



Review article

## Polymeric micelle as a multifunctional therapeutics

Powar Priyatama V\*<sup>1</sup>, Sharma Padmini H<sup>2</sup>

<sup>1</sup>Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth-vadgaon.

<sup>2</sup>Department of Pharmaceutics, Padmashree Dr. D.Y. Patil College of Pharmacy, Akurdi, Pune-411044. India.

### Abstract

Polymeric micelles are nano-scope core/shell structures produced by amphiphilic block copolymers with hydrophobic core and hydrophilic shell. Both the inherent and modifiable properties of polymeric micelles construct them particularly well appropriate for drug delivery purposes. In the last two decades, polymeric micelles have been vigorously studied as an innovative type of drug carrier system, because it possesses high stability both in vitro and in vivo and good biocompatibility, and can solubilize a broad variety of poorly soluble drugs. Polymeric micelles can overcome various limitations of the conventional drug delivery system, acting as carriers able to enhance drug absorption, protection of the loaded drug from the harsh environment of the GI tract, release of the drug in a controlled manner at target sites, prolongation of the residence time in the targeted area, and improve the drug accumulation in effectors area. In this review, polymeric micelle drug carrier systems are discussed with a spotlight on designs, types and classifications of the polymeric micelle system. Advantages and disadvantages are briefly summarized and explained, followed by delivery of different drug category.

**Keywords:** Polymeric Micelles, Nano-scope, Drug Targeting, Drug Carrier System.

**\*Corresponding Author: Powar Priyatama V**, Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth-vadgaon.

### Introduction

Polymeric micelles are nano-constructs, spherical, colloidal, self-assembled from biodegradable and biocompatible amphiphilic block polymers with sizes ranging 10–200 nm, which act as a promising nanocarriers for various class of drugs [1]. It consists of amphiphilic copolymers with a hydrophobic block, hydrophilic block and balance between those two blocks in an aqueous medium induces spontaneous construction of nano-sized particulates which is a competent nano-device for drug and gene delivery as shown in Figure No. 1 [2].

Micelles of amphiphilic copolymers with low CMC values illustrate superior stability even at low concentrations of the amphiphile in the medium. Increasing the hydrophobicity of the copolymer reduces the CMC which in turn, enhances stability. Non-polar molecules are solubilized within the hydrophobic core of micelles by adsorption on micellar surface, whereas molecules with intermediate polarity distribute along the surfactant molecules in intermediate positions.

Nanotechnology is currently at the vanguard of drug delivery research, which delivered

