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Polymeric Micelles: A Nanoscience Technology

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ABSTRACT

One of the most widely studied subjects in nanoscience technology is related to the creation of supramolecular architectures with well-defined structures and functionalities. In the late 1960s, *micelles* drew much attention as drug carriers owing to their easily controlled properties and good pharmacological characteristics. These supramolecular 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 supramolecular structures with a wide array 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. In this article we have reviewed several aspects of polymeric micelles concerning their general properties, preparation and characterization techniques, and their applications in the areas of drug and gene delivery. 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.

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Introduction:

A sudden change in many physicochemical properties is seen in solutions of amphiphilic molecules or surfactant monomers that possess a polar head and a lipophilic tail. The change is associated with the orientation and association of amphiphilic molecules in solution resulting 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. 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 [1,2]. The major driving force behind self-association of amphiphilic molecules is the decrease of free energy of the system. The decrease in free energy is a result of removal of hydrophobic fragments from the aqueous surroundings with formation of a micelle.

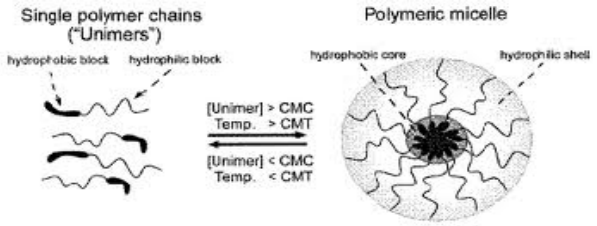

Fig. 1: Effect of CMC and CMT on micelles formation

The factors affecting the process of *micelle formation* are the size of the hydrophobic domain in the amphiphilic molecule, concentration of amphiphiles, temperature, and solvent. The assembly formation starts only when a certain minimum concentration is crossed by the amphiphilic molecules, called as *critical micelle concentration (CMC).*

At low concentrations in medium, these amphiphilic molecules exist separately, and are so small that they appear to be sub-colloidal. Below the CMC, the concentration of amphiphile undergoing adsorption at the air-water interface increases as the total concentration of the amphiphile is increased. Finally at CMC, the interface as well as the bulk phase is saturated with monomers. Any further amphiphile added in excess of CMC results in the aggregation of monomers in the bulk phase, such that the free energy of the system is reduced. The temperature below which amphiphilic molecules exist as unimers and above which as aggregates is the critical micellization temperature (CMT) [1,3,4].

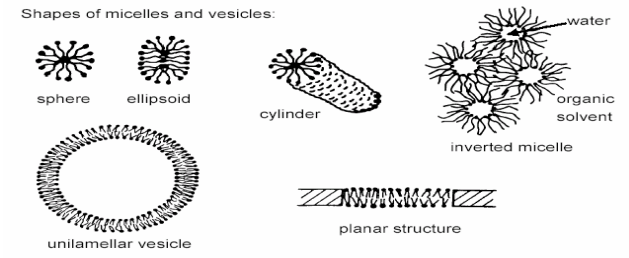

Fig. 2: Shapes of micelles and vesicles.

Polymeric micelles:

Amphiphilic block or graft co-polymers behave in the same manner as that of conventional amphiphiles and in aqueous solution, above CMC, these polymers form polymeric micelles. In contrast to the micelles of conventional surfactant monomers, in polymeric micelles there is a covalent linkage in individual surfactant molecules within the hydrophobic core.

This linkage prevents dynamic exchange of monomers between free solution and the micellar pseudo-phase. This confers rigidity and stability to the polymeric micelles [5]. The aggregation number of polymeric micelles is of the magnitude of several hundreds and the diameter ranges from 10 to 100 nm. Factors controlling the size of the polymeric-micelles include molecular weight of the amphiphilic block co-polymer, aggregation number of the amphiphiles, relative proportion of hydrophilic and hydrophobic chains, and the preparation process [6].

