Review Article

A Comprehensive Review on Polymeric Micelles

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ABSTRACT

Polymeric micelles are the promising tool for the research in the field of drug delivery and drug targeting. Polymeric micelles are self-assembled nano sized colloid particles made up of amphiphilic block co-polymers. Due to their excellent biocompatibility, low toxicity, enhanced blood circulation time and ability to solubilize large quantity of drugs in their micellar core the polymeric micelles have been widely used. Based on the intermolecular forces the polymeric micelles are classified into conventional, polyion complex micelles, non-covalently connected polymeric micelles. There are three types of method of preparation explained in this article. They are direct dissolution, solvent evaporation and dialysis method. The evaluation techniques used here are critical micellar concentration, size and shape, in vitro drug release behavior. Polymeric micelles can be used as a vehicle for targeting drugs to specific sites.

Keywords: Micelles, polymeric micelles, block copolymers, solubilization.

INTRODUCTION

Drugs and therapeutic compounds that are commonly used for curing disorders are having a low solubility in aqueous media. Thus, there has been an increasing attention towards the development of drug delivery system that are not only highly capable but also site specific. Colloidal nanocarriers such as nanoparticles, micelles, liposomes are a type of drug delivery system having high specificity and targeting property. As, there are more complex synthetic compound entering the field of therapy, the delivery systems must undergo changes and accommodate this property. Micellar delivery system can be utilized to deliver such types of complex molecules. Polymeric micelles are type of particulate colloidal carrier system that self assembles in aqueous medium. They comprise of a linear amphiphilic macromolecule having both hydrophilic and hydrophobic block[1-7].

The particle size of polymeric micelles ranges from 10-100nm. These are considerably smaller than liposomes. Temporal and distribution controls are the two primary factors influencing the efficiency of the drug delivery system of block copolymer aggregates. Temporal control describes the time required and the mechanism of drug release from the micelle core. Distribution control describes the distribution and accumulation of drug molecules at the target site[8].

Micelles

As per IUPAC, micelles are particle of colloidal dimensions that exist in equilibrium with the molecules or ions in solutions from which it is formed. Micelles play an important role in the pharmaceutical field since they increase the solubility of mildly soluble substance in water. A typical micelle, in aqueous solution consist of a hydrophilic head and hydrophobic tail. In this, the hydrophilic head phases the solvent molecules and the hydrophobic tail forms a core. The aggregation number is an average number of monomer required to form a micelle will range from 50-200 monomers. Decrease in free energy of a system is the driving force behind the self-association of amphiphilic molecules. Size of the hydrophobic domain, amount of amphiphiles, temperature and solvent are the factors affecting micellar formation. When the amphiphilic molecules exceed the minimum concentration, aggregates are formed this minimum level is known as critical micellar concentration (CMC). At low concentrations amphiphilic molecules exists separately. Below CMC as concentration of amphiphile increases, the concentration of amphiphile undergoing adsorption at the air-water interface increases. At CMC monomers are formed at the interface and the bulk phase thus getting saturated[1].

Polymeric micelles

As per IUPAC, polymeric micelles are an organized auto assembly formed in a liquid and composed of amphiphilic macro molecules in general amphiphilic di or tri block co polymers made of solvophilic and solvophobic blocks. Amphiphilic block copolymers can be used in the formation of polymeric micelles[2]. Micelles have a core shell structure. The core consists of hydrophobic tail which can be used for loading therapeutic active drug. The shell interacts with the solvent and build up nano particles that are stable in liquid. The diameter of polymeric micelles ranges from 10to 100nm. Molecular weight of amphiphilic block co-polymer, aggregation number of the amphiphile, properties of hydrophilic and hydrophobic chains and the preparation process are the factors affecting the size of polymeric micelles. Stimuli sensitive co-polymer is used for the development of intelligent vehicles[10].

TYPES OF POLYMERIC MICELLES

Polymeric micelles can be classified based on the intermolecular forces which apart the core segment interacting with the aqueous environment. They are classified into three groups.

- Conventional
- Polyion complex micelles
- Non-covalently connected polymeric micelles

➢ Conventional

In the aqueous environment the core and the shell interact hydrophobically forming micelles. An example for amphiphilic block co-polymer formed by hydrophobic interactionis poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)[3].

➢ Polyion complex micelles (PICMs)

Polyion complex micelles are formed by means of electrostatic interaction between two oppositely charged moieties. The structure and size of the charged micelles coronas are controlled by electrostatic and the Vander Waals force of interactions. Simple synthetic route, high drug loading capacity, structural stability, prolonged circulation in the blood, self-assembly in aqueous medium are some features of polyion complex micelles. Micelles are prepared in aqueous media without using organic solvent. This will allow to remove the side effects, that may be caused due to residual organic solvent. The core polyion complex micelles can trap many therapeutic agents through electrostatic, hydrophobic hydrogen bonding interactions. These therapeutic agents are released from the core by a suitable trigger. Polyion complex micelles can be used for the delivery of charged drugs, antisense oligonucleotides, DNA and enzymes [4].

➢ Non-covalently connected polymeric micelles

In the non-covalently connected polymeric micelles, polymeric micelles can be prepared in the absence of block co-polymer have the driving force used is inter polymer hydrogen bonding complexation. Core and the corona are non-covalently connected at homopolymer chain end by hydrogen bonding or metal ligand interactions, thus the name non-covalently connected polymeric micelles[13].

METHODS OF PREPARATION

- Direct dissolution method
- Solvent evaporation method
- Dialysis method

➢ Direct dissolution method

It involves the mixing of block copolymer and drug in an aqueous solvent. It commonly used for the hydrophobic copolymer such as poloxamers. The temperature is increased to form micelles form through dehydration of core forming segments. The copolymer and the drug are dissolved separately in an aqueous solvent, then the both solutions are mixed together thus micelles are formed.