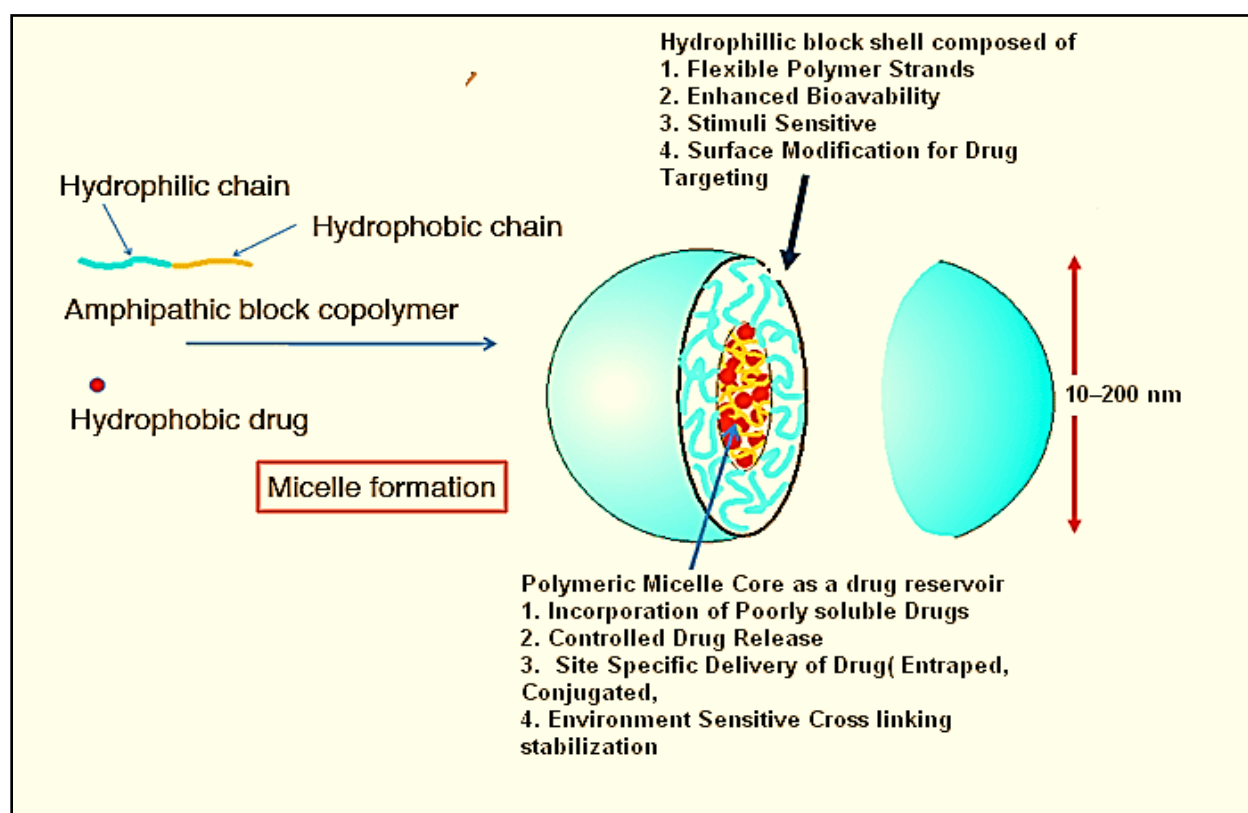
inventive platforms for management of diseases like cancer, which stand a significant challenge for researchers and patients. A diversity of nanoscale systems counting polymeric nanoparticles, liposomes, polymeric micelles, nanogels, nanocapsules, dendrimers, carbon nanotubes, nanocrystals and solid lipid nanoparticles, are currently under active investigation for delivery of small molecule drugs, therapeutic macromolecules (proteins, peptides, DNA and RNA), which increase efficacy, specificity, tolerability, therapeutic index of drugs [3]. The distinctive methods used for enhancement of solubility of poorly water-soluble drugs are

- Micronization
- Complexation

- Micro-emulsification
- Dialysis Method,
- Solid Dispersion Method
- Direct Dissolution
- Chemical Conjugation

Among diverse Novel drug delivery system approaches like nanoparticles, lipid-based vesicles, micelles; polymeric micelles gained extensive attention in the last two decades as a multifunctional nanotechnology-based delivery system, which can overcome some limitations of the conventional delivery system [4].

Due to contemplation of these parameters could facilitate the development of robust nano-systems with many profitable features as mentioned in Figure No. 2.



