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Review Article

POLYMERIC MICELLES: POTENTIAL DRUG DELIVERY DEVICES

Upendra Nagaich, Payal Deepak*, Aman Sharma, Neha Gulati, Amit Chaudhary

Dept. of Pharmaceutics, Bharat Institute of Technology, By-Pass Road, Partapur, Meerut-250103 (U.P.) India

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*Corresponding author
Payal Deepak

Email : payaldeepakmiet.07 @gmail.com

ABSTRACT

Polymeric micelles (PMs) have been the most popular and promising topic of many researches in the field of drug delivery and targeting for the past two decades. Polymeric micelles are the self-assembled nano-sized colloidal particles which are made up of amphiphilic block copolymers i.e. polymers consisting of hydro-phobic block and hydrophilic block. In this highlight, we give an overview of the structure of micelles and polymeric micelles followed by a summary of the methods used for their preparation. We then focus on several kinds of PMs based on intermolecular forces such as polyion complex micelles (PICMs), non-covalently connected micelles (NCCMs) and recently developed smart polymeric assemblies which can respond to the application of external stimuli such as a change in temperature, pH, redox and light to afford novel nanomaterials. The types of polymers used in the preparation of PMs have also been highlighted so as to facilitate its use in drug delivery and targeting. These polymeric micelles nanocarriers have applications in drug delivery primarily such as anticancer therapy, to the brain to treat neurodegenerative diseases, antifungal agents, stimuli-responsive nanocarriers for drug and gene delivery, ocular drug delivery. Targeted drugs will hopefully reduce adverse reactions by limiting their action to cancer tissue only. Finally, this review broadly presents the basic aspects of PMs which help in delivery and targeting of actives with its recent advancements and applications.

Key words: micelles, polymeric micelles, block copolymer, stimuli sensitivity

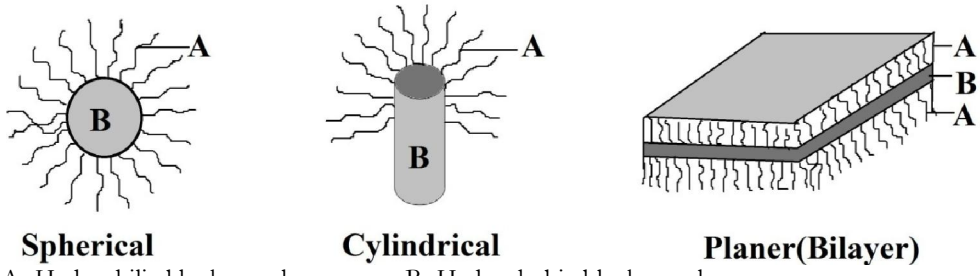
INTRODUCTION

There has been a progressively increasing attention and demand for development of drug delivery systems which are not only highly efficient but also site-specific (Scholz *et al.,* 1998). Colloidal nanocarriers including nanoparticles, micelles and liposome are one of the drug delivery system which fulfills the criteria of site specificity and targeting. Polymeric Micelles (PMs) are particulate colloidal carrier system which get self-assembles in aqueous media and are made up of linear amphiphilic macromolecules possessing both hydrophilic 'blocks' and hydrophobic 'blocks' (AB-type) on a single strand (each copolymer strand is amphiphilic). These polymeric micelles possesses the particle sizes range between 10–100 nm which making them considerably smaller than phospholipids vesicles (liposomes) (Trubetskoy, 1999). In addition to being safe these drug delivery system must possess high loading capacity, extended circulation time and accumulation in the required pathological sites (Moghimi *et al.,* 2001, Couvreur and Vauthier, 2006).

Basically, two primary factors which influence the efficacy of drug delivery system by block copolymer aggregates are temporal and distribution controls. The former term refers to the time required and the process to release the drug molecules from the inside of micelle core to the target and the later term is associated with the drug molecules which get distributed to the target site and accumulated in these special regions without getting lost in other parts of the circulation system. Recently, polymeric micelles have been attracted because of increased attention as a promising vehicle for poorly soluble drugs (Rosler *et al.,* 2001., Wang *et al.,* 2008).

Micelles

Surfactants play a major role in many processes of interest in both fundamental and applied science. The construction of colloidal-



A- Hydrophilic block copolymer B- Hydrophobic block copolymer

Figure 1. Different shapes of micelles

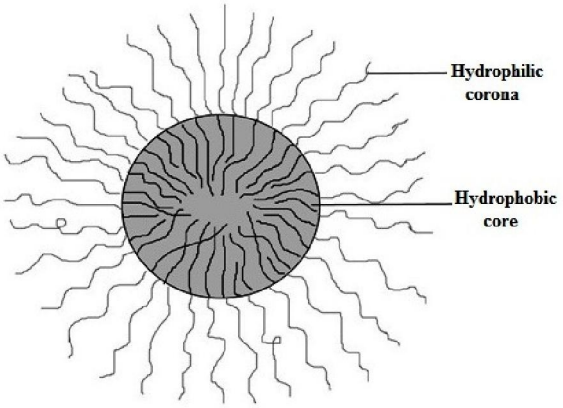


Figure 2. Structure of polymeric micelle

sized clusters in solutions is one of the most important uniqueness of surfactants which is termed as micelles. These micelles possess particular significance in pharmaceutical field because of their capability to increase the solubility of sparingly soluble substances in water. Formation of micelles takes place when surfactant molecules are dissolved in water at concentrations above the critical micelle concentration (CMC) (Mall *et al.,* 1996). CMC is defined as the concentration of surfactants above which micelles form and almost all additional surfactants added to the system go to micelles (Allen *et al.,* 1999).

