IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON POLYMERIC MICELLES

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Abstract:

Polymeric Micelles are amphiphilic block copolymers that create a nanoscopic Core/Shell structure. They are particularly well suited for drug delivery because of both their inherent and modified characteristics. Micelles have attracted much interest since they can carry drugs that are not very water-soluble. Micelles can deliver both hydrophobic and hydrophilic agents, resulting in improved medication pharmacokinetics and tissue distribution, as well as increased drug bioavailability. Oil in water emulsion, Solvent Evaporation, Solid Dispersion, and Dialysis are the most popular procedures for micelle formation. Micellar Association, Morphology, Size, and Stability are all relevant features. Advantages, Disadvantages, Types, Methods, Applications, Evaluation, and Conclusion are the primary highlights of this review.

KEYWORDS: Improved Drug Bioavailability, Polymeric Micelles, Amphiphilic Block Copolymers.

INTRODUCTION :

Polymeric micelles are core-shell nanoparticles that form when block copolymers or graft copolymers self-assemble in specific solvent.Polymeric micelles have a spherical form and a size range of 10-100 nanometers. Surfactant micelles have significantly lower thermodynamic and kinetic stability than polymeric micelles[1]. Drugs and medicinal compounds used to cure ailments have a decreased solubility in watery media As a result, there has been a strong emphasis on designing highly competent and site- specific drug delivery systems.

These are considerably smaller than liposomes[2]. The efficacy of the drug delivery system of block copolymer aggregates is influenced by two key factors: Temporal and Distribution controls. The time required and the

mechanism of drug release from the micelle core are described by temporal control. Distribution control describes the distribution and accumulation of drug molecule at the target site[3].

More innovative research on polymeric micelles, spanning basic science such as the development of newer polymers and their micelles with characterization to applied science such as drug solubilization, drug targeting via various routes of drug administration, and targeting of nucleic acid drugs, is expected as more players embrace this technology.

MICELLES:

The development of Micelles is connected with changes in physicochemical properties caused by the orientation and aggregation of amphiphilic molecules in solution. Micelles are normally spherical and range in size from 2 to 20 nm in diameter, depending on their composition. Micelles have gotten a lot of interest for their ability to deliver medications that aren't highly water-soluble[4]. Micelles are comprised of amphiphilic molecules that self-assemble. The structures have a hydrophilic/polar segment (head) and a hydrophobic/nonpolar section (tail).

Micelles are formed in an aqueous solution, with the polar region facing the micelle's exterior surface and the nonpolar region forming the micelle's core. Both hydrophilic and hydrophobic agents can be administered by micelles. Because these molecules can provide prolonged and controlled release of macromolecules, chemical and physical stability of the encapsulated molecules, improved drug pharmacokinetics,favorable tissue distribution, and improved drug bioavailability, these structures can deliver macromolecules. Micelle formation occurs at concentrations exceeding the critical micelle concentration[5]. Oil in water emulsion, solvent evaporation, solid dispersion, and dialysis procedures are the most popular ways for micelle preparation.

The hydrophilic shell renders the micelle water-soluble, allowing for intravenous delivery, while the hydrophobic core transports a therapeutic payload. The hydrophilic shell of polymeric micelles and their nanoscale dimensions (less than 50 nm) protect them from being eliminated by the reticuloendothelial system, increasing their circulation time and ability to transport the drug to the target [6].