**Figure 1. Structural details of Polymeric Micelle**

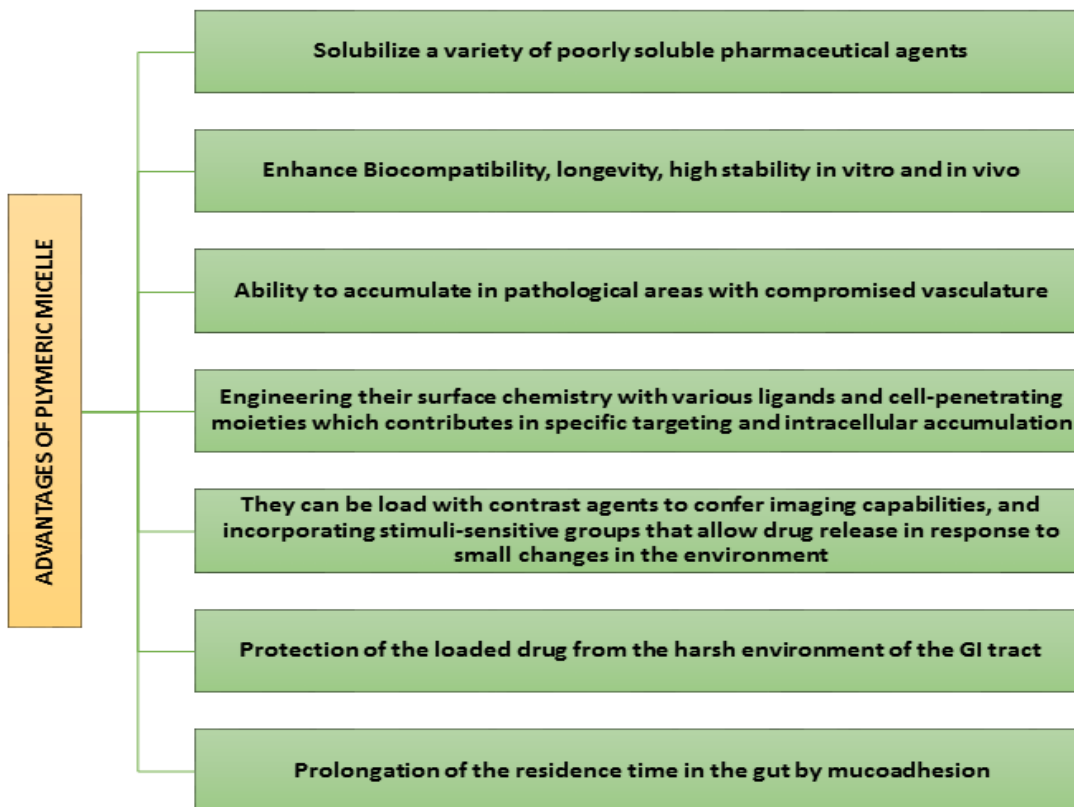


Figure 2. Advantages of Polymeric Micelles

Table 1. Polymers used for polymeric micelles

Sr. No.	Type of micelle forming copolymers	Structure of polymer in micelle  (A - hydrophilic unit; B - hydrophobic unit)	Example of polymers
1	Block copolymers	A-B Di-block  copolymer AB	Poly(styrene)-b-poly(ethylene oxide)
		A-B-A Tri-Block  copolymer ABA	Poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)
2	Graft copolymers	Multi-block structure  Graft copolymer	N-phthaloylchitosan-g-polycaprolactone

### Structural composition of Polymeric Micelle [5]

Pharmaceutical research on polymeric micelles primarily focused on copolymers having an A-B di-block or A-B-A Multiblock structure with A (the hydrophilic shell) and B (hydrophobic core), as shown in Table No. 1. Polymeric micelles consisting of amphiphilic block copolymers which form Polymeric micelles in aqueous solution above critical aggregation concentration (CAC) or critical micelle concentration (CMC). At the CAC or CMC, hydrophobic segments of block copolymers start to associate to minimize the contact with water molecules, leading to the formation of a vesicular or core-shell micellar structure by reestablishing of hydrogen bond network in water which diminishes free energy of the system. The hydrophobic core which generally consists of a biodegradable polymer (PBLA, PDLLA, PCL), 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 [6].

On the basis of the type of intermolecular forces polymeric micelles can be classify in three main categories:

1. Hydrophobic interactions
2. Electrostatic interactions
3. Metal complexation.

#### A. Conventional

These micelles are produced by hydrophobic interactions between core segment and shell region in the aqueous environment. Amphiphilic block copolymer eg. poly(ethylene oxide)-b-poly(propylene oxide)-b poly(ethylene oxide), forms micelles.

#### B. Polyion complex micelles (PICMs)

Which construct from the spontaneous self-assembly of ionic polymers of opposite charges to form a condensate which is dispersed in aqueous media by a hydrophilic segment, usually polyethylene glycol (PEG). The electrostatic forces and the van der Waals force of interaction direct the structure and size of the charged micelle. Eg. (Polyethylene glycol)-g- chitosan encapsulating trans-retinoic acid.