Micelles consist of amphiphiles or surface-active agents i.e. surfactants, which have two different parts: a hydrophilic head-part and a hydrophobic tail part (Dhembre *et al.,* 2011). The radius of a spherical micelle is almost same as the length of a fully extended surfactant monomer i.e. 1-3 nm and thus, micelle lie in the colloidal range (Mourya *et al.,* 2011). Micelles are unstable or labile colloidal clusters, formed when the several individual surfactant monomers are aggregated by noncovalent bond. Therefore, micelles may be spherical, cylindrical, or planar (discs or bilayers) as shown in figure 1. The shape and size of micelles can be controlled by changing the surfactant chemical structure as well as by varying solution conditions such as temperature, composition of surfactant, concentration of surfactants, ionic strength and pH (Yagui *et al.,* 2005). Depending on the targeting site, one can select the size, charge, and surface properties of these carriers by adding new ingredients to the mixture of amphiphilic substances before micelle preparation and/or by variation of the preparation method (Yokoyama *et al.,* 1990., Lee and Yamamoto, 1990., Torchilin, 2001).

The key driving force behind self-association of amphiphilic molecules is the decrease in free energy of the system and this decrease in free energy is a result of removal of hydrophobic fragments from the aqueous surroundings with the formation of a micelle core stabilized with hydrophilic fragments

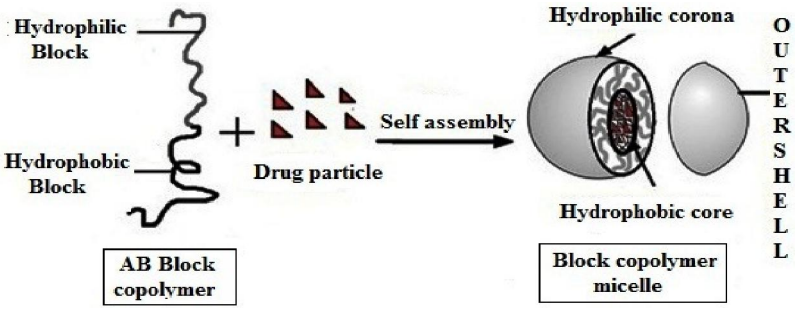


Figure 3. Self-assembly of hydrotropic block copolymer into polymeric micelle

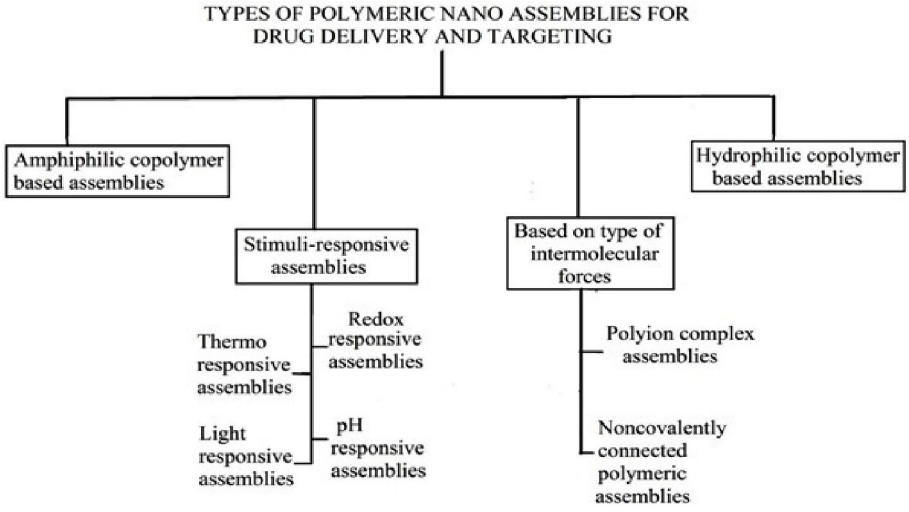


Figure 4. Flowchart illustrated various types of polymeric nanoassemblies

exposed into water (Mourya *et al.,* 2011). The major advantage of Micelles is its ability to solubilize poorly soluble drugs. Once its solubility get increased, the absorption of drug in body will also be enhanced which results in increased bioavailability. Another interesting fact about micelle is to its small size which allows them to accumulate in areas which have leaky vasculature and can circulate long enough in the body (Torchilin, 2001).

Polymeric micelles

Polymeric micelles are nano-sized colloidal carrier system which comprise of polymer chains. These are spontaneously formed by self-assembly in a liquid, generally as a result of hydrophobic or ion pair interactions between polymer segments. Micelles usually have a core-shell structure, in which core contains either the hydrophobic part or the ionic part of the nanoparticles, and can posses either small or bigger molecules such as therapeutic active drugs, while the shell provides interactions with the solvent and construct the nanoparticles which is stable in the liquid (Nostrum and Cornelus, 2012), the structure is shown in figure 2.

Polymeric micelles are formed from amphiphilic block copolymers which comprises of both hydrophilic and hydrophobic monomer units, such as PEO and PPO (polypropylene oxide), respectively. A schematic diagram of the formation of micelles from an amphiphilic molecule and the loading of hydrophobic drugs are shown in figure 3. With the length of the hydrophilic, block exceeding the length of the hydrophobic block and these amphiphilic block co-polymers can form spherical micelles in

aqueous solution (Kwon and Katarka, 1995). Polymeric micelles possess the following characteristic such as water solubility, lack of long-term accumulation in host, non-toxicity, non-immunogenicity, in vivo stability and selective delivery to the target site for valuable drug delivery (Adams *et al.,* 2003).