In aqueous medium amphiphilic block co-polymers can principally self assemble into spherical micelles, worm-like or cylindrical micelles, and polymer vesicles or polymersomes. Main factor governing the morphology of micelles is the hydrophilic–hydrophobic balance of the block co-polymer defined by the hydrophilic volume fraction, f. By using amphiphiles of more complicated molecular design e.g., miktoarm star co-polymers, or by varying the experimental conditions for self-assembly more complex morphologies such as that of crew-cut micelles,

multi-compartment micelles, toroids, etc. may obtained[7].

Polymer micelles in biological environment

- α- and β-globulins significantly destabilized the polymeric micelles
- RBC and γ-globulin does not show much effect on micelles stability
- Mostly the polymeric micelles are internalized by phagocytosis but sometimes by pinocytosis.
- caveolae-mediated endocytosis at lower concentration (<CMC) and clathrin-mediated endocytosis at higher concentration (>CMC).

TYPES OF POLYMERIC 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 i.e., micelles formed by hydrophobic interactions, those resulting from electrostatic interactions (polyion complex micelles), and micelles from metal complexation.

a. 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 co-polymer, poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide), forms micelles as a result of hydrophobic interactions [8].

b. 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 vander Waals force of interaction control the structure and size of the charged micelle coronas. PICMs have some peculiar features such as simple synthetic route, easy self-assembly in aqueous medium, structural stability, high drug loading capacity, and prolonged circulation in the blood. 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 along with antisense oligonucleotides, DNA, and enzymes [9,10].

c. Noncovalently Connected Polymeric Micelles

A novel *"block-co-polymer-free"* technique can also be used for preparing polymeric micelles. Here, polymeric micelles are obtained via self-assemblage of homopolymer, random co-polymer, graft co-polymer 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 [11].

TYPES OF POLYMER USED

Micelle-forming amphiphilic co-polymers can be either block co-polymers (di, tri, tetra or poly) or graft co-polymers. A graft co-polymer is one which comprises a polymer chain as a backbone and another polymer chain as side "grafted" parts. These co-polymers usually demonstrate properties of both, i.e., polymeric backbones as well as of the graft. 'Click' reactions have emerged as a means to incorporate polymer chains onto polymeric backbones to result in well-defined graft co-polymers [12]. *Table 1* shows different possible structures of amphiphilic co-polymers with representative example of each class.

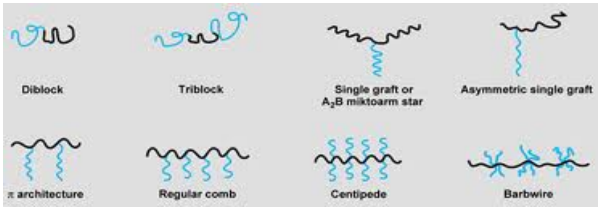

Figure 3: Shapes of some commonly used polymers

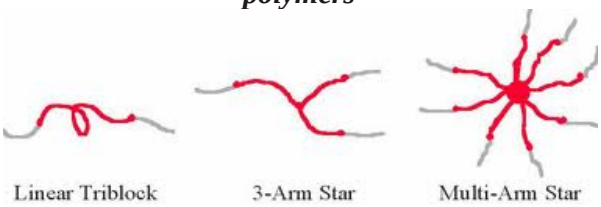

Figure 4: Shapes of some unique polymers used in preparation of polymeric micelles

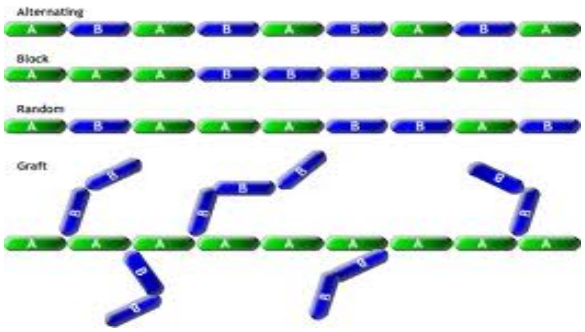

Figure 5: Types of polymers

Usually in aqueous solutions, spherical micelles are formed from self-assemblage of amphiphilic diblock AB-type or triblock ABA-type co-polymers with the length of a hydrophilic block exceeding to some extent that of a hydrophobic one. Whereas, if the length of a hydrophilic block is too large co-polymers exist in water as individual molecules (unimers), and molecules with lengthy hydrophobic blocks develop various structures.