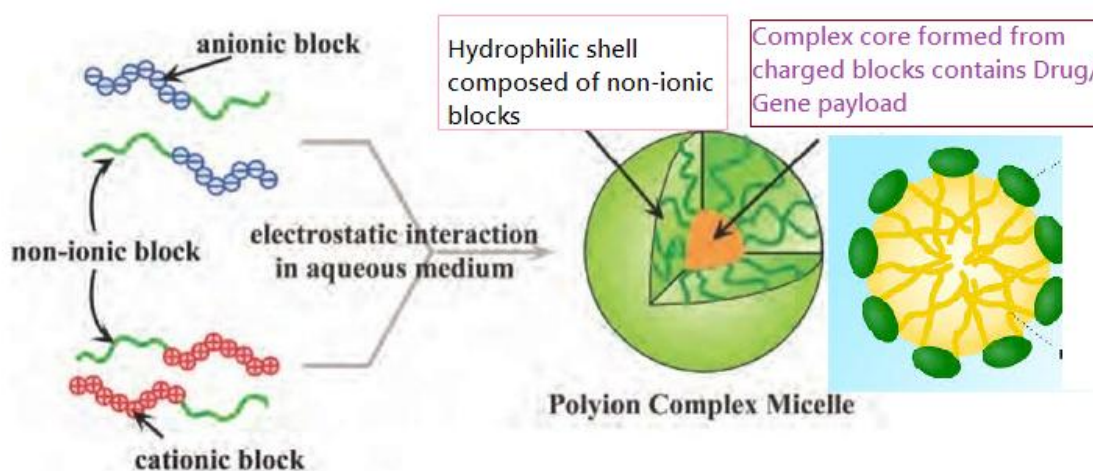
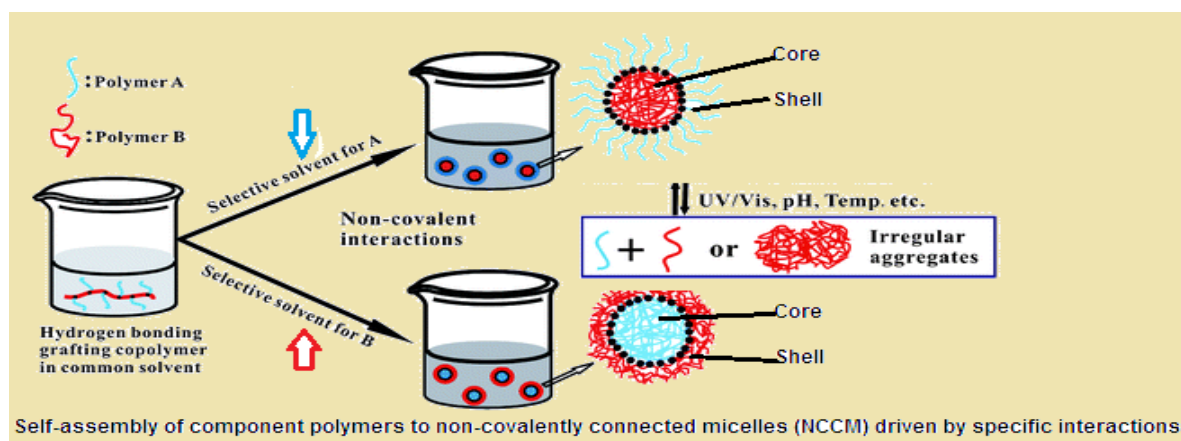


Figure 3. Polyion complex micelles

### C. Noncovalently Connected Polymeric micelle

The components of Noncovalently Connected Polymeric micelle form the core and shell are connected by hydrogen bonding, metal-ligand interactions which serves as the driving force. Both

micellization and structure transition were found to be reversible and associated with H-bonding complexation between the main chain and grafts. Eg. poly(4-vinyl pyridine) as a backbone and carbonyl terminated polybutadiene as the graft.



