated a variety of shapes such as spheres, rods, vesicles, tubules, and lamellae depending on the relative length of hydrophobic/hydrophilic blocks as well as solvent environment [**6-8**]. Morphology of micelles has significant impact on the pharmacokinetic properties of micelles. For example, worm-like micelles have shown ten times longer circulation time compared with the spherical counterpart made of similar material [**9**]. The most commonly used hydrophilic segment of micelles for drug delivery is poly (ethylene glycol) (PEG), with a molecular weight of 2–15 kDa. PEG is highly water-soluble, non-toxic and neutrally charged. PEG forms a hydrophilic corona on the surface of micelles which minimizes the nonspecific interaction with blood components and prolongs the circulation time. Besides PEG, other polymers including poly(N-vinyl pyrolidone) (PVP) [**10**] and poly(N-isopropyl acrylamide) (pNIPAM) [**11**] have also been used as hydrophilic portion of micelles.

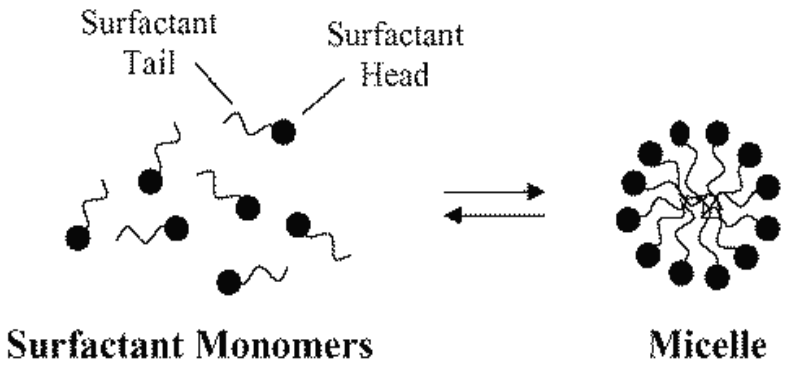

Figure 1: Schemetic diagram of micelles formation

2. Formation of Polymeric micelles

PMs are self-assembled core-shell nanostructures formed in an aqueous solution consisting of amphiphilic block copolymers **[12-14].** Formation of micelles in aqueous solution occur when the concentration of the block copolymer increases above a certain concentration named the critical aggregation concentration (CAC) or critical micelle concentration (CMC). At the CAC or CMC, hydrophobic segments of block copolymers start to associate to minimize the contact with water molecules, leading to the formation of a vesicular or core-shell micellar structure.

Theoretically, the formation of micelles is driven by decrease of free energy. The removal of hydrophobic fragments from the aqueous environment and the reestablishing of hydrogen bond network in water decrease free energy of the system and finally form the micelles. The typical methods used for encapsulation of poorly water-soluble drugs are dialysis method, oil-in-water emulsion solvent evaporation method, and solid dispersion method [**15, 16].** Other methods used are direct dissolution [**17, 18**], complexation [**19**], chemical conjugation [**20**], and various solvent evaporation procedures [**21**].

