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REVIEW ARTICLE

BLOCK COPOLYMERIC MICELLES: BASIC CONCEPT AND PREPARATION TECHNIQUES

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Block copolymeric micelles, the nanoscopic core-shell structures formed by amphiphilic block copolymers, are one of the most well-suited drug delivery carriers among polymeric nanoparticles due to their inherent and modifiable properties. These nanostructures are capable of entrapping wide range of drugs and find limitless applications in the area of drug delivery. The purpose of this article is to briefly highlight basic concept and preparation techniques of polymeric micelles prepared by employing block copolymers.

Key words: Polymeric micelle, Block copolymer, Solvent evaporation, Flash nanoprecipitation.

INTRODUCTION

Since past few decades, the practice of drug delivery has changed dramatically and even greater changes are anticipated in the near and far future. Breakthroughs in medicine and drug delivery would not have been possible without research contributions of various fields including biomedical engineering, polymer and material chemistry, biophysics, biotechnology and molecular pharmacology. These multidisciplinary areas enabled substantially to the understanding of the physiological barriers to efficient drug delivery, such as transport in the circulatory system and drug movement through cells and tissues; mechanisms of drug release and *in vivo* performance, and development of novel patient-friendly drug delivery devices. Our research group has reported several findings to address solubility issues associated with formulation and delivery aspects of immediate and extended release formulations for poorly soluble drugs (Dahiya, 2006; Dahiya and Pathak, 2006a; 2006b; Dahiya and Pathak, 2007; Pathak *et al* 2008; Jain *et al* 2010; Dahiya and Tayde, 2013; Dahiya *et al* 2015; Dahiya *et al* 2019), and freely water soluble drugs for extended delivery (Dahiya *et al* 2008; Dahiya and Tyagi, 2008; Dahiya *et al* 2011; Dahiya and Gupta, 2011; Dahiya and Onker, 2014) using solid dispersion and complexation approaches. Besides, enormous research findings report nanotechnological advancements to address drug delivery challenges associated with poor solubility and poor bioavailability. Among several nanotechnology-based techniques, polymeric micelles have drawn much attention for delivery of poorly water soluble drugs (Verma and Hassan, 2013) and have been studied extensively for drug delivery applications including Paclitaxel, Indomethacin, Amphotericin B, Adriamycin, and Dihydrotestosterone for injectable formulations of polymeric micelles (Mourya *et al* 1998; Yu *et al* 1998; Allen *et al* 2000; Bae *et al* 2005).

Polymeric micelles, the nanoscopic core-shell structures formed by amphiphilic block copolymers, are one of the most well-suited drug delivery carriers among polymeric nanoparticles due to their inherent and modifiable properties.

A copolymer is a polymer derived from more than one species of monomer whereas a block copolymer is a copolymer formed when the two monomers cluster together and form 'blocks' of repeating units. The highly controlled polymerization techniques such as atom transfer radical polymerization (ATRP) (Siegwart, 2012) and reversible addition fragmentation chain transfer (RAFT) (Gregory and Stenzel, 2012) enabled syntheses of block copolymers structures to fit biomedical applications as well as formation of diversified self-assembled morphologies such as micelles, cylindrical micelles, and polymersomes. Various nanostructured carriers such as liposomes, polymer–drug conjugates, nanoparticles, and polymeric micelles have been explored for their drug delivery applications including targeted drug delivery to tumors (Kataoka *et al* 2001; Langer, 2007; Davis *et al* 2008). These nanostructures offer great applications starting from solubility improvement of drugs to the tailoring of pharmacokinetics to attain reduced toxicities of the drugs. The successful clinical translation of several of these nanomedicines further supports the strategy as an efficient therapeutic technique. Polymeric micelles have demonstrated unique advantages for incorporating a wide range of bioactive molecules and overcoming any biological barriers. The special feature of micelles is the core-shell structure that is highly water soluble while still maintaining a hydrophobic core suitable for hydrophobic drugs (Lu and Park, 2013; Kowalczuk *et al* 2014).