**Figure 4. Noncovalently Connected Polymeric micelle**

### Methods of Preparation for Polymeric Micelles

Polymeric micelles can be prepared mainly by three common approaches

- Direct dissolution: Direct dissolution of drug and copolymer in water with stirring, thermal, ultrasound treatments which facilitate dissolution. To enhance drug loading capacity, 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. Eg: Novel Biodegradable Polylactide/poly(ethylene glycol) Micelles Prepared by Direct Dissolution method for controlled delivery of anticancer drugs which shows great potential as carrier of hydrophobic drugs [7].
- Solvent Casting Technique: In this method volatile organic solvent used to dissolve the copolymer & drug. After complete evaporation of solvent there is thin film obtained. Drug loaded micelles are

obtained by reconstitution of film in water. Eg: Paclitaxel-loaded micelles prepare by solvent evaporation process[8].

- Dialysis: When the core forming blocks are long and more hydrophobic, the above-techniques are unsuitable for preparation. In these cases, the dialysis technique can be used in which 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. Eg: Self-Assembled Polymeric Micelles Based on Hyaluronic Acid-g-Poly(D,L-lactide-co-glycolide) Copolymer for Tumor Targeting [9].
- Lyophilization method: It is simple and cost effective method. Tert- Butanol water mixture is used for dissolving drug as well as polymer and then solution is under go polymerization process. Drug loaded polymeric micelles obtained by re-dispersing the lyophilized product in

suitable vehicle. Eg: Diazepam-Loaded Polymeric Micelles [10]. Other methods used are solid dispersion method, complexation, microphase separation method.

**Characterization of polymeric micelles**

Critical micelle concentration, drug release, Size and Shape, zeta potential, loading efficiency and stability are the key characterization parameter for the polymeric micelle.

**A. Critical micelle concentration**

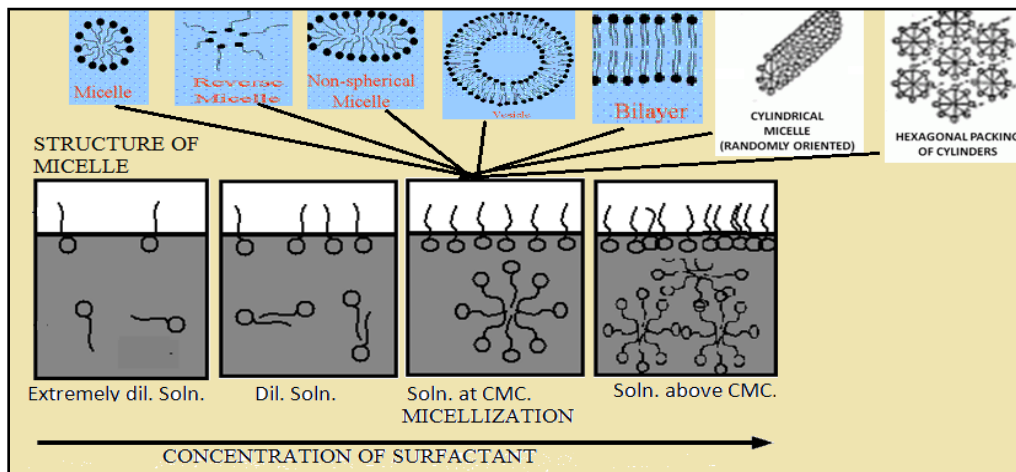
Polymeric Micelles are comparatively small, spherical structures composed of molecules that attract one another to reduce surface tension within the membrane of a cell. When the concentration of surfactant reaches a critical concentration, the hydrophobe of the surfactant will systematize to form micelle. In the micelle, the lipophilic hydrocarbon chains are orientated towards the interior of the micelle, leaving the hydrophilic groups on contact with the aqueous medium. The

concentration above CMC which micelle formation occurred and when diluted below this concentration, the micelles may collapse. Hence, CMC is the key parameter for the configuration and static stability of polymeric micelles which act as a drug carrier systems which sufficiently stable in blood circulation and should not disintegrate upon contact with blood components. Therefore the CMC should be low as possible. Numerous methods are used for determination of CMC

- Surface Tension Measurements
- Chromatography
- Light Scattering
- Small Angle Neutron Scattering
- Small Angle X-Ray Scattering
- Differential Scanning Calorimetry
- Viscometry
- Fluorescent Probes

Micelle formation mechanism involved:

- Stepwise growth model (Isodesmic model)
- Closed aggregation model



**Figure 5. Formation of Polymeric micelle and different shape**

**B. Size and Shape Determination**

Scanning electron microscopy (SEM), transmission electron microscopy (TEM) techniques, cryo-TEM technique, Atomic force

microscopy (AFM), photon correlation spectroscopy, asymmetrical flow field-flow fractionation and small angle neutron scattering have been extensively used for

visualization, size and shape determination of Polymer micelles [11,12].