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

Table 1: Structures of micelles forming co-polymers with examples

Examples of different amphiphilic co-polymers that have been investigated for producing micelles are

1. N-phthaloylcarboxymethylchitosan
2. Poly (2-ethylhexyl acrylate)-b-poly (acrylic acid)
3. Poly (tert-butyl acrylate)-b-poly (2-vinylpyridine)
4. Poly (ethylene oxide)-b-polycaprolactone
5. Poly (e-caprolactone)-b-poly (ethylene glycol)-b-poly (e-caprolactone)
6. Poly (e-caprolactone)-b-poly (methacrylic acid)
7. Poly (ethyleneglycol)-b-poly (e-caprolactone-co-trimethylenecarbonate)
8. Poly (aspartic acid)-b-polylactide
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 etc.,

PREPARATION PARAMETERS

Polymeric micelles are generally prepared by either of the two commonly used methods. Mostly, for block co-polymers with low molecular

weight and short length of the insoluble block, micelles are prepared by *direct dissolution* in a selective solvent for one of the blocks. To facilitate dissolution, *stirring, thermal, or ultrasound* treatments can be used.

The micellar properties remain unchanged once the micelle is trapped in a solvent that is a strong nonsolvent for the core. Alternatively, molecularly dissolved chains of block co-polymer can be obtained in a nonselective solvent. To trigger micellization in the molecularly dissolved chains a selective solvent for one of the blocks and precipitant for the other may be added, or temperature or pH variations may be used [13].

Preparation of Drug-loaded Micelles

Drug-loaded polymeric micelles can be prepared mainly by three common approaches: *direct dissolution, solvent evaporation, and dialysis. Direct dissolution* of the amphiphilic co-polymer and drug in water is the simplest technique of preparing drug-loaded polymeric micelles. At or above CMC, the co-polymer 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 co-polymer.

In *solvent evaporation or solution-casting technique*, a volatile organic solvent is used to dissolve the co-polymer and the drug. A thin film of co-polymer 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 co-polymers 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. 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 [14,15]. 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.

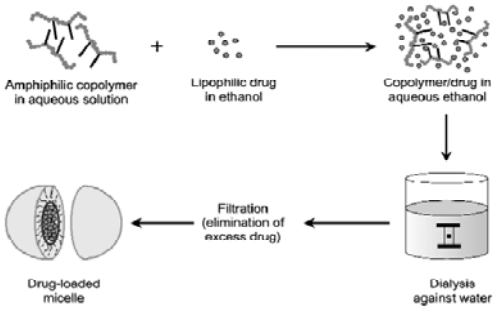

Figure 6: Preparation of polymeric micelles by dialysis method

Drug-loaded polymeric micelles are then obtained by redispersing the lyophilized product in a suitable vehicle [16,17]. 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 and core [18].

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 co-polymers 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 [19].

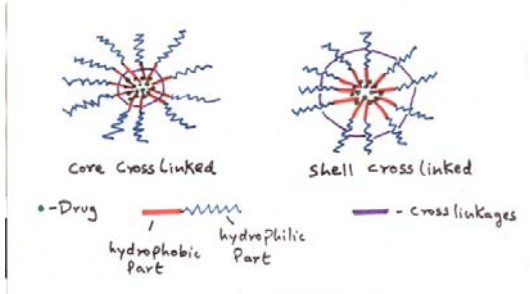

Figure 7: Structure of core and shell crosslinked polymeric micelles

CHARACTERIZATION OF POLYMERIC MICELLES

CMC: Critical micellar concentration

In aqueous media, amphiphilic polymers can exist in the form of micelles when the concentration is higher than CMC, and when diluted below this concentration, the micelles may collapse. Hence, CMC is the key parameter for the formation and the static stability of polymeric micelles. Some of the methods used for determination of CMC in aqueous dispersions of micelles include surface tension measurements, chromatography, light scattering, small angle neutron scattering, small angle X-ray scattering, differential scanning calorimetry, viscometry, and utilization of fluorescent probes.

