CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.3925301

Available online at: http://www.iajps.com *Review Article*

POLYMERIC MICELLE AS A SMART DRUG CARRIER: A REVIEW

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Article Received: April 2020 **Accepted:** May 2020 **Published:** June 2020

Abstract:

One of the most widely needed study is related to the creation of Nano-sized molecule with well-defined structures and functionalities. These Nano molecular structures are generated as a result of self-assemblage of amphiphilic block polymers. Self-assembly of block polymers via hydrophobic and hydrophilic effects, electrostatic interactions, hydrogen bonding, and metal complexation has shown tremendous potential for creating such monomolecular structures with a wide range of applications. Polymeric micelles have gathered considerable attention in the field of drug and gene delivery due to their excellent biocompatibility, low toxicity, enhanced blood circulation time, and ability to solubilize a large number of drugs in their micellar core. Polymeric micelles have recently emerged as a novel promising colloidal carrier for the targeting of poorly water soluble and amphiphilic drugs. Polymeric micelles are considerably more stable than surfactant micelles and can solubilize substantial amounts of hydrophobic compounds in their inner core. Due to their hydrophilic shell and small size they sometimes exhibit prolonged circulation times in vivo and can accumulate in tumoral tissues. This review elaborate the chemical nature of polymeric micelles as well as the methods used to characterize them, Special emphasis is put on drug loading procedures, Potential medical applications. Polymeric micelles can be used as 'smart drug carriers' for targeting certain areas of the body by making them stimuli-sensitive or by attachment of a specific ligand molecule onto their surface.

Keywords: *Polymeric micelles, amphiphilic molecule, tumor targeting, self-assembly*

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Please cite this article in press Hrutuja Deepak Padge et al., ***Polymeric micelle as a smart drug carrier: A review,*** *Indo Am. J. P. Sci, 2020; 07(06).*

INTRODUCTION:

The change in physicochemical properties is associated with the orientation as well as association of amphiphilic molecules in solution that results in the formation of structures called micelles. The micelles internally have a hydrophobic core and externally a hydrophilic surface. Micelles are generally made up of 50 to 200 monomers (an average number of monomers forming micelle at any given time is termed as the aggregation number). The radius of a spherical micelle is almost the same as the length of a fully extended surfactant monomer, which mostly is 1-3 nm, and thus micelles lie in the colloidal range. Polymeric micelles help in delivering potent drug to where they are necessary [1]. Delivery of some drug is still challenging for clinician &pharmaceutical scientists. It is because most of potent drug are small molecule which diffuse freely through diseased cell this induces nonspecific drug distribution in the body. Polymeric micelles is macromolecular drug carrier help to improved efficacy with reduce toxicity [2].

Currently available macromolecular drug carriers may include- water soluble polymer, dendrimer, polymeric micelles, & liposome .among these carriers, only polymeric micelles undergo dynamic physicochemical changes during drug entrapment & drug release. Polymeric micelles are spherical supramolecular nano-assemblies prepared from self-assembling amphiphilic polymer. they feature a sub 100 nm core-shell structure, which provide a nano depot for hydrophobic drug enveloped with hydrophilic shell improving drug solubility [3].

Polymeric micelles are categorized into two group depending on drug loading method-
1) Physical drug entrapment type micelles.
2) Covalent drug conjugation type micelles.
Physical drug entrapment type micelles, they incorporate drug payload through the hydrophobic interaction in micelles core. Drug can be entrapped also in gel –like amorphous core [4].

In contrast, covalent drug conjugation type micelles, have drug binding linker that stably tether drug in micelles core until the polymeric micelles accumulate in the site of action. Covalent type micelles is found to be more stable than the physical type micelles. They have emerged as potential carrier for poorly water soluble drug because they can solubilize those drug in their inner core [5,6].

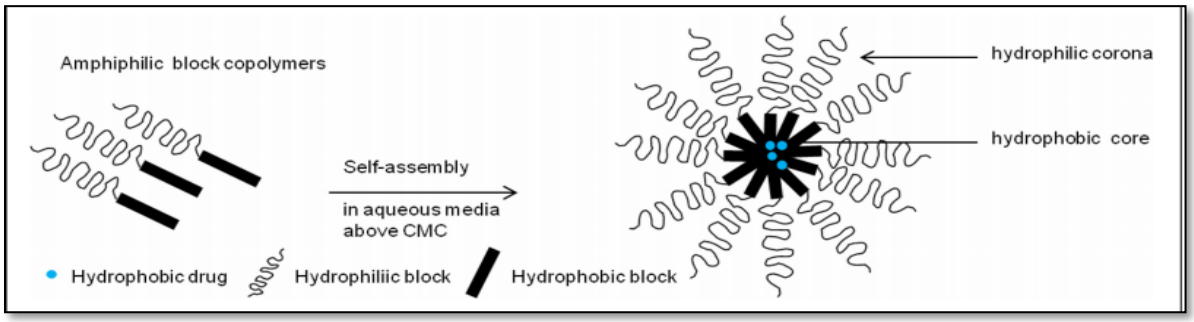

Figure 1: Structure of polymeric micelle

Chemical nature of polymeric micelles

Polymeric micelles are characterized by a core-shell structure. Pharmaceutical research on polymeric micelles has been mainly focused on copolymers having an A-B diblock structure with A, the hydrophilic (shell) and B, the hydrophobic polymers (core), respectively

