Original Article

Review of Polymeric Nanomicelles

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Abstract

It is estimated that 90% of new drugs in development are classified as poorly soluble. Many drug molecules are lipophilic or hydrophobic in nature and thus they usually show low bioavailability, poor absorption properties, low permeation as well as inability to reach an effective therapeutic concentration in blood. To overcome this problem, nano micelles are the breakthrough drug delivery system in which a lipophilic drug can be incorporated into polymeric micelles or surfactant micelles that can provide high solubility as well as high bioavailability. Since Micelles have an inner lipophilic core and outer hydrophilic shell as well as the inner lipophilic core provides space for incorporation of the lipophilic drug, it enhances the permeability of the lipophilic drug even at depth and also at the target site. The present review outline various applications of nanomicelles, their advantages as well as limitations, methods of preparations, and various approaches for applications of nanomicelles.

Keywords: Polymeric Micelles, Critical Micelles Concentration (CMC), Enhanced Permeability and Retention (EPR).

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INTRODUCTION

The major problem being faced by modern pharmaceutical research is the hydrophobic characteristic of drugs, which is associated with ever-increasing solubility problems for the past ten years [1, 2]. Currently, approximately 70% of new drug candidates are insoluble in water and organic media. Besides, 40% of marketed oral drugs are considered hydrophobic drugs [3, 4]. The limited drug dissolution rate and low bioavailability of drugs are among the bad effects of water-insoluble drugs [1, 2. To achieve drug therapeutic effects in blood, increased drug dosage needs to be considered [2]. However, enhanced drug dosage can lead to a variety of problems like high toxicity, high manufacturing cost, difficulties in drug formulation, etc [2, 5]. Numerous drug delivery systems have been introduced by researchers in pharmaceutical industries to solve the problems associated with poorly soluble drugs. According to traditional methods, hydrophobic drugs were encapsulated in nano-sized carriers like liposomes, niosomes, micelle, emulsion, etc [2]. Unfortunately, among these carriers (eg: liposome and noisome), there are some which are not able to hold the hydrophobic compounds although they have the potential of improving hydrophobic drug solubility [6]. Thus, among multiple drug carriers that have been developed or undergoing development, micelles nano-carriers promise to resolve the drug solubility problem. Polymeric micelles are comparatively more stable than surfactant micelles. It can solubilize a substantial quantity of hydrophobic molecules in their central core. Because of their structural aspects like size and hydrophilic shell they possess prolonged circulation times *in vivo* and can accumulate in tumor tissues.[7]. Micelle formation occurs as a result of two forces. One is an attractive force that leads to the association of molecules while the other one is a repulsive force that prevents unlimited growth of the micelles to a distinct macroscopic phase. Amphiphilic copolymers self-associate when placed in a solvent that is selective for either the hydrophilic or hydrophobic polymer as can be seen in figure(1). Polymers at low concentrations exist as single chains. As the concentration increases it reaches a certain value called the critical micelle concentration (CMC), where that chains start to show association to form micelles and assemble in such a way that the hydrophobic part of the copolymer forms the central core and the hydrophilic part forms outer shell as can be seen in figure(2) [8]. Polymeric micelles consist of a core and shell structure; the inner core is the hydrophobic part of the block copolymer, which encapsulates the poorly water-soluble drug, whereas the outer shell or corona of the hydrophilic block of the copolymer protects the drug from the aqueous environment and stabilizes the polymeric micelles against recognition in vivo by the reticuloendothelial system (RES). Polymeric micelles possess several strong advantages, such as their physicochemical properties for tumor targeting by a passive targeting mechanism called the enhanced permeability and retention (EPR) effect. For targeting the tumor at inaccessible sites the drug should be administered by the parenteral route, and pharmaceutical drug carriers