For easy practical determination, CMC is obtained from plots of the surface tension as a function of the logarithm of the concentration. The CMC is said to be attained when the surface tension stops decreasing and reaches a plateau value. Most of the researchers have relied upon use of pyrene as a fluorescent probe for estimating CMC [20].

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 color from light scattering which indicates good micellar preparation, as contrasted with the white color shown by aggregates. Size of polymeric micelles usually falls in the colloidal range. *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 co-polymer micelles. The more recently developed cryo-TEM technique has increasingly started gaining importance for characterization of block co-polymer 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 co-polymer micelles 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 [21,22].

In Vitro Drug Release Behavior

In-vitro drug release behavior 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 [23].

APPLICATIONS

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 co-polymers or physically incorporated into the hydrophobic core of micelles. The solubilization process leads to enhancement of their water solubility and thereby bioavailability [24]. 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 [25]. Thus, polymeric micelles (nanosized) elevate uptake and enhance bioavailability.

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 [26]. 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. The influence on solubilization capacity of hydrophobic block length has been examined for griseofulvin in polyoxyethylene and polyoxybutylene co-polymer 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, after which the solubilization capacity became independent of the same [27]. Some noteworthy contributions for solubilization of drugs are noted in Table 2.

Drug	Amphiphilic polymer	Comment
Camptothecin	Pluronic P105, d- α-tocopheryl polyethylene glycol 1000 succinate	Increased micellar stability; increased cytotoxicity
Griseofulvin	E_mB_n co-polymers, (E = oxyethylene, 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

Table 2: Examples of improvement in solubility of drugs using polymeric micellar system

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 tumours). 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 [29]. As the polymeric micellar drug carriers cannot pass through walls of normal blood vessels, decreased side-effects of the drug are observed.

In tumour neovasculature, there is a poorly developed lymphatic drainage system that leads to enhanced retention of polymeric micelles within the solid tumour as micelles are not efficiently cleared. This feature allows prolonged circulation of polymeric micelles in the circulatory system upon administration [32]. Due to these characteristics, it is possible to achieve *passive drug targeting* using polymeric micelles. The hyperpermeability of tumours 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, prostaglandins, enzyme collagenase, peroxynitrite [30].

Vetvicka and his associates formulated a micellar drug delivery system designed to prolong the blood circulation time and maximize the efficiency of the EPR effect [31]. The micellar system solubilized the poorly water soluble drug and a stable formulation of camptothecin-loaded micelles was obtained. The stability of the formulation was found to strongly depend on the amount of benzyl esters and length of the PEG. The drug-loaded micelles were potentially delivered to tumour sites owing to the EPR effect.

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 (Fig.7).

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 [32]. Release of drug from the micellar system is dependent on the exploitation of differences that exist in normal tissues and pathological tissues. Such a release mechanism from polymeric micelles is also termed as 'intelligent delivery' or 'smart delivery' by other researchers.

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 tumours 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 [34]. 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 [35].

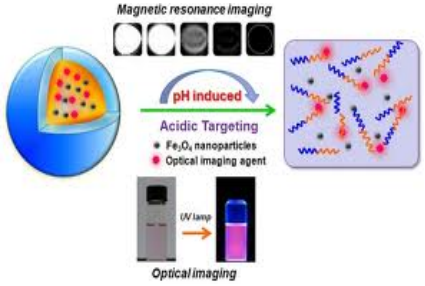

Figure 8: Acid sensitive polymeric micelles

Two main approaches that have been used for developing pH sensitive systems are: involvement of a titrable group into the co-polymer, and inclusion of labile linkages that are destabilized in acidic conditions.