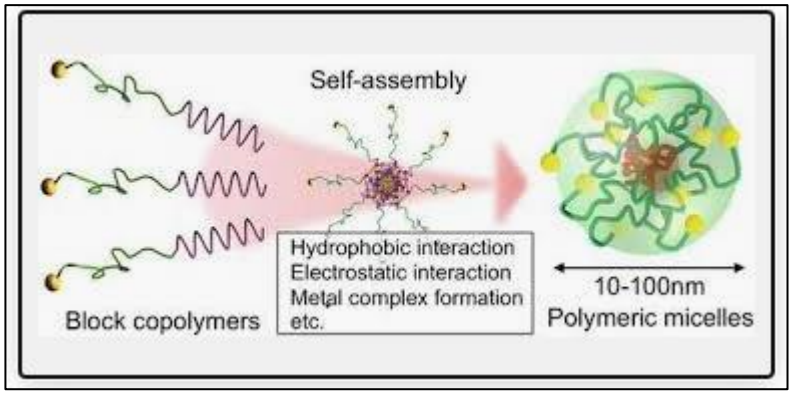

Figure 2: bonding in polymeric micelles

Multiblock copolymers such as e.g. poly(ethylene oxide)± poly(propylene oxide)±poly(ethylene oxide) (PEO±PPO± PEO) (A±B±A) are also self-organize in micelle and have as potential drug carriers .The hydrophobic core which generally consists of a biodegradable polymer such as poly(b-benzyl-l-aspartate) (PBLA) , poly(dl-lactic acid) (PDLLA) or poly(e-caprolac), serves as a reservoir for an insoluble drug, protecting it from contact with the aqueous environment. The core may also consist of a water-soluble polymer (e.g. poly (aspartic acid; P (Asp)) which is rendered hydrophobic by the chemical conjugation of a hydrophobic drug, or is formed through the association of two oppositely charged polyions (polyion complex micelles).The use of non-or poorly biodegradable polymers such as polystyrene (Pst) or poly (methyl methacrylate) (PMMA) are use as constituents of the inner core. These polymers offer interesting properties such as a glassy state which confers remarkable stability to the micelle core [7].

Non-biodegradable polymers must be non-toxic and have a molecular weight low to be excreted via the renal route .The hydrophobic inner core can also consist of a highly hydrophobic small chain such as an alkyl chain or a diacyllipid (e.g. distearoyl phosphatidyl ethanolamine (DSPE)) [8]. The hydrophobic chain can be either attached to one end of a polymer or randomly distributed within the polymeric structure. The shell is responsible for micelle stabilization and interactions with cell membranes. It usually consists of chains of hydrophilic non-biodegradable, biocompatible polymers such as PEO. The bio distribution of the carrier is mainly dictated by the nature of the hydrophilic shell. Other polymers such as poly (Nisopropylacrylamide) (PNIPA) and poly (alkyl acrylic acid) impart temperature or pH-sensitivity to the micelles, and could eventually be used for bio adhesive properties [9].

Amphiphilic block copolymers consist of multiple segment. Generally two or three segments are conjugated linearly to prepare amphiphilic block copolymers. Depending on the thermodynamic conditions, amphiphilic block copolymers may form nano structures such as lamellas, globules, cylinders, vesicles, and micelles. In particular amphiphilic block copolymers from hydrophilic and hydrophobic segments undergo spontaneous self-assembling in the aqueous solutions, sequestering hydrophobic segments from aqueous environments by hydrophilic segments. This phenomenon is useful to dissolve hydrophobic and fatty materials as likely seen in low molecular weight surfactants (LMWS) forming micelles [10]. Compared to LMWS micelles, polymeric micelles prepared from amphiphilic block copolymers are superior in stability and high capacity for the incorporation of drug molecules in the core. Although any types of amphiphilic block copolymers could form micelle structure, poly (ethylene glycol)-poly (amino acids) (PEG-PAA) block copolymers are possibly the most facile components to design the polymeric micelles. PEG is a biocompatible water-soluble polymer, which is widely used in the biopharmaceutical industry because of its excellent water solubility, chain mobility, and non-immunogenicity. PEG is non-toxic and can be cleared from the body through renal filtration with a molecular weight of less than 30,000. When it comes to PAA, it is also highly biocompatible, non-toxic, and economic with versatile functional groups such as hydroxyl, carboxyl, amino, and thiol groups. Such a variety of functional groups is of great benefit to modify the chemical structure of the core for drug conjugation [11].