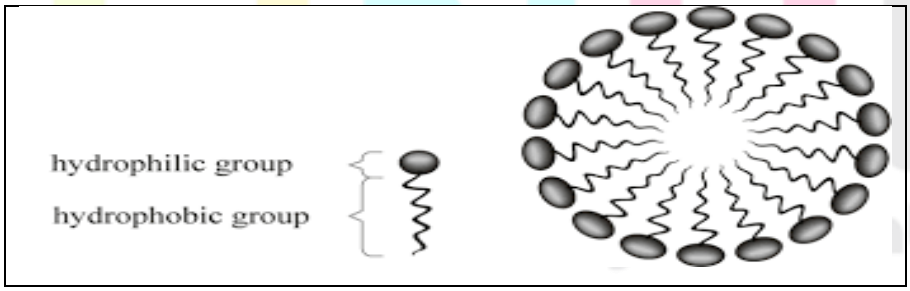

Fig. 1: Structure of micelles

The aggregation number is the average number of monomers necessary to form a micelle, which can range from 50 to 200. The self-association of amphiphilic molecules is driven by a decrease in a system's free energy. The micellar formation is influenced by the size of the hydrophobic domain, the number of amphiphiles present, the temperature,

and the solvent[7]. When the concentration of amphiphilic molecules exceeds a certain threshold, aggregates develop; this threshold is known as critical micellar concentration (CMC).

Amphiphilic compounds exist separately at low concentrations. The concentration of amphiphiles undergoing adsorption at the air-water interface increases when the concentration of amphiphiles below CMC increases. Monomers develop at the interface at CMC, allowing the bulk phase to become saturated [8].

POLYMERIC MICELLES:

As per IUPAC, polymeric micelles are an established auto assembly formed in a liquid and composed of amphiphilic macromolecules in general amphiphilic di or tri-blockcopolymers made of solvophilic and solvophobic blocks. Polymeric micelles can be created using amphiphilic block copolymers.

Polymeric micelles have a diameter of 10 to 100 nanometers. The size of polymeric micelles is determined by the molecular weight of amphiphilic block copolymers, the amphiphile's aggregation number, the characteristics of hydrophilic and hydrophobic chains, and the manufacturing procedure. The creation of intelligent vehicles uses a stimuli-sensitive co-polymer [9].

The behavior of amphiphilic block or graft copolymers is similar to that of conventional amphiphiles. When a water-soluble polymer is attached to an insoluble polymer in solution, micelles of amphiphilic block copolymers develop, giving the polymer structure and flow characteristics that are distinct from either parent polymer. The hydrophobic core contains surfactant molecules that prevent dynamic monomer exchange between the free solution and the micellar pseudo-phase. The polymeric micelles develop rigidity and stability as a result of this. Polymeric micelles have a diameter of 10 to 100nm. Amphiphilic diblock polymers are defined as those with a molecular mass between 5000 and 30,000 Da, as opposed to surfactants, which have a molecular mass between 100–500Da b [10].

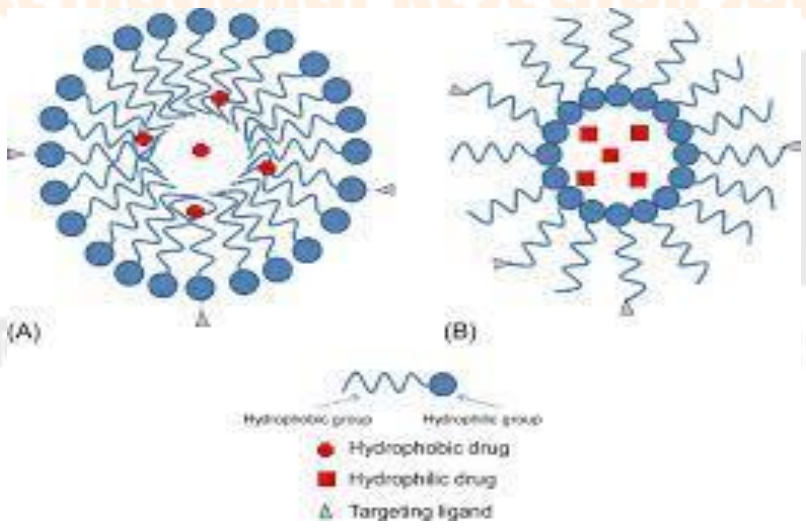

Fig.2: Polymeric micelles

Individual polymeric surfactant molecules usually have a covalent bond within the hydrophobic core that prevents dynamic interchange of monomers between free solution and the micellar pseudo-phase, which is a major distinction between ordinary surfactant monomers and polymeric surfactants. The polymeric micelles acquire rigidity and stability as a consequence of the above. Polymeric micelles have a diameter of 10 to 100nm [11].