There are a few factors which control the size of the polymeric micelles which include molecular weight of the amphiphilic block copolymer, relative proportion of hydrophilic and hydrophobic chains, aggregation number of the amphiphiles, and the preparation process (Jones and Heroux, 1999). Moreover, polymeric micelles are generally much more superior to the surfactant micelles by exhibiting slower dissociation rates, lower critical micelle concentrations (CMCs), and longer retention of loaded therapeutic drugs (Torchilin, 2002). Polymeric micelles may lead to the development of 'intelligent vesicles' by the use of stimuli-sensitive polymers i.e. pH or temperature sensitive copolymers. Such intelligent vesicles are at present being explored for achieving controlled drug release (Otsuka *et al.,* 2003). Polymeric micelles provide a powerful multifunctional platform for the delivery of therapeutic drugs and diagnostic imaging applications (Ai *et al.,* 2005). Because of the multifunctional nature of polymeric micelles, it appears to fulfill a number of tasks essential for an ideal carrier capable of selective drug delivery at different levels (Li *et al.,* 1999., Kataoka *et al.,* 1993., Klaikherd *et al.,* 2009).

TYPES OF POLYMERIC MICELLES

Several types of polymeric assemblies are fabricated for drug delivery at the target sites. These are illustrated in the form of flowchart in figure 4 and discussed below in detail.

Amphiphilic copolymers based assemblies

Most of the polymeric micelles used for drug delivery and targeting are fabricated by amphiphilic copolymers, in which one or more hydrophobic blocks are covalently linked with one or more hydrophilic parts. It can be seen that various polyesters are widely engaged as hydrophobic blocks which including polylactide(PLA), poly (lactide-co-glycolide) (PLGA), poly (lactide-co-caprolactone), poly (*p*-dioxanone), poly (*p*-dioxanone-co-lactide), and polyorthoester. Water soluble polymers including polyalkylene glycols, polyvinyl alcohol (PVA), poly*N*-(2- hydroxypropyl) methacrylamide (PHPMA), poly (*N*-vinylpyrrolidone) (PVP), poly (acrylic acid) and polyacrylamides are widely employed as hydrophilic block (Zhanga *et al.,* 2009).

For hydrophobic compounds, amphiphilic copolymers based assemblies are most suitable carriers. An amphiphilic block copolymer of PEG-*b*-poly (aspartic acid) chemically conjugated with Dox is the micelles preparation which is intensively studied in Kataoka's lab. This polymeric micelle can efficiently entrap free Dox in the inner core, and the augmented preparation called NK911 which is now under a phase II clinical assessment (Matsumura *et al.,* 2004).

Hydrophilic copolymers based assemblies

Kataoka *et al* reported the first drug delivery system fabricated by a hydrophilic copolymer and drug molecule 'Cisplatin', an anticancer drug which interacts with a hydrophilic block copolymer of PEG-b-poly (aspartic acid) to form nano-assemblies via the metal ligand coordination between platinum and carboxylic acid groups (Yokoyama *et al.,* 1996). Currently, host-guest interactions have been implemented to make core-shell nano-assemblies via a double hydrophilic copolymer with one β cyclodextrin (β-CD) and another containing PEG block wherein hydrophobic compounds (either polymers or small molecules) served as the guest molecules. For hydrophobic drugs, this kind of host-guest assemblies can be used as delivery vehicles (Zhang *et al.,* 2009).

Stimuli responsive or stimuli sensitive or smart polymer assemblies

Polymer assemblies have been proposed to have potential as delivery vehicles for controlled encapsulation and release. To efficiently accomplish this, it is essential that the polymer vesicles should respond to the external stimuli such as a change in pH, oxidation/reduction, light, temperature etc. This external stimulus permits the prompted release of a payload or the selective uptake of a payload, which modifies the assembly (Du *et al.,* 2009).

Figure 5. Types of block copolymer

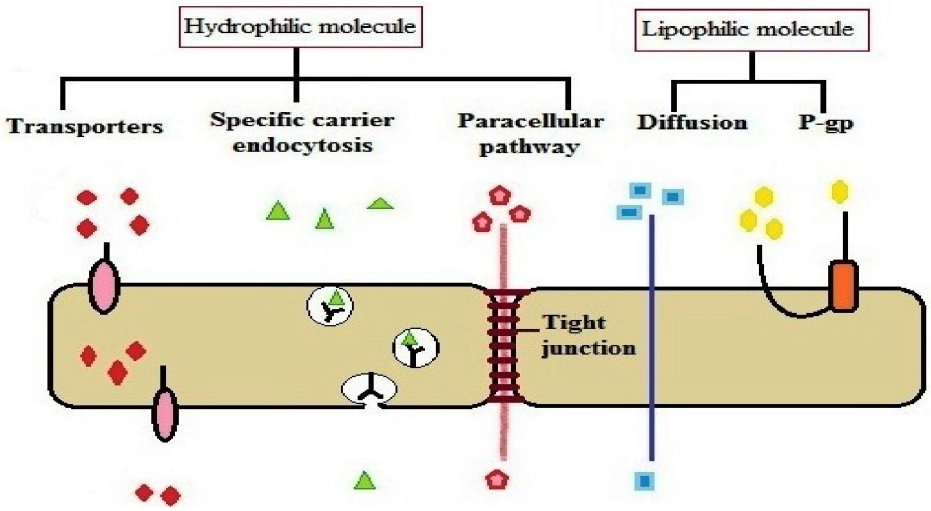


Figure 6. Schematic demonstration of the transport of molecules across the BBB.