Amino acids can be polymerized by traditional solid-phase peptide synthesis methods. One of the most common synthetic routes for polypeptide synthesis is polycondensation of monomers protected at one carboxyl and activated for polymerization at the other, followed by protecting group removal. A set of recursive protection/conjugation/deprotection process allows one to construct artificial PAA chains with theoretically unlimited sequences. For PEGPAA block copolymer synthesis, α-methoxy ω-amino PEG is generally used as a macro initiator [12].

In early studies, poly (ethylene glycol)-poly (β-benzyl L-aspartate) (PEG-PBLA) block copolymers are synthesized to prepare the polymeric micelles. The balance between PEG and PBLA segments is of importance to prepare stable polymeric micelles for certain therapeutic agents because the ratio between hydrophilic and hydrophobic segments directly influences self-assembly structures and stability.

Type of micelles

On the basis of the type of intermolecular forces governing the segregation of the core segment from the aqueous environment, polymeric micelles can be classified in three main categories-

1) Conventional
2) Polyion Complex Micelles
3) Non-covalently Connected Polymeric Micelles

1) Conventional

These micelles are formed by hydrophobic interactions between the core segment and the corona region in the aqueous environment. One of the simplest amphiphilic block copolymer, poly (ethylene oxide)-b-poly (propylene oxide)-bpoly (ethylene oxide), forms micelles as a result of 16 hydrophobic interactions [13].

2) Polyion Complex Micelles

Electrostatic interactions between two oppositely charged moieties, such as polyelectrolytes, also allows for the formation of polymeric micelles. When oppositely charged polymers are added in the solution, they can penetrate in the corona of the micelle and give rise to polyionic micelle. Such formed micelles are termed polyion complex micelles (PICMs).

The electrostatic forces and the van der Waals force of interaction control the structure and size of the charged micelle coronas. PICMs have some features such as simple synthetic route, easy self-assembly in aqueous medium, structural stability, high drug loading capacity, and prolonged circulation in the blood [14].

The preparation of micelles is carried out in aqueous medium without involvement of any organic solvents, thus removing the associated side-effects produced by the residual organic solvents. The core of the PICMs can entrap many therapeutic agents such as hydrophobic compounds, hydrophilic compounds, metal complexes, and charged macromolecules through electrostatic, hydrophobic, hydrogen bonding interactions and release them after receiving suitable trigger. Because of these reasons, the PICMs have a great potential for drug release, especially for the delivery of charged drugs [15,16].

Recently, polymeric micelles of methoxy poly(ethylene glycol)-grafted-chitosan encapsulating all-trans retinoic acid through the formation of a polyion complex between the amine group of chitosan and the carboxylic acid group of all-trans retinoic acid. The PICMs were designed for drug delivery to the brain tumor. The sizes of PICMs were about 50 to 200 nm and the loading efficiency 19 of micelle was higher than 80% (w/w) [17].

3) Non-covalently Connected Polymeric Micelles

A novel “block-copolymer-free” technique can also be used for preparing polymeric micelles. Here, polymeric micelles are obtained via self-assemblage of homopolymer, random copolymer, graft copolymer or oligomer for which interpolymer hydrogen bonding complexation serves as the driving force. Core and shell are non-covalently connected at their homopolymer chain end by specific intermolecular interactions such as H-bonding or metal-ligand interactions in the resultant structures and hence these are termed as non-covalently connected micelles. Prepared the intermolecular complexes with poly (4-vinylpyridine) as the backbone and carboxyl terminated polybutadiene as the grafts due to hydrogen 21 bonding in a common solvent, chloroform [18].

Types of polymer use

Micelle forming amphiphilic copolymers can be either block copolymers (di, tri, or tetra) or graft copolymers. A graft copolymer is one which comprises a polymer chain as a backbone and another polymer chain as side "grafted" parts shown in table1 [19].

Type of micelle forming copolymer	Representation of structure	Example of polymers
Block copolymer	di-block AAAAAAABBBBBBB	Poly(styrene)-poly(ethylene oxide)
	Tri-block AAAABBBBBAAAAAA	Poly(ethylene oxide)b-poly (propylene oxide)-b-poly(ethylene oxide)
Graft copolymer	AAAAAAAAAAAA B B B B B B B	N-phthaloylchitosan-g-polycaprolactone

Table 1: Type of the polymers

A-Hydrophilic copolymer

B-Hydrophobic copolymer

Example of polymer

SR.NO	EXAMPLE OF POLYMER
1	N-phthaloylcarboxymethylchitosan
2	Poly(2-ethylhexyl acrylate)-b-poly(acrylic acid)
3	Poly(tert-butyl acrylate)-b-poly(2-vinylpyridine)
4	Poly(e-caprolactone)-b-poly(ethylene glycol)-b-poly(e-caprolactone)
5	Poly(e-caprolactone)-b-poly(methacrylic acid)
6	Poly(ethyleneglycol)-b-poly(e-caprolactone-co-trimethylenecarbonate)
7	Poly(aspartic acid)-b-polylactide
8	Poly(ethylene oxide)-b-polycaprolactone
9	Poly(ethylene glycol)-block-poly(aspartate-hydrazide)
10	Poly(N-isopropyl acrylamide-co-methacryl acid)-g-poly(D,L-lactide)
11	Stearic acid-grafted chitosan oligosaccharide

Table 2: Example of polymer

Mechanism of polymeric micelle

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, a repulsive force, 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.