carrying the drug in plasma should possess properties like biodegradability, small particle size, high loading capacity, prolonged circulation, and accumulation in the required pathological site in the body(9). Poorly water-soluble, hydrophobic agents. Are known to be associated with problems in therapeutic applications such as poor absorption and bioavailability, as well as drug aggregation-related complications such as embolism. On the other hand, poor water solubility is associated with many drugs, especially anticancer drugs [10]. Polymeric micelles promisingly increase the water solubility of such drugs by 10 to 5000 fold. However; the drug should have sufficient hydrophobicity to penetrate a cell membrane and the presence of hydrophobic group(s) for sufficient affinity toward the target receptor. Interestingly, the hydrophilic micelle corona keeps the polymeric micelles stable in plasma for a longer duration and also prevents their opsonization, and ultimately circumvents the RES. Block copolymers with the cationic block and the hydrophilic block associate with polyanionic nucleic acids to form PIC micelles. PIC micelles make it possible to incorporate charged macromolecules of biological and synthetic origin that may be nucleic acids or proteins in the core of the micelles Polymer micelles have been used widely in the delivery of various therapeutic drugs, which are also known as active pharmaceutical ingredients (APIs) (11). A very large number of chemicals are hailed as new drug candidates, but almost one-third of them are poorly water-soluble. Polymer micelles consisting of amphiphilic block copolymers or lipids form a hydrophobic core, in which lipophilic drugs can be physically incorporated [12].

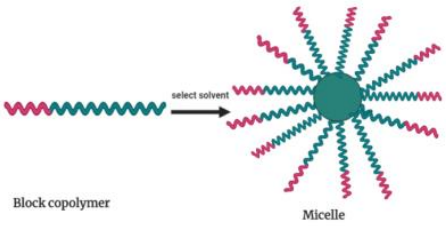

Figure (1): micelles structure

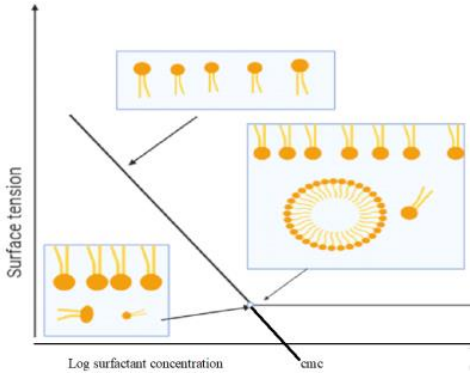

Figure (2): critical micelles concentration (CMC).

1. Advantages of nanomicelles

1. Nanomicelles formulation prevents the drug from the harsh environment and, reduces the chances of drug degradation.
2. It is a suitable carrier for the delivery of hydrophobic drugs.
3. In transdermal drug delivery drug passes through coenocytes along with keratinous fibers in the stratum cornea so, a lipophilic drug has a tendency to pass through it, so also suitable for transdermal drug delivery.
4. Risk of adverse effects is low.
5. Drug permeation is improved.
6. There is no irritation or reduced irritation.
7. Ocular and transdermal bioavailability is high through nano micelles carriers [13].
8. From the last few years nanomicelles are also used for the diagnosis and treatment of any diseases.
9. Nanomicelles have particles of smaller size so, retain for the desired time in blood.
10. Hydrophilic shells prevent the interaction of drug molecules from plasma components [14].
11. Nanomicelles enhanced the stability by forming the hydrogen bond with an aqueous system.
12. Nanomicelles are used for targeted and controlled drug delivery systems [15, 16].
13. Blood-brain barrier is an obstacle to drug penetration all barrier but nano micelles is one of the most appropriate modification to penetrate [17].
14. Nanomicelles are also used in cancer treatment through the oral route [15].

2. Disadvantages of nanomicelles

1. The industrial growth of polymeric micelles is hindered by the high cost of preparation and the difficulty in drug loading [16].
2. When the polymer is sufficiently hydrophilic it can be dissolved directly along with the drug to yield drug-loaded polymeric micelles
3. Drug loading in polymeric micelles is then affected by emulsification or dialysis techniques. However, emulsification usually involves the use of chlorinated solvents which are not safe. [17].
4. Owing to extreme dilutions by the blood upon intravenous injections of a micellar solution, polymeric micelles are prone to deformation and disassembly which may lead to leakage and burst release of loaded drugs. However, this limitation can now be overcome by improved interaction of the drug and polymer via chemical conjugation or by cross-linking of the shell [18-19].
5. The loss of hydrophilic and hydrophobic balance upon increased loading of hydrophobic drug into the core region also has been related to decreased stability of the polymeric micelles. (20,21).