Destabilization of micelles as a consequence of stimulation by either physiological or external trigger is termed as 'stimuli-sensitivity' or 'environmental sensitivity' of the micelles (Zhang *et al.,* 2006).

Thermo-responsive assemblies

Polymers which are responsive to temperature changes are the most studied class of external stimuli sensitive polymers (Gil and Hudson, 2004). As the temperature increases, the thermo responsive micelles undergo a structural change which results in the deposition of the drug and easier drug absorption by cells (Zhang *et al.,* 2002). A thermo-sensitive polymer shows a lower Critical Solution Temperature (LCST) in aqueous solution. Lower critical solution temperature (LCST) is defined concisely as the phase transition temperature of a thermo-sensitive polymer below which the polymers are water soluble and above which they become water insoluble. Thermo-responsive polymeric micelles can be fabricated by the self assembly of a thermo- responsive block polymer and hydrophobic block polymer. The outer shell of this polymeric micelle acquires the property of thermo-sensitivity and plays the role of aqueous solubilization while the hydrophobic inner core is loaded with the water-insoluble drugs. For instance, thermo responsive part of poly (*N*-isopropylacrylamide-*co*-*N*,*N*-dimethylacrylamide) [P (NIPAM-*co*- DMAAm)] and hydrophobic part of poly (D,L-lactide) were prepared by a combination of reversible addition–fragmentation chain-transfer (RAFT) and ring-opening polymerization. The thermo-responsive micelles obtained from these polymers were approximately 25nm when below the LCST of 40°C, and their sizes get increased to an average of approximately 600nm above the LCST due to aggregation of the micelles (Akimoto *et al.,* 2009).

pH-responsive or acid sensitive assemblies

pH-sensitive polymeric assemblies are those in which polymer contain weak acidic or basic groups in the block copolymer at different pH, which either accept or release protons in response to changes in

environmental pH (Du *et al.,* 2009). For instances pH sensitive polymers with anionic groups are poly (carboxylic acid) or poly (acrylic acid) (PAA) or poly (methacrylic acid). Polysulfonamides (derivatives of *p*-aminobenzenesulfonamide) are the another kind of polyacidic polymer and poly (*N,N*-diakyl-aminoethylmethacrylates), poly(lysine) (PL), poly (ethylenimine) (PEI) and chitosan are few examples of cationic polyelectrolyte. pH-sensitive polymers have been used in several biomedical applications, the most important being their use as drug and gene delivery systems, and glucose sensors (Aguilar *et al.,* 2007). Both block copolymers and synthetic block copolypeptides have been used to make pH-responsive polymer vesicles or micelles (Du *et al.,* 2009)

Licciardi *et al.* (2005) prepared the tumor-targeting polymeric micelles by using the folic acid (FA)-functionalized diblock copolymers consisting (MPC) 2-(methacryloyloxy)-ethyl phosphorylcholine and either 2-(dimethyl-amino) ethyl methacrylate (DMA) or 2-(diisopropylamino) ethyl methacrylate (DPA). These diblock copolymers are good candidates for drug delivery and gene therapy because of the cell-targeting agent folic acid (Licciardi *et al.,* 2005).

Redox-responsive assemblies

There is a significant concern in the preparation of polymeric assemblies which respond to a change in redox environment. Polymeric micelles with a redox-responsive property have attracted researchers in recent years (Du *et al.,* 2009). Sun *et al.* prepared a new category of shell-sheddable micelle based on the biodegradable disulfide linked dextran-*b*-poly (*ε*-caprolactone) diblock copolymer (Dex-SS-PCL) by using doxorubicin (DOX) for intracellular drug delivery. It is well known that the disulfide bond breaks in the presence of a reducing agent. Without the reducing agent polymeric micelles are stable for a long time, whereas they will undergo a fast shedding process when subjected to reduction conditions (glutathione (GSH), at a higher level in a cancer cell than that in a normal cell *in vivo*), which was confirmed by the diverse changes in size and rapid drug release. Thus these reduction-responsive biodegradable micelles have appeared highly promising for the targeted intracellular delivery of hydrophobic chemotherapeutics in cancer therapy (Sun *et al.,* 2010).

Light responsive polymeric assemblies

In comparison to pH- or redox responsive polymeric assemblies, light responsive assemblies proposed the advantage, that no extra chemical additives are mandatory to induce the response in the controlled release of encapsulated molecules (Zhanga *et al.,* 2009). To trigger the release of drug from the polymeric micelles, ultraviolet (UV) and near infrared (NIR) light can be used. UV light is not able to penetrate deeply into the body because it get absorb by the skin so it can be utilizes to trigger the drug release from topical preparation of polymeric micelles. NIR is able to penetrate deeply into the body because hemoglobin, water and lipids have low absorption in the NIR region (650–900 nm) (Oerlemans *et al.,* 2010).

The main basic concept for the preparation of light-responsive polymer assembly is to introduce a chromophore like liquid crystalline azobenzenes (LC-Azo) into the structure of the hydrophobic block, whose photoreaction can result in a conformational or structural change. However, these azobenzene-based polymer self-assemblies cannot be completely demolished by light. The principle of light-changeable or light-switchable amphiphilicity may be extended to many polymer/chromophore combinations. For example, spirabenzopyran can form a zwitter ionic species and triphenyl methane leucohydroxide can produce charges upon light irradiation to afford a hydrophobicity change (Zhanga *et al.,* 2009).