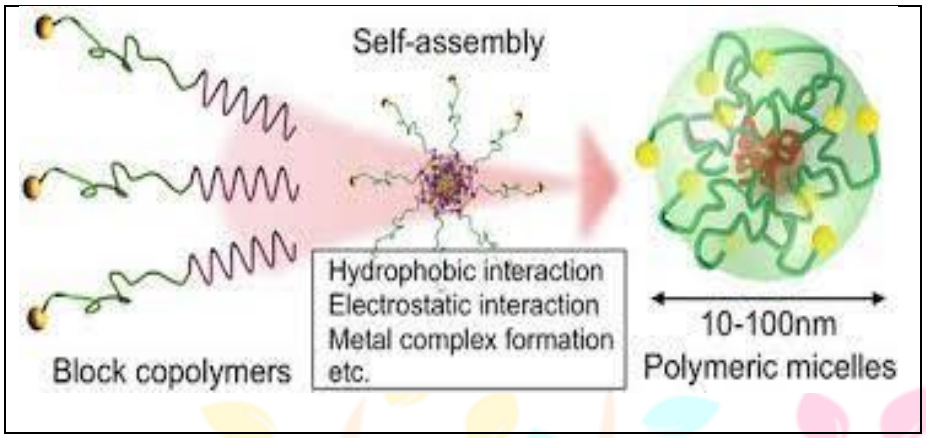

Fig. 3: Self-assembly of polymeric micelles

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TYPES OF POLYMERIC MICELLES

The intermolecular forces that separate the core segment from the aqueous environment can be used to classify polymeric micelles. They are divided into two categories.

1. Conventional
2. Polyion complex micelles

1. Conventional

These micelles were produced in an aqueous environment via hydrophobic interactions between the core segment and the corona area. Poly (ethylene oxide) b-poly (propylene oxide)-b-poly (ethylene oxide) generates micelles as a result of 16 hydrophobic contacts, rendering it one of the simplest amphiphilic block copolymers.

2. Polyion complex micelles (PICMs):

Polymeric micelles are formed by electrostatic contact between two oppositely charged moieties, such as polyelectrolytes. When oppositely charged polymers are added into the media, they can penetrate the micelle's corona, resulting in polyionic micelles. Polyion complex micelles are the term given to such micelles (PICMs). The form and size of charged micelle coronas are controlled by electrostatic forces and the van der Waals force of interaction. The preparation of micelles is done in an aqueous medium without the use of any organic solvents, which eliminates the related side-effects of residual organic solvents. Many therapeutic agents, including hydrophobic chemicals, hydrophilic compounds, metal complexes, and charged macromolecules, can be entrapped in the core of polyion micelles and released after receiving a proper trigger through electrostatic, hydrophobic, and hydrogen bonding interactions. Charged medicines, antisense oligonucleotides, DNA, and enzymes can all be delivered using polyion complex micelles.

Formation of polymeric micelles:

Polymeric Micelles are amphiphilic block-based self-assembled core-shell nanostructures generated in an aqueous solution. When the concentration of a block copolymer reaches over a certain level, called the critical aggregation concentration or critical micelle concentration, micelles form in an aqueous solution. Block copolymers begin to associate hydrophobic regions with minimizing water molecule interaction at CMC, resulting in the formation of a vesicular or core-shell micellar structure [12].