The micellization process of amphiphilic copolymers is similar to the process described for low molecular weight surfactants. At very low concentrations, the polymers only exist as single chains. As the concentration increases to reach a critical value called the critical micelle concentration (cmc), polymer chains start to associate to form micelles in such a way that the hydrophobic part of the copolymer will avoid contact with the aqueous media in which the polymer is diluted [20].

At the cmc, an important quantity of solvent can be found inside the micellar core and micelles are described as loose aggregates which exhibit larger size than micelles formed at higher concentrations. At those concentrations, the equilibrium will favor micelle formation; micelles will adopt their low energy state and the remaining solvent will gradually be released from the hydrophobic core resulting in a decrease in micellar size. Amphiphilic copolymers usually exhibit a cmc much lower than that of low molecular weight surfactants. Some amphiphilic copolymers exhibit much higher cmc, reaching values up to 0.01±10% in the case of poloxamers [21].

Amphiphilic with high cmc may not be suitable as drug targeting devices since they are unstable in an aqueous environment and easily dissociate upon dilution. The micellization of amphiphilic copolymers can result in two different types of micelles depending on whether the hydrophobic chain is randomly bound to the hydrophilic polymer or grafted to one end of the hydrophilic chain. Micelles from randomly modified polymers are smaller than end-modified polymers. The micellar size is mainly determined by the hydrophobic forces which sequester the hydrophobic chains in the core and by the excluded volume repulsion between the chains which limits their size, a difference in the balance of these two forces in random and end-modified copolymers may account for their different size [22]. When terminal hydrophobic groups associate to form micelles, the water clusters immobilized around the hydrophobic segments are excluded from the core and no direct interaction exists between the core and the hydrophilic shell which remains as mobile linear chains in the micellar structure. Randomly modified polymers,

however, associate in such a manner that hydrophobic and hydrophilic parts of the polymer are entangled together allowing possible contact between the core and the aqueous media [23].

Characterization of polymeric micelle

1) Determination of critical micelle concentration

The cmc can be determined by several methods. Theoretically, any physical property (e.g. interfacial tension, conductivity, osmotic pressure) that shows sudden changes at or near the cmc could be used. Usually, variation in the plot of such properties as a function of concentration is used as an indicator of the onset of micellization. However, for polymeric micelles, the cmc is generally too low to be determined by such methods.

A preferred method to determine the cmc involves the use of fluorescent probes. Among which pyrene is the most widely used. Pyrene is a condensed aromatic hydrocarbon that is highly hydrophobic and sensitive to the polarity of the surrounding environment. Below the cmc, pyrene is solubilized in water, a medium of high polarity. When micelles are formed, pyrene partitions preferentially toward the hydrophobic domain afforded by the micellar core and thus, experiences a non-polar environment. Consequently, numerous changes such as an increase in the fluorescence intensity, a change in the vibrational structure of the emission spectra and a red shift of the (0, 0) band in the excitation spectra, are observed. a parent cmc can be obtained from the plot of the fluorescence of pyrene [24].

2) Molecular weight and aggregation number

Light scattering is widely used for the determination of the molecular weight and aggregation number of micelles. However the onset of micellization can be detected only if the cmc falls within the sensitivity of the scattering method which is rarely the case for polymers in water. Gel permeation chromatography (GPC) under aqueous conditions can be employed since single chains and micellar chain fractions of copolymers exhibit different elution volumes. Adsorption of the polymer on the column may prove to be a problem, especially at concentrations close to the cmc, where micelles consist of large loose aggregates [25].

3) Size and Shape Determination

After the preparation of the micelles useful information regarding the polydispersity index of the prepared structures is obtained by examining the micellar solution with quasielastic light scattering technique. Monodisperse micelles produce blue colour from light scattering which indicates good micellar preparation, as contrasted with the white colour shown by aggregates. Size of polymeric micelles usually falls in the colloidal range [26].

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) techniques have been widely used past many years for the direct visualization, size and shape determination of block copolymer micelles. The more recently developed cryo-TEM technique has increasingly started gaining importance for characterization of block copolymer micelles in aqueous medium. SEM or atomic force microscopy (AFM) reveals information regarding size distribution when chemically attached micelles to surfaces are presented. Direct visualization of block either in the dried state or directly “in situ” within a liquid cell can be achieved by AFM. Hydrodynamic diameters and polydispersity indices of micelles are obtained using photon correlation spectroscopy. Recently size characterization of drug-loaded polymeric micelles was done using asymmetrical flow field-flow fractionation and the structure of assemblies was determined by small angle neutron scattering [27].