Micelles and polymeric micelles

The differences between the solubility of the hydrophilic and hydrophobic blocks of an amphiphilic copolymer in an aqueous solution drive the formation of distinctive and unique polymeric micelles with a core–shell architecture as depicted in **Figure 1a, 1b**. Amphiphilic block or graft copolymers also behave in the same manner as that of conventional amphiphiles or surfactant molecules and these polymers form polymeric micelles in aqueous solution above CMC. Polymeric micelles are nano-sized colloidal carrier system which comprise of polymer chains and are formed from amphiphilic block copolymers which comprises of both hydrophilic and hydrophobic monomer units, such as polyethylene oxide (PEO) and polypropylene oxide (PPO), respectively. These are spontaneously formed by self-assembly in a liquid, generally as a result of hydrophobic or ion pair interactions between polymer segments. Polymeric micelles usually have a core-shell structure, in which core contains either the hydrophobic part or the ionic part of the nanoparticles, and can possess either small or bigger molecules such as therapeutic active drugs, while the shell provides interactions with the solvent and construct the nanoparticles (Mourya *et al* 2010).

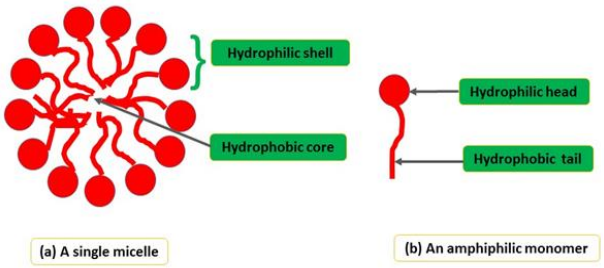

Fig. 1. Illustration of (a) a single micelle with core-shell structure, (b) an amphiphilic monomer

Spontaneous formation of micelles takes place when surfactant molecules are dissolved in water at concentrations above the critical micelle concentration (CMC). CMC is defined as the concentration of surfactants at and above which micelles form and almost all additional surfactants added to the system go to form micelles. The spontaneous formation of micelles from amphiphilic copolymers in aqueous media, when the CMC is achieved, is shown in **Figure 2**.

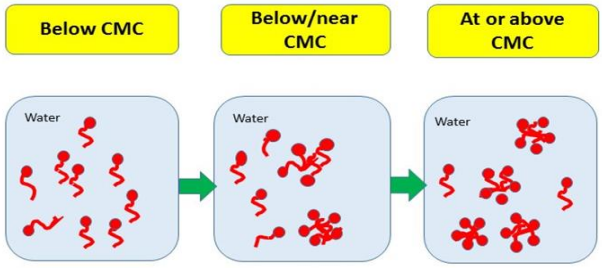

Fig. 2. Spontaneous micelle formation in water

Unlike the micelles of conventional surfactant monomers, polymeric micelles do possess a covalent linkage in individual surfactant molecules within the hydrophobic core. This linkage prevents dynamic exchange of monomers between free solution and the micellar pseudo-phase. This confers rigidity and stability to the polymeric micelles. Other advantages of polymeric micelles over conventional surfactant micelles are depicted in **Figure 3**.