3. Preparation of polymeric micelles

Dialysis method

The dialysis method involves the addition of small amounts of water to the solution of polymer and drug in a water-miscible organic solvent like dimethyl formamide with stirring followed by dialysis against an excess of water for several hours using a dialysis bag for the removal of organic solvent(9).

Oil-in-water emulsion solvent evaporation method

The drug along with the polymer is dissolved in a water-immiscible organic solvent like tetrahydrofuran, chloroform, acetone, or a mixture of solvents like chloroform and ethanol, and this solution is slowly added to the distilled water under vigorous stirring to form an emulsion with an internal organic phase and continuous aqueous phase, which rearranges the polymer to form micelles. Sometimes surfactants like polyvinyl alcohol are used in an aqueous solution. This emulsion is then kept open to air with stirring to evaporate all the organic solvents (9).

Solid dispersion method

In this method, the drug along with the polymer is dissolved in the organic solvent, and a solid polymer matrix is obtained after the evaporation of the solvent under reduced pressure. Drug-loaded polymeric micelles are obtained after the addition of water to the preheated polymer matrix(9).

Microphase separation method

In this method, the drug and polymer are dissolved in (organic solvent) tetrahydrofuran, and the solution is added dropwise in water under magnetic stirring. Polymeric micelles are formed spontaneously, and drugs are entrapped in the inner part of the micelles. An organic solvent is removed under reduced pressure, and a blue-colored polymeric micelles solution is formed [22].

4. Applications of polymeric micelles Solubilization of drug molecules

The poorly water-soluble drugs or contrast agents may be entrapped within the hydrophobic core or linked covalently to the surface of polymeric micelles to improve their aqueous solubility. Solubilization is controlled by the characteristics of the drug as well as those of the micellar systems. The molecular weight and partition coefficient of the drug are important parameters, while the hydrophobic block length of the micelle is also equally important. - times, steric hindrance and interaction of drug and polymer may lead to an unfavorable aggregation process. Thus, the selection of an amphiphilic polymer for solubilization of drugs is a critical issue and requires an in-depth understanding of the selectivity of micellar systems which is achieved by studying various types of intermolecular interactions for solubilization of drugs in a given micellar system [23–25]. In the pharmaceutical industry, micellar solubilization finds an important application for the enhancement of solubility and bioavailability of drugs. It is noted that nearly half of the approved active pharmaceutical ingredients are poorly water-soluble and show very low bioavailability. Polymeric micellar solubilization may realize their usage [26,27]. Solubilization of drug in polymeric micelles is expressed by the partitioning of the drug described as the ratio of molar drug concentration in the micelle to the molar concentration of drug in the aqueous phase. The extent of solubilization depends upon the micellization process, the compatibility between the drug and the core-forming block, the chain length of the hydrophobic block, the concentration of polymer, and temperature [28].

Targeting

The site of action of the drug is mostly at distant locations from the site of administration. The drug has to take a complicated path to reach the desired site, during which it might be destroyed or distributed to many unwanted tissues. This usually is associated with increased side effects on the body. Also, it results in a sub-therapeutic concentration of drug in target organs. Thus, drug targeting is a major issue for avoiding all the related problems. Some of the factors of polymeric micelles that govern drug targeting include size, chain length, drug content, stability and degradation of micelles in aqueous solutions, and hydrophobic inner core. Owing to their characteristic size, the polymeric micelles may represent suitable targeting vehicles utilizing the EPR effect through passive targeting (28).

Conclusion

Owing to their many advantages, polymeric micelles are considered important pharmaceutical drug carriers. The most pertinent trait of block copolymer micelles for drug delivery is their ability to form prominent core-shell structures. Poorly water-soluble drugs can easily be loaded into the hydrophobic core of the polymeric micelles, thus providing an opportunity to enhance the solubility and bioavailability of such drugs. Importantly, stable polymeric micelles possessing an excellent ability to carry a variety of poorly water-soluble drugs can effectively be used to target certain pathological areas in the body with compromised vasculature such as tumors and infarcts owing to their size and the EPR effect. Targeting can also be achieved by attaching specific ligands or specific antibodies onto their surface.

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