4) Intrinsic viscosity of the micellar core

The viscosity of the micellar core may influence the physical stability of the micelles as well as drug release.The intrinsic viscosity of the hydrophobic core, or micro viscosity, can be determined by using fluorescent probes such Dipyre is sensitive to both polarity and viscosity changes in its local environment [28].

1H-nuclear magnetic resonance (NMR) also provides some information on the viscosity of the micellar core .The copolymers are usually dissolved in D2O and in a solvent where micelle formation is not expected and where all the peaks proper to the hydrophilic and hydrophobic part of the polymer can be detected (e.g. CDCl3). In D2O, the presence of micelles with a highly inner viscous state results in a restricted motion of the protons within the micellar core as demonstrated by the weak signals associated with the hydrophobic part of the copolymer. Highly viscous states were found to exist in PEO-PDLLA and PEO-PBLA micelles [29].

***5) In Vitro* Drug Release Behaviour**

In-vitro drug release behaviour from micelles is easily studied by placing the micellar solution in a dialysis tube. The dialysis bag is immersed into a flask containing release medium, kept at a constant temperature. At predetermined time intervals, aliquots of the release medium are taken and replaced by fresh medium. The content of drug released in the medium can be measured by spectroscopic or other suitable method [30].

Preparation of Drug-loaded Micelles

Drug-loaded polymeric micelles can be prepared mainly by three common approaches:

Direct dissolution

Solvent evaporation

Dialysis.

1) Direct dissolution

Direct dissolution of the amphiphilic copolymer and drug in water is the simplest technique of preparing drug-loaded polymeric micelles. At or above CMC, the copolymer and the drug self-assemble in water to form drug-loaded micelles. But this method usually is associated with low drug loading. To enhance drug loading, this technique can be combined with an increase in temperature or alternately a thin evaporated film of drug can be prepared before the addition of copolymer [31].

2) Solvent evaporation

In solvent evaporation or solution-casting technique, a volatile organic solvent is used to dissolve the copolymer and the drug. A thin film of copolymer and drug is obtained after the solvent is removed by evaporation. Drug-loaded polymeric micelles are obtained by reconstitution of film with water. When the core forming blocks are long and more hydrophobic, the two above-mentioned techniques are unsuitable. Micelles from such copolymers have more potential to solubilize large amounts of poorly water-soluble drugs. In these cases, the dialysis technique can be used to prepare drug-loaded micelles [32].

3) Dialysis

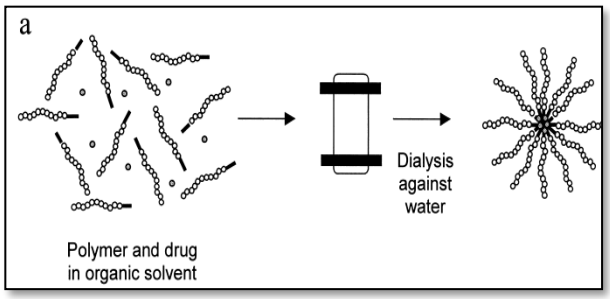

Figure 3: Drug loading by dialysis

Solutions of the drug and the polymer in organic solvent are placed in the dialysis bag, and the solvent is exchanged with water by immersing bag into water, inducing micelle assembly. However, emulsification involving use of chlorinated solvents is not safer and dialysis process often requires more than 36 hours for efficient loading.

Nevertheless, the above mentioned limitations can be overcome by employing a simple and cost-effective method in which water/tert-butanol mixture is used for dissolving drug as well as polymer and then the solution is lyophilized. Drug-loaded polymeric micelles are then obtained by redisposing the lyophilized product in a suitable vehicle [33].Owing to extreme dilutions by blood upon intravenous injections of 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. The loss of hydrophilic and hydrophobic balance upon increased loading of hydrophobic moiety (drug) into the core region also has been related to decreased stability of the polymeric micelles. Drugs or copolymers prone to hydrolytic cleavage in aqueous systems may as well pose stability problems. However, lyophilized polymeric micelle formulations have shown to possess improved long-term stability for intravenously administered preparations [34].

Stimuli-responsive polymeric micelle

Colloidal carriers are frequently used to transport and deliver drugs through the body for the reason of protecting the drug against degradation and/or excretion, to prevent adverse side effects of toxic drugs, or to accomplish targeted drug delivery. Examples of such carriers are micro/Nano spheres, polymer–drug conjugates, liposomes, and (polymeric) micelles. They have been emerging as a convenient carrier system. Polymeric micelles are formed in aqueous solution from amphiphilic block or graft copolymers. They contain hydrophobic segments, which form the core of the micelles, while the soluble segments form the corona, Polymeric micelles have been used to carry hydrophobic drugs, which are physically entrapped in and/or covalently bound to the hydrophobic core [35].