Liu *et al.* (2012) prepared the near-infrared light-sensitive polymeric micelles for the enhanced intracellular delivery of doxorubicin (DOX), an anticancer drug. These micelles were prepared from dextran-graft-(2-diazo-1,2-naphthoquin-one)(Dex-DNQ) amphiphilic copolymers which were synthesized by modification of hydrophilic dextran with hydrophobic DNQ molecules. The hydrophobic DNQ molecule is an attractive photo-trigger group. Thus Dex-DNQ micelles will promptly release encapsulated drugs due to the micelle dissociation under UV or NIR

irradiation. This smart drug nanocarrier is potentially useful for cancer chemotherapy (Liu *et al.,* 2012).

Based on type of intermolecular forces

On the basis of type of intermolecular forces, polymeric micelles can be classified in two main categories. Intermolecular forces including hydrophobic, steric, electrostatic, hydrogen bonding, and van der Waals interactions which control the separation of the core segment from the aqueous environment. Following are the two main categories:
polyion complex micelles; Noncovalently Connected Polymeric Micelles (Mourya *et al.,* 2011); Polyion Complex Micelles.

Polyion complex (PIC) micelles are made up of two block copolymers with opposite charges. The formation of PIC micelles was first proposed by Harada and Kataoka (Harada and Kataoka, 1997). The assemblies which are formed via electrostatic forces by block copolymers contain at least one ionic block , one non-ionic block and ionic polymers with charge opposite to that of the copolymers, are known as polyion complex (PIC) micelles or polyelectrolyte. These assemblies have been widely studied for gene delivery recently (Nishiyama and Kataoka, 2006). The sizes of PICMs were about 50 to 200 nm and the loading efficiency of micelle was higher than 80% (w/w) (Jeong *et al.,* 2006). PICMs have some unique characteristics such as simple synthetic route, easy self-assembly in aqueous medium, structural stability, high drug loading capacity, and prolonged circulation in the blood. Thus, one can find the application of PICMs for the delivery of charged drugs along with antisense oligonucleotides, DNA, and enzymes (Ranger *et al.,* 2001, Zhang *et al.,* 2009).

Noncovalently Connected Polymeric Micelles (NCCMs)

The core and shell forming components are connected by hydrogen bonding instead of the normal covalent bonding that exists in all micelles formed from block copolymers. The field of NCCM has been significantly broadened by the introduction of host–guest interactions as new driving forces. The enormous accumulation of knowledge and data of host–guest interactions in supramolecular chemistry offers a productive basis for the further developments of NCCMs (Guo and Jian, 2009). Jiang *et al.* synthesized the intermolecular complexes with poly (4-vinylpyridine) as the backbone and carboxyl terminated polybutadiene as the grafts in a common solvent, chloroform due to hydrogen bonding (Wang *et al.,* 2001)

TYPES OF POLYMER OR COPOLYMER USED IN POLYMERIC MICELLES FABRICATION

Polymeric micelles are usually made up of two types of polymers i.e. :Block copolymers; Graft copolymers; Block copolymers.

These are generally linear polymers that are composed of a sequence of at least two polymer parts that differ in aspect of physico-chemical properties, e.g. charge and/or polarity. Block copolymers can be categorized according to their architecture as AB-type diblock, ABA- or BAB-type triblock, and multiblock, where A represents the soluble block in a selected solvent and B describes the insoluble block. Different types of block copolymers are shown in figure 5.

In the simplest case, a diblock copolymer AB consists of two different homopolymers linked end to end. Addition of this concept leads to ABA or BAB triblocks and to (AB)n linear multiblocks, whereas ABC copolymers are gained by the incorporation of a polymer sequence having a third composition. Examples of such block copolymer s are PS–poly (diene) di- and triblock, PPO–PEO as hydrophilic–hydrophobic copolymers, acrylic copolymers and many others (Qiu and Bae, 2006).

Reversible addition fragmentation chain transfer (RAFT) polymerization, atom transfer radical polymerization (ATRP) are the two controlled radical polymerization (CRP) techniques which are used in the synthesis of most of block copolymers used in self-assembly of the polymeric micelles. Among them, ATRP is one of the most prevailing and adaptable CRP technique. It enables precise control over molecular weight, molecular weight distribution, and functionality (Siegwart *et al.,* 2012).

Table I. Structures of micelle-forming copolymer

Type of micelle forming copolymers	Example of polymers	Representation of structure
Graft copolymers	*N*-phthaloylchitosan-g-polycaprolactone	AAAAAAAAAAAAA B B B B B B B
Block copolymers	Poly(styrene)-b-poly(ethylene oxide) Poly(ethylene oxide)-b-poly (propylene oxide) -b-poly (ethylene oxide)	di – block AAAAAAABBBBBB tri - block AAAABBBBBAAAA

Graft copolymers

In graft copolymers, side chain parts are grafted to a main polymer chain. Fully hydrophilic block or graft copolymers in which one of the parts carry a charge which may form stable complexes in water together with oppositely charged (macro) molecules, for instance-polyion complex micelles or polyelectrolyte micelles (Qiu and Bae, 2006). In the formation of polymeric micelles, Graft copolymers have some advantages over block copolymers i.e. they contain multi-grafted hydrophobic polymer chains along a hydrophilic polymer backbone. The delicate hydrophilic/ hydrophobic balance in a graft copolymer structure can be readily controlled by changing the relative grafting density between the grafted hydrophobic polymer and the hydrophilic back bone polymer (Jeong *et al.,* 2003). Table I shows different possible structures of micelle forming copolymers with representtative example of each class (Mourya *et al.,* 2011).