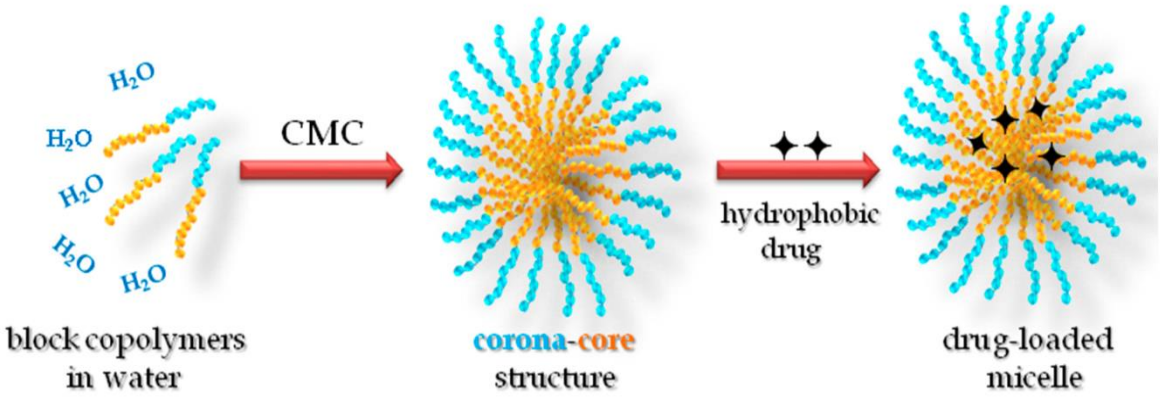

Figure 2: formation of drug loaded micelles

3. pH sensitive PMs

The potential disadvantage of normal PMs can be solved by application of additional stimuli that cause micelle destabilization in a specially controlled manner thus increasing the selectivity and efficiency of drug delivery to target sites. External factors such as heat [**22, 23**], light [**24**], and sound (ultrasound) [**25,26**] have already been studied by many researchers. However, these external stimuli may only activate the carriers that are situated closely underneath the skin but not those deeply distributed in the body. The intracellular signals also play an important role in regulating drug release which causes a great deal of interests, and here we focus our attention on pH-responsive systems.

4. Mucoadhesive PMs

Nanocarriers for oral administration should adhere to mucus and cross the mucus layer. Drugs delivered to mucosal surfaces are usually efficiently removed by mucus clearance mechanisms [**27**]. The luminal surface of mucosal tissues is protected by a highly viscoelastic layer [**28**], and the protective coatings rapidly remove foreign particles from the GI tract which probably lead to low bioavailability. Unlike the relatively high requirements of intravenous infusions, oral formulations could include high-molecular weight polymers as long as these components are metabolizable and cannot find their way into the systemic circulation. Hence, it may be an effective means of increasing uptake of drugs with mucoadhesive PMs [**29, 30**], and there have been considerable interests in the concept of mucoadhesive PMs.

5. Micelles with built-in drug-interactive domain as improved delivery systems

The drug-loading capacity of polymeric micelles is critically dependent on the compatibility between the drug and the micelle core [**31**]. A series of studies have demonstrated that

the drug-loading capacity of micelles can be greatly enhanced by optimizing chemical structures of the inner core segment for stronger drug/carrier interaction. A typical example of the strategy for enhanced compatibility between drug and block copolymer is the development of hydrotropic polymers. Hydrotropy refers to a phenomenon that the aqueous solubility of a poorly soluble compound is significantly enhanced by the presence of large amounts of a second solute, named hydrotrope [**32**]. The hydrotropes aggregate only above a certain concentration, which is known as the minimal hydrotrope concentration (MHC) [**33**]. Various studies have been carried out to elucidate the process of hydrotropic solubilization. Although the exact mechanism is not fully clarified, it may involve multiple non-covalent interactions including hydrophobic interaction, hydrogen bonding [**30**] as well as parallel stacking effect [**34, 35**].

6. PEG-drug conjugates as dual-function carriers for cancer targeted delivery

PEG-Vitamin E Conjugates as Dual-Function Carriers for Cancer-Targeted Delivery D-α-tocopheryl polyethylene glycol (PEG) 1,000 succinate (TPGS) is a PEG-derivatized natural vitamin E which has been approved by FDA as a safe pharmaceutical adjuvant for drug formulation. In recent years, the application of TPGS in drug formulations has been extensively studied, such as emulsifier in poly (lactic-co-glycolic acid) (PLGA) nanoparticles, solubilizer and permeation enhancer [**36**], TPGS based liposomes [**37**], copolymers [**38**], and nanocrystal [**39**]. By inhibiting the function of P-glycoprotein (P-gp), TPGS also helps to overcome the multidrug resistance [**40**] and enhance the oral bioavailability of anticancer drugs [**41**]. In addition, TPGS-doxorubicin conjugate was develop ed as a prodrug for enhanced therapeutic effect [**42**].