Usually, physical entrapment is achieved by electrostatic interaction between drug and polymer (the resulting particles are called polyion complex (PIC) micelles), by dialysis from an organic solvent, or by oil-in-water emulsion procedures. For drug delivery purposes, large variations in the composition of the core have been reported, e.g. polyesters, poly (amino acids), poly (meth) acrylates, and poly (acrylamides). However, the corona has almost exclusively been constituted from poly (ethylene glycol) (PEG), because it is a highly biocompatible polymer which show little or no undesirable interactions with proteins and cells. PEG is frequently used to 'shield' colloidal drug carriers from its environment in order to extend the residence time in the blood circulation. There are a number of reasons why polymeric micelles are interesting as drug carriers [36].

As a solubilizing agent for hydrophobic drugs they have a clear advantage over low molecular weight surfactants in view of the higher stability of the micelles. This higher stability is reflected in terms of the usually very low critical micelle concentration (CMC) of polymeric surfactants. This means that polymeric micelles are resistant to dilution effects,

upon for example i.v. administration of the drug formulation. Another important characteristic of micelles, when compared with, e.g. microspheres or many liposomal formulations, is their small and uniform particle size. In theory, particle sizes can go down to the order of 10 nm for non-loaded polymeric micelles. This size is still large enough to accomplish passive targeting to, e.g. tumors and inflamed tissues by the so-called enhanced permeation and retention (EPR) effect. The hydrophilic corona of the micelles may prevent interaction with blood components. This characteristic and their small size will prevent recognition by proteins and macrophages, and thus long circulation times in the blood stream may be achieved. Finally, active targeting is possible by modifying the peripheral chain ends of the polymers with targeting ligands. For the release of the drugs once the micelles have reached their targets, degradable or stimuli-responsive micelles have been developed. Since many photosensitizers usually display some toxicity against healthy cells and tissues, carriers are preferentially required to deliver them at the pathogenic sites by passive or active targeting. Since many photosensitizers are insoluble in water, polymeric micelles are useful as a solubilization and delivery vehicle [37].

Mechanism and some examples of stimuli-responsive micelle [38, 39]

Internal Stimuli

Micelle components	Payload	Stimulus	Mechanism
Chondroitin sulfate-histamine	Doxorubicin	pH	Protonation of His residue alters the hydrophilic-hydrophobic balance of CS-His conjugate to release DOX at low pH
Poly(ketal adipate)-co-PEG (PKA-PEG)	Camptothecin/Nile red	pH	Ketal linkages in the backbone cleaved under acidic pH to release payloads
mPEG–PCL–CH2R4H2C (cell penetrating peptide)(C:Cys, H:His, R:Arg)	VEGF siRNA	GSH (redox)	siRNA condensed in micelles through disulfide links via Cys (in CPP) released upon S-S cleavage in cytoplasm
siRNA-SS-Poly(D,L-lactic co-glycolic acid)/linear PEI	GFP siRNA	GSH (redox)	Reductive cleavage of disulfide bond to release GFP siRNA in cytoplasm
PEG-*b*-poly(2-methyl-2-carboxyl- propylene carbonate)-*g*-Gemcitabine-*g*-dodecanol (PEG-*b*-PCC-*g*-GC-*g*-DC)	Gemcitabine	Enzyme Cathepsin B	Cathepsin B cleaves amide bonds used to conjugate drug to polymer and enhances release, or acts on amide bonds in hydrolytically dissociated micelles to release free drug
PEG-b-poly(L-glutamic acid)-*b*-poly(L-phenylalanine) (PEG-*b*-PGlu-*b*-PPhe)	Cisplatin (CDDP) and paclitaxel	Enzyme Cathepsin B	Cathepsin B induced disintegration of polypeptide based building blocks in micelles to release drugs, also facilitated by pH

Table 3: Internal stimuli- responsive polymeric micelle and mechanism

External Stimuli

Micelle components	Payload	Stimulus	Mechanism
Pluronic F105 (PEO-PPO-PEO)	Doxorubicin	Ultrasound	70 kHz ultrasound induced transient cavitation led to micelle disruption to release DOX
Hetero-assembly of mPEG-b-P(L-lysine) micelles with siRNA and gas cored liposomes to form siRNA nanobubbles (NB)	SIRT2 siRNA	Ultrasound	Low freq. ultrasound induced cavitation of siRNA-nanobubbles (NB) to release siRNA-micelles from NB and deliver them to the cell cytoplasm by a sonoporation effect
Folic acid/dextran-retinoic acid	Doxorubicin and magnetic NPs	Magnetic field	Localization and internalization of micelles in cells driven by MNPs in response to external magnetic field (0.42T)
PEG-*b*-PCL	Doxorubicin and SPIO	Magnetic field	Hyperthermia due to heating of SPIO caused DOX release from micelles
P-(NIPAAm-co-NHMAAm)-b-PCL	Doxorubicin	Thermo- responsive	Increased DOX release above LCST(38◦C) due to hydrophilic to the hydrophobic transition in the poly-(NIPAAm-co-HMAAm) shell resulting in collapse of micelle structure
PEC micelles assembled from chitosan-g-PNIPAAm and carboxymethyl cellulose-g-PNIPAAm	5-fluorouracil	Thermo- responsive also pH	Deformation of micelles and controlled release of5-FUaboveLCST(37◦C)
PEO-*b*-P(LGA-*co*-COU)	Paclitaxel/Rifampicin	NIR Light	wo-photon absorption of NIR light by coumarin moiety causes shift in the hydrophilic-hydrophobic balance toward destabilization of micelles to release drugs
Dialkoxycyanostilbene polymethacrylate-*b*-PEO (PDACS-b-PEO)	Curcumin	UV light	T rans-cis photoisomerization of stilbene upon UV irradiation reduces hydrophobicity of polymer and disrupts micelles to release curcumin