Some commercially used polymers

Various polymers can be used for the formation of polymeric micelles with variations in the hydrophilic and hydrophobic blocks generating for possible drug delivery vehicles. These PMs plays a significant role for delivering and targeting a therapeutic drug to the body and then digested by the body. Polymers that are used in the formation of polymeric micelles must be an FDA approved devices; these requirements limit the choice for the various blocks. Poly (ethylene glycol) (PEG) is most commonly used polymer because it is inexpensive and has low toxicity. PEG is a non biodegradable in nature, due to which it is easily removed from the body through the excretion pathway if under a mol.wt. of 15 kDa (Karine *et al.,* 2008). Another polymer that are widely used is poly (*N*-vinyl-2-pyrrolidone) (PVP), which is repeatedly considered as a primary alternative to PEG. Similar to PEG, this polymer is highly biocompatible and was used in preparation of such particulate drug carriers as liposomes, nanoparticles, microspheres and diblock polymer micelles (Torchilin, 2007). From the currently disclosed patents, it can be seen that polyesters, including polylactide (PLA), poly (lactide-co-glycolide) (PLGA), poly (ε-caprolactone) (PCL), poly (lactide-co-caprolactone), poly(*p*-dioxanone), poly(*p*-dioxanone-co-lactide), poly(p-dioxanone-cocaprolactone), poly(3-hydroxybutyrate), and polyorthoester**,** are widely employed hydrophobic blocks. Other biodegradable polymers such as polyanhydride**,** derivatives of poly(amino acid**)** and non-degradable polymers like poly(alkylacrylate) are also patented hydrophobic segments (Zhanga *et al.,* 2009).

A list of different polymers/copolymers used to prepare micelles loaded with various pharmaceuticals is shown in table II.

Table II. List of actives loaded in polymeric micelles during past years

Block copolymer	**Micelle-incorporated Pharmaceuticals**
Poly(2-ethyl-2-oxazoline)-b-poly(e-caprolactone)	Paclitaxel
PEG- lipid	Dequalinium Soya bean trypsin Paclitaxel Camptothecin Tamoxifen Porphyrine Vitamin K_3 Amphotericin B
Poly(2-ethyl-2-oxazoline)-b-poly(L-lactide)	Doxorubicin
Poly(vinylalcohol-co-vinyloleate)	Retinylpalmitate
Poly(*N*-vinyl-2-pyrrolidone)-b-poly(D,L-lactide)	Indomethacin
Pluronics	Doxorubicin Cisplatin Carboplatin Epirubicin Haloperidol
Pluronic/polyethyleneimine Polycaprolactone-b-PEG	ATP Polynucleotides FK506 Cyclosporine 125-I(diagnostic)
Poly(benzyl-L-aspartate)-b-PEG	Doxorubicin Indomethacin Amphotericin B Camptothecin
Poly(delta-valerolactone)-b-methoxy-PEG Polycaprolactone-b-methoxy-PEG	Paclitaxel Indomethacin Cisplatin Paclitaxel
Poly(caprolacton/trimethylene carbonate)-PEG	Risperidone Ellipticin
Poly(aspartic acid)-b-PEG	Doxorubicin cisplatin Lysozyme Adriamycin
PEGYPE/egg phosphatidylcholine (mixed micelles)	Paclitaxel
Poly(*N*-isopropylacrylamide)-poly(vinylpyrrolidone)-poly (acrylic acid)	Ketorolac
Poly(*N*-isopropylacrylamide)-based micelles(pH-sensitive) Mice (77) Poly(*N*-isopropylacrylamide)-b-poly(alkyl(meth)acrylate) (pH-sensitive)	Phtalocyanine

ADVANTAGES OF POLYMERIC MICELLES

Polymeric micelles posses some advantages in pharmaceutical field which are describe as follows. High structural stability is the first advantage of polymeric micelles. Polymeric micelles retain high structural stability provided by the entanglement of polymer chains in the inner core. The high structural stability of polymeric micelles is an important key to *in vivo* delivery in micellar forms and simultaneously eliminates the possible contribution of single polymer chains to drug delivery.

The second main advantage is the very small size of polymeric micelle. Polymeric micelles have a diameter range from 10nm to 100nm which is considered ideal for the achievement of stable, long-term circulation of the carrier system in the bloodstream. Alternatively, the small size of polymeric micelles posses a greater advantage in the sterilization processes in pharmaceutical productions. Hence polymeric micelles are basically free of micro-sized particle's contamination.

The third advantage of the polymeric micelle is its high water solubility. Polymeric micelles can incorporate a large number of hydrophobic drug molecules in the micelles' inner core, and simultaneously, the micelles may maintain their water solubility by inhibiting inter micellar aggregation of the hydrophobic cores with a hydrophilic outer shell layer that works as a barrier against inter micellar aggregation.