### **C. *In Vitro* Drug Release Behavior of Polymer micelles**

*In-vitro* drug release studied carried out by placing the Polymeric micellar solution in a dialysis tube/ bag. The dialysis bag is immersed into a flask containing release medium, kept at a constant temperature. At pre-programmed time intervals, aliquots of the release medium are taken and replaced by fresh medium. The content of drug released in the medium can be calculated by spectroscopic method [13].

### **Applications**

The applications of polymeric micelle include solubilization of poorly soluble molecules, targeted drug delivery, sustained release, size advantages, protection of encapsulated substances/ drug from degradation and metabolism.

#### **A. Solubilization**

The solubilization practice leads to augmentation of water solubility and bioavailability [14]. It is often observed that the gastrointestinal (GI) uptake of particles is affected by particle size. 100 nm in diameter particle size which enhance the uptake by 15 to 250-fold by GI tract.

These delivery system can be used for Oral pH-Sensitive Polymeric micelle, Mucoadhesive Polymeric micelle, Mucoadhesive Polymeric micelle for Enhancement of Bioavailability. Eg: Camptothecin Pluronic p-105, d-tocopherol Peg 1000 succinate increased micellar stability and bioavailability

#### **B. Target delivery system**

Micelle-based delivery systems can be superior by engineering their surface for specific applications. Numerous targeting

ligand molecules can be used for attachment at specific cell or intracellular accumulation at a site of interest. pH-, thermo-, ultrasound-, enzyme- and light-sensitive block-copolymers allow for controlled micellar dissociation and triggered drug release in response to the pathological environment-specific stimuli or externally applied signals at specific site.

### **C. Nano drug delivery system**

The Pluronic block copolymers cause various functional alterations in cells. Pluronic polymers incorporate into membranes followed by translocation into the cells and affecting diverse cellular functions, such as mitochondrial respiration, ATP synthesis, activity of drug efflux transporters, apoptotic signal transduction, and gene expression. Which causes extreme sensitization of MDR tumors to various anticancer agents, improve drug transport across the blood-brain and intestinal barriers, and cause transcriptional activation of gene expression both *in vitro* and *in vivo*. Polymeric micelles utilized for delivery of CNS drugs across the blood-brain barrier, oral delivery of drugs, and tumor-specific delivery of antineoplastic agents [15].

### **D. Gold nano particles**

Gold nanoparticles are a great deal of recent interest in the context of emerging nanotechnology applications. At the nanoscale, they exhibit unique quantum and surface properties, different from those of atoms as well as bulk materials.

### **E. Mesomorphous behavior**

Aggregated structure of tri-block copolymers is controlled by temperature, concentration, and concentration of additives, they used as structure-directing organic materials for the synthesis of inorganic materials with a controlled size, shape and structure. The blends of block copolymers can interact and

tend to self assemble into cross-linking micellar structures during the solvent evaporation process, which provides a suitable template for the construction of meso-structures.

#### **F. Sustained Release Profile**

Polymeric micelles are more stable with low CMC, less dissociation, retention of loaded drugs for a longer period of time, and achieve a superior accumulation of the drug at the target site. Muco-adhesive properties of polymeric micelles can lengthen the residence time in the gut. Polymeric micelles improve drug absorption through the GIT mucosa by escalating membrane permeability to the drug and/or carrier or by inhibiting drug efflux transporters in the mucosa (P-gp inhibitors). This sustained release ability requires following properties

- Micelles must be stable to dilution due to their high thermodynamic stability (low CMC)
  - High kinetic stability
  - Low chain mobility core properties
  - Drugs with low diffusion coefficients
- Eg: Pluronic-PAA (poly(acrylic acid) micellar formulations used for oral drug delivery systems. [16].