Polymeric micelles for intelligent drug delivery are currently an interesting research topic in the field of drug delivery and targeting. They're nano-sized colloidal particles with polymer chains that self-assemble. By composing with hydrophobic polymeric segments, they can be self-assembled units in any liquid [13]. Micelles often have a core-shell structure, with the core carrying either the hydrophobic part of the ionic composition of the nanoparticles containing drug molecules within it or the hydrophobic part of the ionic composition of the nanoparticles containing drug molecules within it. The shell reacts with the solvent, forming stable nanoparticles in any liquid medium.

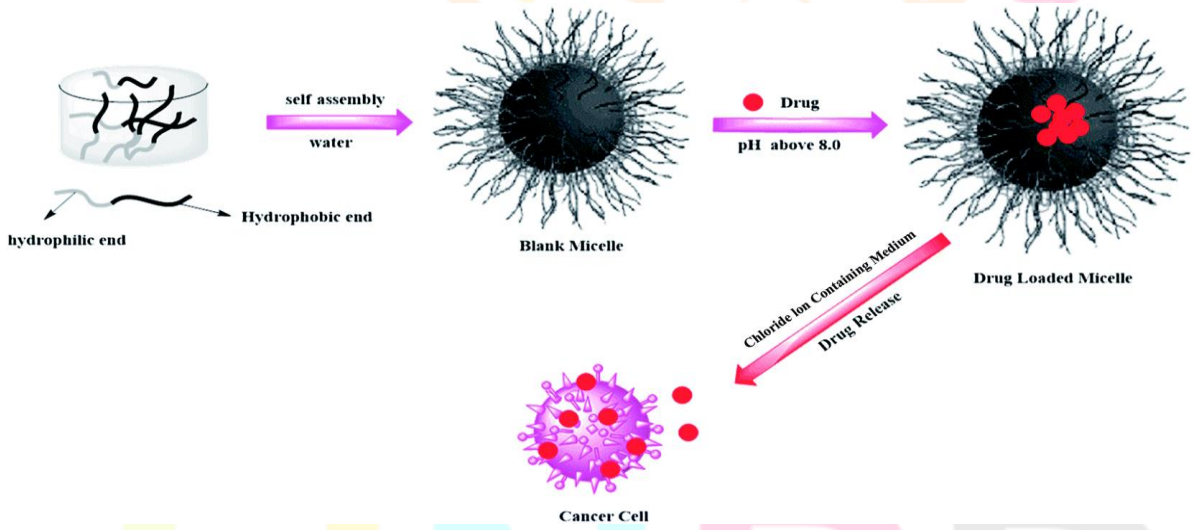

Fig. 4: Formation of polymeric micelles [12]

Structure analysis and chemistry of polymeric micelles:

The main distinction between conventional monomer micelles and polymeric micelles is that individual polymeric surfactant molecules within the hydrophobic core usually have a covalent bond that prevents dynamic monomer exchange between free solution and the micellar pseudo-phase. The polymeric micelles acquire rigidity and stability as a consequence of this. The polymeric micelle's diameter spans from 10 to 100nm. A hydrophobic domain is produced by the micellar core. To overcome solubility concerns, most poorly water-soluble drugs can be easily absorbed into the core of polymeric micelles.Solubility enhancement is frequently linked to improved oral bioavailability of hydrophobic drugs [14]. By hydrophobic interactions, the inner core of the Polymeric micelles was created with hydrophobic blocks of the copolymers. Polyion complex (PIC) micelles can also be produced through electrostatic interactions employing charged block copolymers containing oppositely charged

macromolecules. Micelles are generated when any surfactant molecule is dissolved at a concentration above CriticalMicelleConcentration[15].