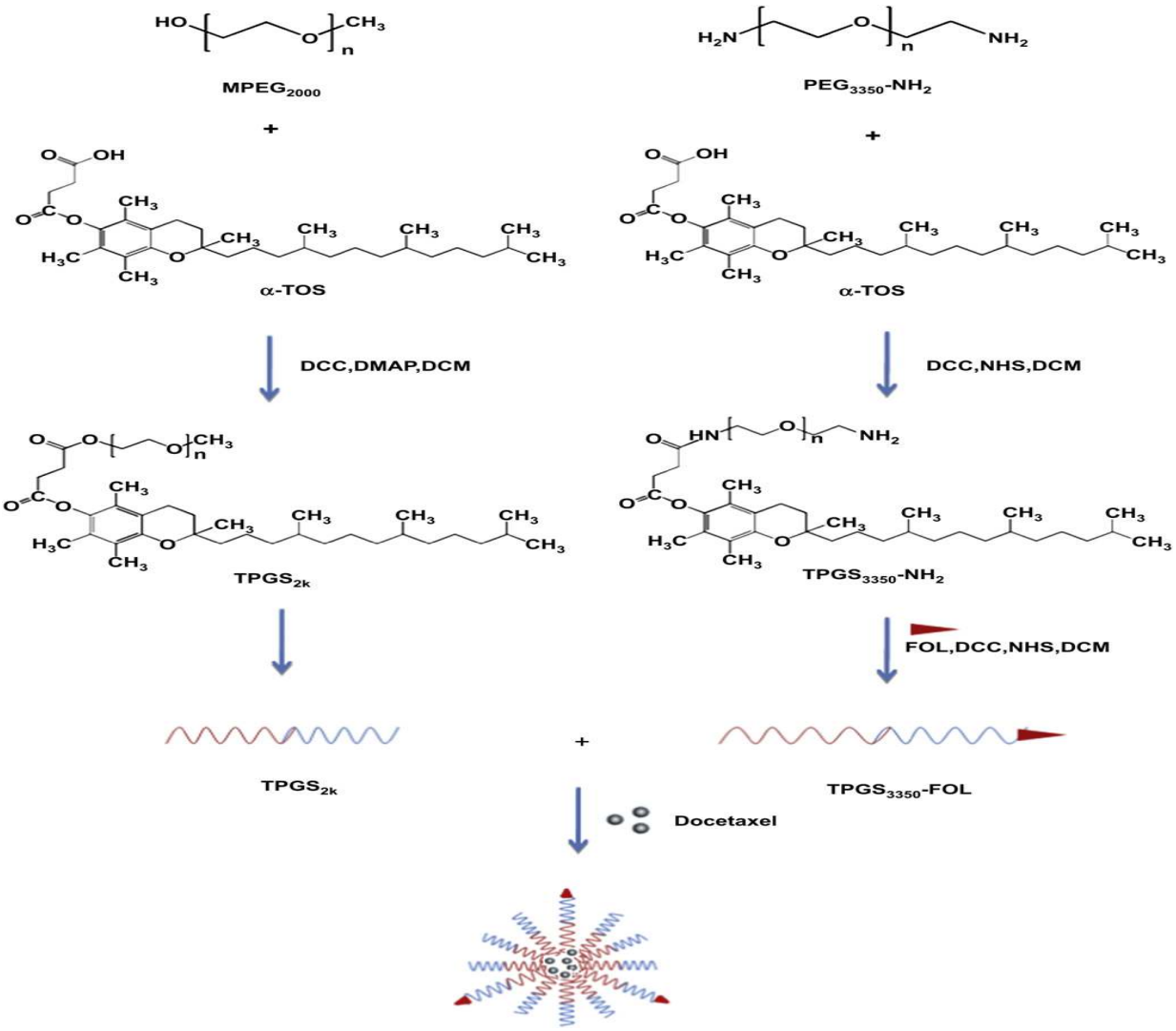

Figure 3: Preparation scheme for folic acid conjugated TPGS2k micelles loaded with Docetaxel as a model drug.

7. PEG-derivatized Embelin as a nanocarrier

Bearing a long lipophilic chain, embelin is extremely hydrophobic and water-insoluble. In an attempt to explore the PEG modification as an approach to increase its water solubility, we have found that PEG-derivatized embelin forms micelles in aqueous solution [**43**]. This is not a surprise considering the structural similarity between embelin and vitamin E. Interestingly, the antitumor activity of embelin was well retained after coupling with PEG chain [**43**]. In addition, the PEG-embelin micelles are highly efficient in solubilizing various types of anticancer agent such as paclitaxel [**43, 44**]. Furthermore, PEG-embelin, at nanomolar range, showed synergistic effect with paclitaxel in several cancer cell lines tested [**45**]

8. Conclusion

Overall study revealed that the polymeric micelles have potential to be act as a targeted nanocarrier for delivery of various therapeutic agents. Hence polymeric micelles can be used for the drug delivery application.

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