➢ Solvent evaporation method

In this method volatile organic solvent are used to dissolve both copolymers and drugs. This method can be used only when both copolymer and drug dissolves in a common solvent and also where they do not dissolve in water. The organic solvent is removed by evaporation and thus the thin film of copolymer and drug are formed. Water is added to the above film to obtain drug loaded polymeric micelles.

➢ Dialysis method

Drug in copolymer are mixed together in an organic solvent the above solution is poured into a dialysis bag dialysis bag is placed into a beaker containing water. This solution and the water moves in and out. Dialysis method is commonly used that are having poor solubility. The dialysis process is taken more than 36 hoursfor appropriate drug loading[14].

CHARACTERISATION OF POLYMERIC MICELLES

In order to achieve its bioavailability, characterization of polymeric micelles is an important step. Since these molecules varies in size as well as solubility, it must be checked thoroughly in order to prove its stability. The evaluation of polymeric micelle is done by detecting its critical micellar concentration, size and shape, in vitro drug behavior.

➢ Critical micellar concentration

CMC is an important factor for the stability of polymeric micelles. In aqueous dispersion of micelles CMC can be determined by using different methods such as surface tension, X-ray scattering, differential scanning calorimetry and utilization of fluorescent, chromatography[(6)].

➢ Size and shape determination

Polydispersity index of prepared micellar solutions structure can be determined by using quasi elastic light scattering technique. From the light scattering technique, a monodisperse micelle can produce blue color and the aggregates produce white color. If they show blue color, it indicates that the prepared micelle solution is good. The size and shape of block copolymer can be determined by scanning electron microscopy (SEM), transmission electron microscopy (TEM) technique. Atomic force microscopy (AFM) is used for the direct visualization of block copolymer micelles in the dried or liquid state. The size of drug loaded polymeric micelles can be determined by asymmetric flow field flow fractionation. The structure of micellar assembly determined by small angle neutron scattering.

➢ In vitro drug release behavior

In in vitro drug release study, a dialysis tube is used to hold micellar solution. The dialysis bag is immersed into a flask containing medium, here the temperature is kept constant. At different time intervals some amount of the

medium is removed and is replaced by fresh medium. This removed medium is used to detect the concentration of drug released through spectroscopic methods[5].

APPLICATIONS

1. Solubilization

Micellar core is a best environment for incorporating the water insoluble molecules that is the hydrophobic molecules. The hydrophobic molecules can be covalently bonded to block copolymers or it can be physically taken in to the hydrophobic core of the micelles. Solubilization process increases the water solubility, also its bioavailability. Nano sized polymeric micelles increase the absorption. The degree of absorption depends upon micellization process, temperature, the compatibility between the drug and the core forming block, chain length of the hydrophobic block and the concentration of the polymer.

- **Drug delivery to the brain**

The structure of blood brain barrier is very complex, so it must be thoroughly investigated in order to deliver the drug to the brain. In some neurodegenerative disorders such as, Parkinson's, Alzheimer's disease, the blood brain barrier is partly disrupted for drug release. To improve the delivery of therapeutic drug to brain mainly two approaches have been adopted using polymeric micelles. The former approach is a modification of polymer micelles with antibodies or ligand molecules, that will cross the epithelial cells via transcytosis. The later approach is to hinder the drug efflux system using Pluronic block copolymer[6]. For example, poloxamer micelles are bounded with antibodies and improves the haloperidol distribution in to brain, this improves drug efficacy. Another example is that the Pluronic unimers helped to penetrate the molecule such as rhodamine, digoxin, doxorubicin in to bovine mammary epithelial cells by inhibiting P-gp [11].

2. Formulation of an antifungal agent

In immunocompromised AIDS, surgery, cancer patients, if a systemic fungal infection arises, there must be a safe and effective manner for the delivery of chemotherapeutic agents. The major drawback of antifungal agent is low solubility and high toxicity. For example, amphotericin B have low compatibility with the core of polymeric micelle. To avoid this problem, as well as to increase its solubility, stearate side chains were bound with methoxy-PEO-b-poly(L-aspartate), the core-forming block[13].

3. Passive drug targeting to solid tumors

Drug targeting to specific sites will decrease the adverse reaction, since the action will only be limited to specific sites. Polymeric micelles can be used to target specific sites and may be a promising candidate for the delivery of drugs to solid tumors. The passive targeting is a method used for the polymeric micelles to reach the desired site. This is achieved due to its enhanced permeability and retention effect (EPR effect). The size of the polymeric micelles has an important role in passive targeting as well as in determining its biological fate. The higher permeability of drugs to tumors showing EPR effect is based on excessive production and secretion of chemicals such as vascular endothelial growth factor bradykinins, nitric oxide, enzyme collagenase, peroxynitrite.

CONCLUSION

Polymeric micelles have an attractive property. Therefore, it has been emerged as an important pharmaceutical drug carrier. The preparation of polymeric micelles is simple. There are various methods used for preparation of micelles. They include direct dissolution method, solvent evaporation method, dialysis method. Polymeric micelles can be used as a carrier for poorly soluble drug, targeting to tumors, gene delivery and increasing its bioavailability. Targeting can also be done by binding of ligands or antibodies to core forming blocks. Polymeric micelles will possibly be most simplistic, adaptable and effective method in chemotherapeutic treatments. The polymeric micelles can also be used in the early diagnosis of cancer. Thus, polymeric micelles have a promising future for the delivery of drug.

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