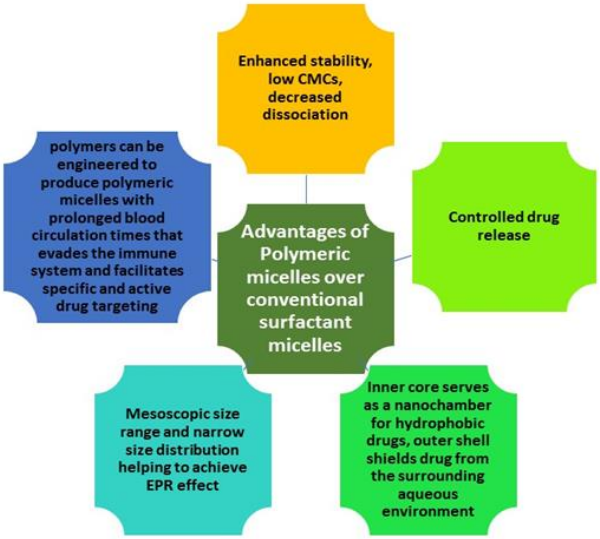

Fig. 3. Advantages of polymeric micelles over surfactant micelles

The aggregation number of polymeric micelles can be several hundreds and the diameter ranges from 10 to 100 nm. Factors controlling the size of the polymeric micelles include molecular weight of the amphiphilic block copolymer, aggregation number of the amphiphiles, relative proportion of hydrophilic and hydrophobic chains, and the preparation process (Jones and Leroux, 1999).

Selection of block copolymers

A range of commercially available block copolymers may be employed for the design of amphiphilic structures. The fabrication of polymeric micelles mainly involves the use of amphiphilic diblock copolymers, although graft and triblock copolymers can also be used. These three copolymer types possess exclusive benefits that can be utilized for the delivery of drugs, such as the prolongation of drug circulation time, control of the drug-release profile, or the ability to add targeting ligands. In addition, block copolymers can be further complemented by other amphiphilic polymers such as star polymers, miktoarm star polymers, and multiblock copolymers, to enable the formation of compartmentalized micelles. Irrespective of the architecture chosen, the basic consideration for the polymer selection should be the compatibility between the drug and the polymers (Kowalczuk *et al* 2014) because the polymer-drug interaction plays an important role in the drug-loading capacity of a carrier and the stability of the drug in the matrix which in turn affects the shelf-life of the carrier. Another important parameter is the miscibility of a drug with the polymeric matrix. This can be described by the Flory-Huggins theory which contains both entropy and enthalpy components, expressed by the Flory-Huggins interaction parameter χ that describes the interaction between the polymer and the drug. In other words, the Flory–Huggins parameter χ is a measure of compatibility between polymer and drug. However, many drugs have a strong tendency to crystallize where the presence of the homogenous mixture is determined by the miscibility curve of its phase diagram which is based on fast equilibrium. It does not usually happen in case when the polymers with high glass transition temperature (T_g) values traps the drug in the matrix resulting in a kinetically stable system.

In this scenario, the most suitable way to start with is "like dissolves like" based on the Scatchard-Hildebrand solubility parameter of the drug and polymer, indicating that the polymers that are chemically similar to the drug should enable the highest loading capacity. Polymeric micelles have been specifically explored in order to facilitate the delivery of hydrophobic drugs. Suitable amphiphilic block copolymers are obtainable *via* controlled synthesis by varying the block ratio, the total molecular weight, and the chemical structure. By adjusting the structure of the amphiphilic copolymers, the size and morphology of the resulting polymeric micelles can be easily controlled. Various classes of block copolymer commonly employed for the fabrication of polymeric micelles are summarized in **Table 1** (Croy and Kwon, 2006).

Preparation techniques of drug-loaded polymeric micelle

Drugs that have a low drug loading efficiency are best delivered by conjugating them to the block copolymer directly, instead of relying on physical attraction alone. The direct mixing of the hydrophobic drug and the micelle in water is suitable for some selected systems, however, it is rarely capable of dissolving both the drug and polymer. Therefore, other drug loading techniques must be used to ensure solubilization of both the drug and the polymer. A common solvent is capable of fully dissolving both the drug and the block copolymer into the monomeric state. A clear solution serves as an initial indication that the polymer has dissolved, however, it is advisable to test for the absence of micelles or other aggregates using light scattering techniques to ensure full solvation.

Schematics of drug-loading techniques are described in **Figure 4**. The brief description of various preparation techniques with their example methods are discussed.