#### **G. Passive Targeting**

This phenomenon is called the 'EPR' effect. This is an entrenched phenomenon that under certain circumstances such as inflammation or hypoxia which is typical for tumors, infarcts, and other pathological situations. At those sites, the defensive endothelial lining of the blood vessel wall is impaired by secreted factors such as kinin which results in leaky vessels. Therefore, nanoparticles that achieve interstitial access to the tumor have higher retention times than in normal tissues with following properties:

- Small size i.e less than 200nm to avoid RES uptake
- Hydrophilic shell
- High molecular weight

Eg: Paclitaxel incorporated in PEG-b-poly (4-phenyl-1-butanoate)-l-aspartamide conjugates has shown better accumulation in tumors than its commercial formulation Taxol [17].

#### **H. Active targeting**

Which enhance drug delivery and reduce side effects by increasing the selective uptake by targets site. There are two approaches for active targeting:

- Utilize biologically specific interactions
- Utilize locally applied signals (external or internal).

In case of tumor microenvironment, overexpression of cell surface tumor-associated antigens that are found at low levels in normal tissues. Nanocarriers functionalized with targeting ligands are internalized upon binding of the ligand-modified nanocarrier with the cell-surface receptor and then translocated intracellularly through endosomal vesicles. Therefore, increased specific cellular uptake and improved therapeutic efficacy can be reached with a much lower dose.

#### **I. Photodynamic Therapy**

Photodynamic Therapy is a promising approach for the treatment of tumors and macular degradation. which involves the systemic administration of photosensitizers, followed by the local application of a laser with a specific wavelength to the diseased sites. Upon photoirradiation, the photosensitizers generate highly reactive singlet oxygen, leading to light-induced cytotoxicity (photocytotoxicity). Polymeric micelles improve the selectivity and efficacy of Photodynamic Therapy as well as prevent side effects such as skin hypersensitivity. A study

by Guo et al. reported photosensitizer-loaded micelles incorporating a cyanine dye as potential theranostic micelles for tumor localization via dual photoacoustic/near-

infrared fluorescent (NIRF) imaging, and simultaneous superior cancer therapy via sequential synergistic photothermal therapy/photodynamic therapy [18].

**Table 2. Stimulus Responsive Drug Release [19]**

<b>Polymeric Micelles</b>	<b>Name of Polymer</b>
pH-Sensitive Polymeric Micelles	poly(ethylene glycol)-poly(aspartate hydrazone adriamycin) micelles with adriamycin
Thermo-Sensitive Micelles	Poly(N-isopropylacrylamide)
Light-sensitive (UV, NIR)	dextran-graft-(2-diazo-1,2-naphthoquinone) (Dex-DNQ) with doxorubicin (DOX)
Enzyme-responsive	Polypeptide, polysaccharide, polyethylene oxide, gelatin, dextran
Redox-active	Polypyrrol, Ferrocenylakyl, polystyrene and poly(ferrocenylsilane)
Stimuli-Sensitive Polymers	PLGA-PEG block copolymers

## Conclusion

Nanotechnology will presume an vital place in drug delivery and human therapeutics. Nanotechnology which provide opportunities for physicists, chemists and biochemists to develop systems that may eventually match in sophistication and precision of biological structures elaborated by nature.

The past decade has witnessed an explosive development of polymeric micelles for targeted and controlled drug delivery. Polymeric micelles have emerged as important pharmaceutical carriers because of their attractive properties. Polymeric micelles can prepared by various methods depend of drug profile and can be easily loaded with a wide variety of poorly soluble drugs, which improved bioavailability and other properties of these drugs. Importantly, these can be effectively used to target certain pathological areas in the body with the help of diverse variety of polymers. Their unique nanoscopic core-shell structures formed by copolymers have established exceptional features as controlled and targeted nanocarriers with elevated translational potential. Thus polymeric micelles, as drug carriers, have a promising future.