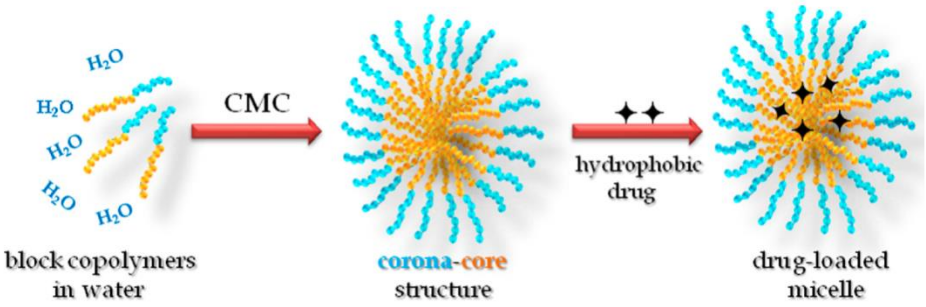

Fig. 5: Polymeric micelles

ADVANTAGES:

1. Polymeric micelles help to increase the solubility of the original drug thus increase in the biocompatibility.
2. The Hydrophilic shell and Nanoscopic size prevent mechanical clearance.
3. Various functional groups can be incorporated by physical entrapment.
4. High kinetic stability helps to maintain integrity.
5. It hasa high drug loading capacity of the inner core.
6. It can be used for receptor-mediated drug delivery systems.
7. Suitable for intravenously drug delivery system.

DISADVANTAGES:

1. The industrial growth of polymeric micelles is hindered by the high cost of preparation and difficulty in drug loading.
2. Drugs are copolymers prone to hydrolytic cleavage in aqueous systems, stability problems.

METHODS OF PREPARATION:

1. Direct dissolution method

2.Solvent evaporation method

3.Dialysis method

1. **Direct dissolution:**

The procedure involves blending the block copolymer and the drug in an aqueous solution. It's a term that's widely used to describe hydrophobic copolymers such as poloxamers. Micelles are formed by increasing the temperature

and dehydrating the core-producing segments. Separately, the copolymer and the drug are dissolved in an aqueous solvent, and then the two solutions are mixed to form micelles.

2. **Solvent evaporation method:**

Both copolymers and drugs are dissolved in this technique utilizing volatile organic solvents. This approach can only be utilized when both the copolymer and the drug dissolve in about the same soluble and do not dissolve in water. Evaporation removes the organic solvent, resulting in the formation of a thin copolymer and drug film. To produce drug-loaded polymeric micelles, water is added to the above film.

3. **Dialysis method:**

The drugs in the copolymer are mixed in an organic solvent, then poured into a dialysis bag, which is then placed in a water-filled beaker. This solution and the water go in and out. Dialysis is a typical method for people with low solubility. More than 36 suitable drug loadings are performed during the dialysis process [16].

Polymeric micelles can be used for enhancement of bioavailability:

The polymeric micelles can protect the loaded drug from the hostile environment of the GI tract and release the drug in a regulated form at the targeted site; the polymeric micelles can also extend the drug's residence period by muco-adhesion [17]. The polymeric micelles are modified in several ways, such as particle size, to make them simpler to pass the intestinal epithelium [18]. To improve bioavailability, polymeric micelles can be produced on a variety of carrier systems[19].

1. Mucoadhesive polymeric micelles
2. pH-sensitive polymeric micelles
3. Temperature-sensitive polymers
4. Light sensitive polymeric micelles
5. Ultrasound sensitive polymeric micelles

Table: 1.Multifunctional polymeric micelles for delivery of drugs:

Micelle components/ formulation	**Drugs(s)**
PRE-CLINICAL	
PEG2000-PE	Docetaxel
PEG2000-PE/Vitamin E	Paclitaxel and curcumin Paclitaxel and Elacridar
PEG2000-PE/Hydrogenated phosphatidylcholine (PEG200-PE/HSPC)	Doxorubicin