Table 1. Commonly employed block copolymers for polymeric micelles

Polymer	Core forming block	Features
Poly(ester)s	poly(D,L-lactic acid-co-glycolic acid) poly(D,L-lactide) poly(ε-caprolactone)	Susceptible to hydrolysis, resulting in degradation to non-toxic species and leading to the expectation for safe systemic administration The poly(ester)s are not as amenable to chemical modifications as poly(L-amino acid)
poly(L-amino acid)s	poly(L-aspartate) poly(2-hydroxyalkyl-L-aspartamide) poly(β-benzyl-L-aspartate) poly(β-benzyl-L-glutamate)	Amino acids may be biodegradable into naturally occurring substances in the body by hydrolysis or enzymatic degradation Free amine or carboxylic acid functional groups of the amino acids can be chemically tailored to improve compatibility with the intended solubilizate or to improve the stability of the micelle
poloxamers	P85, P105 L61 F127, F98 F87, F68	Well-soluble in aqueous systems and form micelles spontaneously upon direct addition to water, allowing for simple preparation Do not biodegrade upon administration

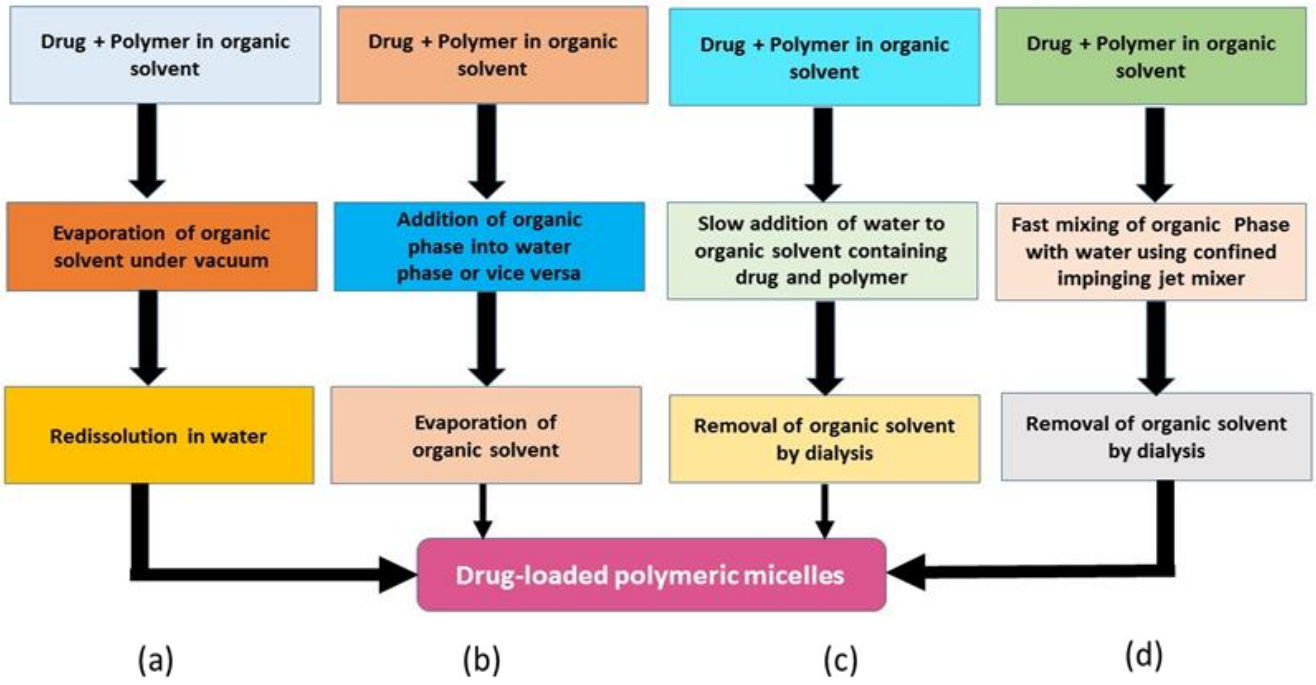

Fig. 4. Schematic representation of polymeric micelles' preparation techniques (a) solvent evaporation, (b) co-solvent evaporation, (c) Illustration of (a) a single micelle with core-shell structure, (b) an amphiphilic monomer) dialysis, (d) flash nanoprecipitation