The fourth advantage of polymeric micelles is that a range of chemical species can be incorporated into polymeric micelles. These drugs can be incorporated into the micelle inner core either by chemical conjugation to the inner-core-forming polymer block or by physical entrapment owing to hydrophobic interactions between the entrapped drug molecules and the hydrophobic inner-core forming polymer block. Low toxicity is the fifth advantage of the polymeric micelles. Generally, polymeric surfactants are known to be less toxic than low-molecular-weight surfactants, such as sodium dodecyl sulfate.

DISADVANTAGES OF POLYMERIC MICELLE AS A DRUG CARRIER

Everything in this world has positive and negative aspects so polymeric micelles have also some negative aspects which are describe as follows. The first negative aspect of polymeric micelles is that relatively high levels of polymer chemistry are needed in the polymeric micelle studies. The second negative aspect for the polymeric micelle systems is the immature technology for drug incorporation in a physical manner. Yokoyama *et al*., reported that physical incorporation efficiencies were dependent on various factors in drug-incorporation processes. Presently, there seem to be no universal incorporation method applicable to any polymer. The third negative aspect is much slower extravasations of polymeric carrier systems than that of low-molecular weight drugs. This outcome from a difference in extravasation mechanisms between low molecular-weight drugs and polymeric carrier systems (Yokoyama, 2011).

METHODS OF PREPARATION OF POLYMERIC MICELLES

By using the self-assembly of block copolymers there are two general methods for the preparation of polymeric micelles. One is the direct dissolution method or the organic-solvent-free method and the other is the solvent evaporation or solution-casting technique or 'solvent-switch' method

The organic-solvent-free method or direct dissolution method

In this method for the dissolution of the block copolymer only water is mandatory to allow for self-assembly. It involves direct dissolution of the amphiphilic copolymer and drug in water for preparing drug-loaded polymeric micelles. But low drug loading is the disadvantage of this method so to enhance drug loading, this technique can be combined with an increase in temperature or alternately before the addition of copolymer, a thin evaporated film of drug can be prepared. Du and Armes recently reported the direct dissolution of poly(3-caprolactone)-b-poly(2-aminoethyl methacrylate) [PCL-b-PAMA] or

poly(3-caprolactone)-b-poly[2-(methacryloyl-oxy) ethyl phosphorylcholine] [PCL-b-PMPC] block copolymers in pure water without the need of organic solvent.

Solvent evaporation or solution-casting method

In this method, a volatile organic solvent is employed to dissolve the block copolymer and the drug because most amphiphilic block copolymers are not directly soluble in water. 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. But 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 (Mourya *et al.,* 2011, Du *et al.,* 2009).

APPLICATION OF POLYMERIC MICELLES

The studies on the application of PMs in drug delivery and drug targeting have mostly focused on the following areas that are considered below

Drug delivery to the brain

Presence of blood–brain barrier (BBB) is the major obstacle in drug delivery to the brain and neurodegenerative diseases such as Parkinson's and Alzheimer's diseases because it limits the drug penetration even if in certain pathological situations the BBB is partly disrupted (Garcia *et al.,* 2005). A schematic representation of different mechanisms used to cross the BBB is shown in figure 6. Two approaches have been used by polymeric micelles to improve the delivery of therapeutic drugs to brain. The first approach is proposed on the basis of the modification of polymer micelles with antibodies or ligand molecules capable of transcytosis across brain microvessel endothelial cells, comprising the BBB. The second approach uses Pluronic block copolymers to hinder drug efflux systems, particularly, Pgp, and selectively augment the permeability of BBB to Pgp substrates (Dhembre *et al.,* 2011). Kabanov et al. have demonstrated that poloxamer (Pluronic™) micelles conjugated with antibodies may improve brain distribution of haloperidol which is a neuroleptic agent; this approach has resulted in a dramatic improvement of drug efficacy. This result specifies that Pluronic™ micelles offer an effective transport of solubilized neuroleptic agents across the BBB (Kabanov *et al.,* 1992). Recent investigations made by the same group revealed that only Pluronic™ unimers allowed cell penetration in bovine mammary epithelial cells (BMEC) monolayer of molecules such as rhodamine, digoxin or doxorubicin by inhibition of the P-gp mediated drug efflux system (Batrakova *et al.,* 2001, Miller *et al.,* 2001 and Alakhov *et al.,* 1999).

Ocular drug delivery

Eye remains a challenging task for the efficient drug delivery to the pharmaceutical scientists due to the several anatomical barriers and the clearance mechanisms prevailing in the eye. Conventional drug delivery systems, such as eye drop solutions, suffer from low bioavailability. More invasive methods, such as intravitreal injections and implants, cause adverse effects in the eye. Recently, an increasing number of scientists have turned to nanomaterial based drug delivery systems to address the challenges faced by conventional methods (Liu, 2012). For topical ophthalmic application, micro and nanoparticles are presently being researched based on nanotechnology in which drugs can be administered as an eye drop. Poorly water soluble or insoluble drugs can be successfully fabricated as valuable systems to provide easy administration to ocular tissues and convenience to the patient for adjustment of dose and dosing frequency according to disease therapy. Biodegradable polymers can be combined with drugs successfully in such a approach that the drug is released into the eye in a very accurate and controlled manner. Nanoparticle formulations provide protection for agents liable to degradation or denaturation in region of harsh pH, and also prolong the duration of exposure of a new drug by increasing retention of the formulation through bioadhesion. In this context, more clinical studies are necessary to provide further information and insight into this new