Table 4: External stimuli-responsive polymeric micelle and mechanism

Application

1) Solubilization

The micellar core is a compatible micro-environment and a hub for incorporating water-insoluble guest molecules. The hydrophobic molecules can be covalently coupled to the block copolymers or physically incorporated into the hydrophobic core of micelles. The solubilization process leads to enhancement of their water solubility and thereby bioavailability. It is often observed that the gastrointestinal (GI) uptake of particles is affected significantly by particle size.

A 15 to 250-fold higher uptake efficiency of particles approximately 100 nm in diameter by the GI tract was noted than that of the micrometer-sized particles. Thus, polymeric micelles (nanosized) elevate uptake and enhance bioavailability [40].

The extent of solubilization depends upon the micellization process, the compatibility between the drug and the core forming block, chain length of the hydrophobic block, concentration of polymer, and temperature. Above CMC, there is a sharp increase in the solubility of drug as it gets more space to occupy in the aggregates of the hydrophobic part of the micelle. The occupancy of the core region by drug leads to an increased Rc of the micelle.

E.g. The influence on solubilisation capacity of hydrophobic block length has been examined for griseofulvin in polyoxyethylene and polyoxybutylene copolymer micelles with varying number of hydrophobic block lengths and hydrophilic block lengths sufficient for formation of spherical micelles. It was found that the solubilization capacity was dependent on the hydrophobic block length upto a certain extent (15 units of hydrophobic block), after which the solubilization capacity became independent of the same [41].

Drug	Amphiphilic polymer	Comment
Camptothecin	Pluronic P105, d- á -tocopheryl polyethylene glycol 1000 succinate	increased micellar stability; increased cytotoxicity
Docetaxel	Poly(ethylene oxide)-blockpoly(styrene oxide) (PEO-b- PSO) and PEO-b-poly(butylene oxide) (PEO-b-PBO)	PSO-based copolymers were associated with higher solubilizing capacities than PBO due to the aromatic structure of the core forming polymer
Griseofulvin	E B copolymers (E = oxyethylene, m n B = oxybutylene, subscripts denote number-average block lengths in repeat units)	solubilization independent of B block length when it exceeds about 15B units
Paclitaxel	N-octyl-O-sulfate chitosan	improved bioavailability and reduced toxicity
Paclitaxel	mixed micelles of polyethylene glycol-phosphatidyl ethanolamine (PEG-PE) and vitamin E	mixed micelles efficiently solubilized poorly soluble drug as compared to PEGPE micelles

Table 5: Example of improvement of solubility of some drug by polymeric micelle

2) Enhanced Permeability and Retention Effect (EPR Effect)

Owing to their nanoscopic size, polymeric micelles passively accumulate at the interstitial spaces of various pathological sites by extravasating leaky capillaries (especially of solid tumors). They also have been shown to distribute to some of the cytoplasmic organelles, and infarct tissues, infected areas, inflammatory sites that have compromised barrier function. As the polymeric micellar drug carriers cannot pass through walls of normal blood vessels, and decreased side-effects of the drug are observed. In tumor neovasculature, there is a poorly developed lymphatic drainage system that leads to enhanced retention of polymeric micelles within the solid tumor as micelles are not efficiently cleared. This feature allows prolonged circulation of polymeric micelles in the circulatory system upon administration. Due to these characteristics, it is possible to achieve passive drug targeting using polymeric micelles [42].