Adamantine terminated PEG and ß-cyclodextrin based 7-armedpoly (L-glutamic acid) (mPEG -Ad@ß-CD-7PLGA/CDDP)	CDDP
Stearate grafted dextran	Doxorubicin
mPEG -b-poly (D, L-lactide)	Docetaxel
PluronicP123/F127	Paclitaxel
CLINICAL	
Genexol®-PM, mPEG -PDLLA (Ph-IV/approved in Korea)	Paclitaxel
NK105, PEG- p(Asp) (Ph-III)	Paclitaxel
SP1049C, Pluronic L61 and F127 (Ph-III)	Doxorubicin
NK012, PEG-P(Glu)-SN38 (Ph-II)	SN-38
NC-6004, PEG-P(Glu)-cisplatin (Ph-I/II)	Cisplatin
NK911, PG-P(Asp)-DOX (Ph-II)	Doxorubicin
NC-4016, PEG-P(Glu)DACHPt (Ph-I)	DACHPtb

CHARACTERISATION OF POLYMERIC MICELLES:

Characterization of polymeric micelles is a key step in achieving bioavailability. Because these molecules vary in size and solubility, they must be carefully examined to ensure their stability. In vitro drug behavior is used to evaluate polymeric micelles by determining their critical micellar concentration, size, and shape.

1. Critical Micellar Concentration:

It is a key component in the stability of polymeric micelles. CMC may be evaluated in aqueous micelle dispersion using several methods such as surface tension, X-ray scattering, differential scanning calorimetry, and fluorescence chromatography [20].

2. Determination of size and shape:

Using a quasi-elastic light scattering technique, the polydispersity index of prepared micellar solutions can be determined. A monodisperse micelle can provide blue color and aggregates can produce white color using the light scattering technique. If they are blue in appearance, the prepared micelle solution is acceptable[21]. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) techniques can be used to determine the size and shape of block copolymers. The direct visualization of block copolymer micelles in the dried or liquid condition is achieved using atomic force microscopy (AFM). Asymmetric flow field flow fractionation can be used

to measure the size of drug-loaded polymeric micelles. Small-angle neutron scattering was used to determine the structure of the micellar assembly[22].

3. In vitro drug release behavior:

In in vitro drug release study, a dialysis tube is used to hold the micellar solution. The dialysis bag is submerged in a flask holding medium, which maintains a consistent temperature.At different time intervals, some amount of the medium is removed and is replaced by a fresh medium. This removed medium is used to detect the concentration of drug released through spectroscopic methods [23].

4. Determination of solubilizing efficiency:

When compared to pure drug form, the solubilization ability of polymeric micelles was correlated to its enhancement capacity[24]. To evaluate the enhancement capability, the pure drug and polymeric micelles were suspended in distilled water, mechanically agitated, and centrifuged at a very high speed for 24 hours. After that, a UV Spectrophotometer was used to examine the filtrate collected from the drug.

5. Determination of particle size, polydispersity and zeta potential:

Dynamic light scattering was used to evaluate particle size, polydispersity, and hydrodynamic diameter. Atomic force microscopy techniques are used to determine the multi-model size distribution of polymeric micelles. Single, fused, and aggregate particles can all be distinguished using this technique.

6. Determination of polymeric micelle encapsulation efficiency:

The drug-loaded polymeric micelles were dissolved in alcoholic solutions, and micelles were dissolved with the help of the sonication process. The polymeric micelles are examined using a UV Spectrophotometer.

The encapsulation efficiency is determined using the following formula:

Encapsulation capacity = actual weight/ theoretical weight* 100

CONCLUSION:

Polymeric micelles have a desirable characteristic. As a result, it has become a significant pharmaceutical drug carrier. Polymeric micelles are very easy to make. Micelle preparation can be accomplished in several methods. Direct dissolution, solvent evaporation, and dialysis are some of the options. Polymeric micelles can be utilized to transport poorly soluble drugs, as well as to target malignancies, deliver genes, and increase bioavailability. The binding of ligands or antibodies to core-forming blocks can potentially be used to target cells. In chemotherapy treatments, polymeric micelles may be the most straightforward, versatile, and effective technique. The polymeric micelles can potentially be utilized to detect cancer in its early stages. As a result, polymeric micelles have a bright future in drug delivery.

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