ophthalmic drug delivery system (Ramesh *et al.,* 2009). Ribeiro *et al.* prepared and evaluated the polymeric micelles of single and mixed poloxamines (Tetronic) regarding their ability to host the antiglaucoma agent ethoxzolamide (ETOX) for topical ocular application. Three highly hydrophilic varieties of poloxamine (T908, T1107 and T1307) and a medium hydrophilic variety (T904), possessing a similar number of propylene oxide units but different contents in ethylene oxide, were chosen for the study. Micellar size ranged between 17 and 120 nm and it was not altered after the loading of ETOX (2.7–11.5 mg drug g–1 poloxamine). Drug solubilization ability ranked in the order: T904 (50-fold increase in the apparent solubility) > T1107 ≈ T1307 >T908. Mixed micelles illustrated an intermediate capability to host ETOX but a greater physical stability, maintaining almost 100 per cent drug solubilized after 28 days. Furthermore, the different structural features of poloxamines and their combination in mixed micelles enabled the tuning of drug release profiles, sustaining the release in the 1–5 days range. These findings together with promising hen's egg test-chorioallantoic membrane biocompatibility tests make poloxamine micelles promising nanocarriers for carbonic anhydrase inhibitors in the treatment of glaucoma (Ribeiro *et al.,* 2012).

Passive drug targeting to solid tumors

Targeting of drugs to specific sites will successfully diminish adverse reactions as the action will be limited to cancer tissue only. Polymeric micelles can easily be functionalized to target specific types and may be promising delivery and imaging in the treatment of cancer (Dhembre *et al.,* 2011). Passive targeting is defined as a method whereby the physical and chemical properties of carrier systems amplify the target/nontarget ratio of a quantity of a delivered drug. The passive targeting of polymeric micelles on solid tumors can be achieved owing to the enhanced permeability and retention effect (EPR effect) (Matsumura, 2008). EPR effect can be viewed in almost all human cancers with the exception of hypovascular tumors such as prostate cancer or pancreatic cancer. For passive targeting to be successful, the PMs require to circulate in the blood for longer periods so that there will be multiple chances for the PMs to pass by the target site. Their size is known to play a significant role in achieving passive targeting and determining their biological fate. The hyper permeability of tumors associated with the EPR effect is based on excessive production and secretion of vascular permeability factors stimulating extravasation within cancerous tissue. Commonly secreted chemicals are vascular endothelial growth factor bradykinins, nitric oxide, 61 prostaglandins, enzyme collagenase, peroxynitrite (Matsumura, 2008).

Currently, many drug-loaded polymeric micelles are under investigation for anticancer therapy in preclinical studies to improve drug efficacy. Five micellar formulations have been tested in clinical trials and they are presented in table III.

Active drug targeting

The goal of the active targeting is to augment the drugs delivery to the target sites by employing biologically specific interactions or by utilizing the heating and sonication i.e. locally applied signals (Matsumura, 2008). Specific interactions between the targeting components and antigens displayed on target tissues causes the selective amassing of drug in the target tissue. The active targeting can be achieved by molecular identification of the diseased cells by polymeric micelles, over expressed at the diseased site or via the ligand-receptor or antigen-antibody interactions. Attachment of a ligand to the polymeric mielles's surface increases cellular uptake through interaction between the ligand and its receptors which are over-expressed at the cancerous cell surface. The ligand involves pairing of Polymeric micelles with polymeric immunomicelles, epidermal growth factor (EGF), the folate receptor and transferring (Pua, 2012).

Polymeric immunomicelles

Attachment of antibodies to micelle surface refers the largest opportunities in terms of variety of targets. Thus, many researchers have tried to develop this opportunity via covalently attaching an antibody to polymeric micelles for producing the 'immunomicelles' (Mourya *et al.,* 2011). Recent studies have

verified that certain nonpathogenic monoclonal antinuclear autoantibodies with the nucleosome-restricted specificity (for instances mAb 2C5) can identify the surface of a range of different tumors and specifically connect to cancerous cells *in vitro*, but not normal cells by tumor cells surface-bound nucleosomes. Consequently, these antibodies serve as specific ligands for drug delivery and drug carriers into tumors. Torchillin (2009) reveal the efficacy of using immunomicelles in targeting of cancer by the solubilization of paclitaxel and camptothecin in mixed micelles of polyethylene glycol-phosphatidyl ethanolamine and vitamin E. These micelles were tailored with antinucleosome monoclonal antibody 2C5 (mAb 2C5), which can particularly transport micelles to tumor cells *in vitro*. These mixed micelles and mAb 2C5-immunomicelles established significantly higher *in vitro* cytotoxicity against various cancer cell.

CONCLUSION

With the advent of nanotechnology, polymeric micelles have emerged as an important pharmaceutical carrier because of their attractive properties. As compared with the other novel drug delivery systems preparation of polymeric micelles appears to be relatively simple. Recently these carrier systems have been gathered much more considerable attention in the drug delivery, gene delivery and targeting field because of their high loading capacity for drug carrier as well as their unique disposition characteristics in the body. More importantly, the success of several thoroughly developed micellar formulations in clinical trials have paved the way for making polymer therapeutics based on other assemblies clinically available. At the same time, much attention has been paid to polyion complex core-shell assemblies and non covalently connected polymeric assemblies for the delivery of the actives and genes. In every case, it is obvious that smart or intelligent drug delivery using the PMs will possibly bring the most facile, versatile, and efficient methodology in chemotherapy treatments for human diseases. Apart from it, fundamental research and the development of novel advanced polymeric micelles are ongoing. Thus, polymeric micelle based nanocarriers will continue to hold a promise for the delivery of drugs.

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