Solvent evaporation technique

In the solvent evaporation technique, both polymer and drug are dissolved in an organic solvent with a low boiling point, followed by evaporation and subsequent dehydration (Pérez *et al* 2002). The chosen organic solvent is selective toward one block, which results in the formation of micelles in non-aqueous solutions. The product quality is influenced by the type of solvent, the concentration of polymer and drug, and the rate of evaporation. The limitation of this approach lies in the limited choice of solvents, and there is no guarantee the resulting particles will be well-defined core-shell particles that can be easily re-dissolved in water. For example, methanol or any other low-boiling solvent that can dissolve both components may be employed for this technique.

Co-solvent evaporation technique

Co-solvent evaporation proceeds by adding water directly to the organic solvent to achieve the self-assembly of the micelle and encapsulation of the drug. The outcome is controlled by the type of solvent, the ratio between organic solvent and water, the concentration of water and drug, rate of solvent evaporation, and the order and rate of mixing (Boury *et al* 1995). Although this approach is limited by the choice of solvent, it usually results in higher drug encapsulation efficiencies. For example, acetone, tetra hydro furan (THF) or acetonitrile can be used as organic solvent. Also, the addition of water is dropwise to the organic solvent or vice versa and mixed for at least four hours before evaporating the organic solvent.

Dialysis

Dialysis is one of the most versatile and most common technique used for drug encapsulation since it allows the use of high-boiling solvents such as dimethylsulfoxide (DMSO) which is removed by dialysis and replaced with water. Dialysis approach is applicable to many solvent systems and the drug loading efficiency is usually lower than the co-solvent evaporation. Further, the technique can be slow which can aid the formation of thermodynamically stable morphologies. The final dialysis step is done to remove solvent and collect the free drug. This step is often crucial to obtain a product free of organic solvent while maintaining maximum drug loading. If extensive dialysis is performed, it can assist in the thorough purification of the product, but it also can cause the release of the already encapsulated drug, giving rise to low drug encapsulation efficiencies. The example method for dialysis is given as follows. For example, organic solvent like dimethyl formamide (DMF) can be used in this method. The rate of addition of water can be controlled using a syringe pump. Finally, the solution is dialyzed against water using a tubular cellulose membrane.

Flash nanoprecipitation

Flash nanoprecipitation is a relatively new technique that offers a more rapid solution than other time-consuming methods as it involves fast mixing and precipitation into a non-solvent for the drug and one polymer block resulting in a kinetically trapped structure. Although, this resulting structures do not have well-defined internal phase boundaries like thermodynamically stable structures, the approach provides an alternative to achieve a fast throughput (York *et al* 2012). For example, THF can be used as organic solvent and the solution is mixed with water using a confined impinging jet mixer. The exit stream is introduced into water:THF (9:1% *v/v*) followed by dialysis against water using a tubular cellulose membrane.

CONCLUSIONS

Block copolymeric micelles are being explored for the drug delivery applications, specifically for the enhancement of solubility of the hydrophobic drugs. The efficiency of drug loading in these micelles depends on compatibility between the drug and the block copolymer employed. The drugs that have a low drug loading efficiency are best delivered by conjugating them to the block copolymer directly, instead of relying on physical attraction alone. Polymeric micelles can be prepared by various techniques such as solvent and co-solvent evaporation, flash nanoprecipitation and dialysis. The polymeric micelles are versatile nanosystems that demonstrate limitless avenues for modification enabling delivery of wide varieties of therapeutic agents.

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