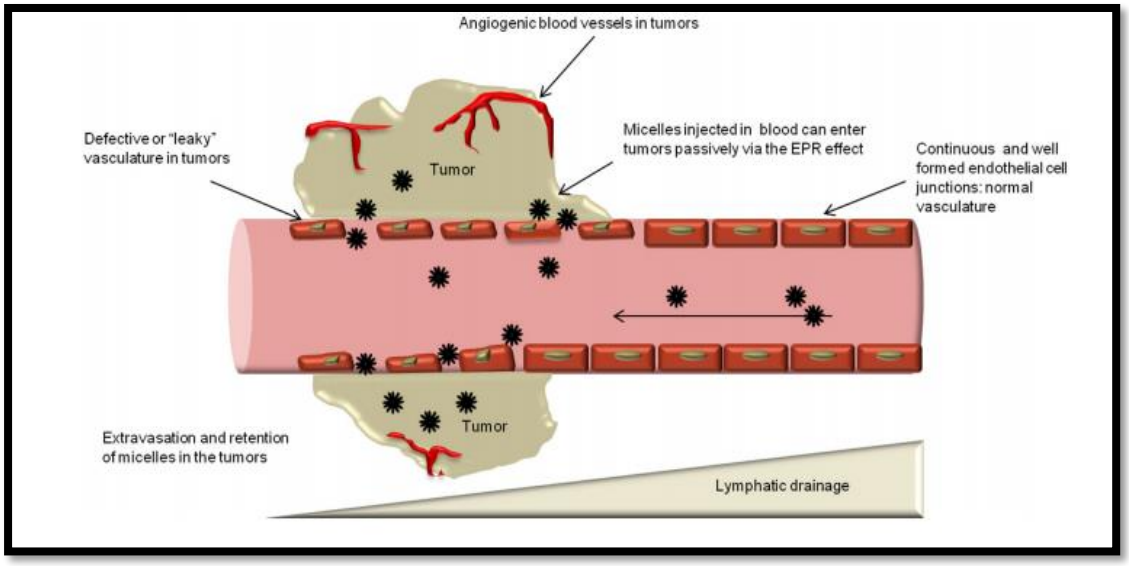

Figure 4: Enhanced Permeability and Retention Effect (EPR Effect)

3) Stimuli-Sensitivity

For ideal drug targeting, there should not be any drug release from the micelle during circulation. The drug should be released only after the polymeric micelles accumulate at the targeted tissue, by means of some internal trigger such as pH, particular enzyme, etc. or by an external trigger including temperature, light, ultrasound or magnetic field. Depending on the stimulus applied varied responses may be observed including disruption of the structure, changes in shape, volume, permeation rates, hydration state, swelling/collapsing, hydrophilic/hydrophobic surface, or conformational changes. Destabilization of micelles as a result of stimulation by either physiological or external trigger is termed as 'stimuli-sensitivity' or 'environmental-sensitivity' of the micelles [43].

4) Thermosensitive Polymeric Micelles

The thermosensitive micelles undergo a structural change as a response to temperature increase, resulting in the deposition of the drug and easier drug absorption by cells. Thermosensitive polymers at a certain temperature produce a volume phase transition associated with a sudden change in the solvation state. This transition temperature is termed as critical solution temperature. Polymers solubilized upon heating possess an upper critical solution temperature, and those which become insoluble possess lower critical solution temperature (LCST). Temperature changes can be internal, e.g. hyperthermia during inflammation, or can be external [44].

5) Complexing Targeting Ligand Molecules to Micelles

An impressive strategy to enhance cellular internalization of polymeric micelles at desired target tissue is attachment of cell-specific ligands on the surface of these nanocarriers. Thus, covalent attachment of cell specific ligands,

E.g. Sugars, peptides, and monoclonal antibodies, on the surface of polymeric micelles has been pursued to enhance drug delivery to various cells [45].

6) Acid-Sensitive Polymeric Micelles

There are a number of pH gradients that exist in normal and pathophysiological states inside the body. Acid-sensitive or pH-sensitive polymeric micelles exploit these differences in pH for drug targeting. In tumors and inflammatory tissues a mildly acidic pH is encountered (pH approx. 6.8). This is a slightly low value as compared with the pH of blood and normal tissues (pH approx. 7.4). Micelles can also be taken up into the cell by the process of endocytosis and may as well enter cell organelles as endosomes, lysosomes, etc. The pH value inside these organelles is nearly 5.5. This has served as the basis for the development of pH-sensitive polymeric micelles. E.g. negatively charged oligo/poly (nucleic acids) can be delivered intracellularly by complexing them with cationic polymers. Once into endosomes, these are deprotonated causing disruption of endosomal membrane and releasing nucleic acids in the cytosol [46].

CONCLUSION:

In summary, the drug loaded polymeric micelles can be utilized as nanometer-sized vehicles for hydrophobic drug molecule. Studies to date suggest that polymeric micelles solubilize hydrophobic anticancer drugs. Because of their distinct advantages, such as small size, high solubility,

simple sterilization, controlled release of drugs, polymeric micelles seem to be the prototype of an ideal carrier for poorly water soluble drugs. However, the physical stability of this carrier is a critical issue since rapid release of the incorporated drug may occur in vivo. Still much work remains to be done in order to design micelles which will be able to deliver a drug to its site of action. Preparation of polymeric micelles appears to be relatively simple as compared with the other novel drug delivery systems. Polymeric micelles can be easily loaded with a wide variety of poorly soluble drugs, thus resulting in enhanced bioavailability of these drugs. Importantly, these can be effectively used to target certain pathological areas in the body with compromised vasculature such as tumors, infarcts because of their size and EPR effect. Targeting can also be achieved by attaching specific ligands or specific antibodies onto their surface. Thus polymeric micelles, as drug carriers have a promising future.

Acknowledgement

I am thankful to my guide Principal. Dr. Mrs. Sudha Rathod, Department Of Pharmaceutics, Oriental College of Pharmacy, Sanpada, Navi Mumbai, supports for doing this review work.

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