Incorporation of titrable groups such as amines, carboxylic acids into the backbone of the co-polymer leads to an alteration of the solubility of the polymer upon protonation. This in effect may disrupt the micellar structure. Inclusion of acid-labile linkages, such as benzoic imine linkage, in polymeric structures has shown to cause change in micellar integrity or complete destruction of the micellar structure when these polymers encounter low-pH environment [36].

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). With regard to the thermal targeting strategy, LCST is the most important parameter [37]. Temperature changes can be internal, e.g. hyperthermia during inflammation, or can be external. Heat can be generated inside target tissues by locally applied ultrasound or by locally applied high frequency causing the oscillation of target-accumulated magneto-sensitive micelles.

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. For tumour targeting, cancer-specific peptides are more appropriate as peptides can easily be derivatized and engineered to achieve better *in vivo* stability and tissue specificity.

Active Targeting using Immunomicelles

Attachment of antibodies to micelle surface provides the broadest opportunities in terms of diversity of targets. Thus, many researchers have tried to exploit this opportunity by covalently attaching an antibody to polymeric micelles for generating the 'immunomicelles' [38]. To demonstrate the effectiveness of using immunomicelles in targeting of cancer, Torchillin *et al.* solubilized paclitaxel and camptothecin in mixed micelles of polyethylene glycol-phosphatidyl ethanolamine and vitamin E. These micelles were additionally modified with antinucleosome monoclonal antibody 2C5 (mAb 2C5), which can specifically bring micelles to tumour cells *in vitro*. These mixed micelles and mAb 2C5-immunomicelles demonstrated significantly higher *in vitro* cytotoxicity against various cancer cell lines.

FEW OF PATENTS IN POLYMERIC MICELLES

Patents No.	Polymers	Title	Observations
US20050019303	Polycaprolactone (PCL) and Polyethylene glycol (PEG)	Biodegradable co-polymer, and polymeric micelle containing the same	The micelles possess good drug and bioactive agent delivery characteristics and are suitable for use in drug delivery or cosmetic applications.
US20060216342	Polyethylene glycol and phosphatidylethanolamine	Micelle delivery system loaded with a pharmaceutical agent	A drug delivery system comprising a targeted form of a polyethyleneglycol (PEG)/lipid-conjugated micelle, which is capable of stabilizing poorly soluble pharmaceutical agents.
US20060240092	Propyne-aryl-poly(ethylene glycol)-b-Poly(aspartic acid)-b-[Poly(phenylalanine)-co- Poly(tyrosine)]	Polymeric micelles for drug delivery	The present invention relates to the field of polymer chemistry and more particularly to multiblock co-polymers and micelles comprising the same.
US20077262221	Poly(ethylene glycol) (PEG) and Poly (ethylene imine) (PEI)	Amphiphilic starlike Macromolecules for drug delivery	The present invention provides polymeric compounds that can form micelles in solutions. These compounds have a hydrophobic, core that is coupled to a plurality of hydrophilic moieties.

Table 3: Patents Describing the Development of Polymeric Micelles for the Improvement of Technological Aspects of Drugs

MARKETED PRODUCTS

Product	Application	Company
Genexol PM	Non-small cell lung cancer	Samyang
Estrasorb	Estrogen therapy	Novavax
Medicelle	Cancer treatment	NanoCarrier
Flucide	Anti-influenza	NanoViricides
Basulin	Long acting Insulin	Flamel Technologies
DO/NDR/02	Paclitaxel delivery	Dabur Research Foundation
DDS-2001	Not disclosed	LaboPharm

Table 4: Marketed products of polymeric micelles [40]

POLYMERIC MICELLES IN CLINICAL TRIALS

Polymer	Drug	Size (nm)	Status	Maximum Tolerated Dose	*Ref.*
MPEG-*b*-*PDLLA* (2000−1750)a	Paclitaxel	30–60	Phase I/II	300 mg/m2 intravenous infusion for 3 h, once every 3 weeks	*39*
Pluronic L61/F127 (~2,000/~12,600)	Doxorubicin	~25	Phase I	70 mg/m2 intravenous infusion for 12.5 min, once every 3 weeks, six cycles	*40*

Table 5: Drug, polymer used, status of clinical trials

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