## References

1. Gong, J.; Chen, M.; Zheng, Y.; Wang, S.; Wang, Y. Polymeric micelles drug delivery system in oncology. *J. Control. Release* 2012; 159:312–323.
2. Kazunori Kataoka. Development of Polymer-based Nanodevices for Pinpoint Therapy and Diagnostics. *Advanced Polymers for Nanobiotechnology* 2009; Vol. 58, No. 1.
3. J. B. Hall, M. A. Dobrovolskaia, A. K. Patri, and S. E. McNeil. Characterization of nanoparticles for therapeutics. *Nanomedicine* 2007; 2(6):789–803.
4. R. G. Strickley. Solubilizing excipients in oral and injectable formulations. *Pharmaceutical research* 2004; 21(2):201–230.
5. C. J. H. Porter and w. N. Charman. In vitro assessment of oral lipid based formulations. *Advanced drug delivery reviews* 2001; 50(1):127–147.
6. M.-C. Jones and J.-C. Leroux. Polymeric micelles—a new generation of colloidal drug carriers. *European Journal of Pharmaceutics and Biopharmaceutics* 1999; 48(2):101–111.
7. M. Yokoyama, G.S. Kwon, T. Okano, Y. Sakurai, T. Seto, K. Kataoka. Preparation of micelle-forming polymer-drug conjugates. *Bioconjugate Chem.* 1992; 3:295-301
8. Liu Yang et al. Novel Biodegradable Polylactide /poly(ethylene glycol) Micelles Prepared by Direct Dissolution Method for Controlled Delivery of Anticancer Drugs. *Pharmaceutical Research* 2009; 26(10): 2332-2342.
9. Zhenjiaoa, Na Liua, Zhiming. Selection suitable solvents to prepare paclitaxel-loaded micelles by

- solvent evaporation method, loaded micelles by solvent evaporation method. *Chen Pharmaceutical Development and Technology* 2012; 17(2):164-169.
10. Dae Hwan Kang, Gyung Mo Son, Hyun Yul Kim, Je Ho Ryu, Chong Woo Chu, Su Bum Park, Young-IL Jeong, Self-Assembled Polymeric Micelles Based on Hyaluronic Acid-g-Poly(D,L-lactide-co-glycolide) Copolymer for Tumor Targeting, *Int. J. Mol. Sci.* 2014, 15, 16057-16068
  11. Jiraphong Suksiriworapong, Tanaporn Rungvimolsin, Atitaya A-gomol, Varaporn Buraphacheep Junyaprasert, Doungdaw Chantasart, Development and Characterization of Lyophilized Diazepam-Loaded Polymeric Micelles, *AAPS Pharm Sci Tech.* 2014 Feb; 15(1): 52-64.
  12. Kang DY, Kim MJ, Kim ST, Oh KS, Yuk SH, Lee S. Size characterization of drug-loaded polymeric core/shell nanoparticles using asymmetrical flow field-flow fractionation. *Anal Bioanal Chem* 2008; 390:2183-88.
  13. Ramzi A, Rijcken CJF, Veldhuis T, Schwahn D, Hennink WE, Nostrum CF. Core-shell structure of degradable, thermosensitive polymeric micelles studied by smallangle neutron scattering. *J Phys Chem B* 2008;112:784-92.
  14. Dong PW, Wang XH, Gu YC et al. Self-assembled biodegradable micelles based on star-shaped PCL-b-PEG copolymers for chemotherapeutic drug delivery. *Colloids Surf A: Physicochem Eng Aspects* 2010;358:128-34.
  15. Chi SC, Yeom D, Kim SC, Park ES. A polymeric micellar carrier for the solubilization of biphenyl dimethyl dicarboxylate. *Arch Pharm Res* 2003; 26:173- 81.
  16. Pragnesh N Dave, Vijender Singh, Poonam Khullar, Navjot Kaur, Micelles, mixed micelles, and applications of polyoxypropylene (PPO)-polyoxyethylene (PEO)-polyoxypropylene (PPO) triblock polymers, *International Journal of Industrial Chemistry* 2013, 4:12,1-18
  17. Lukyanov AN, Torchilin VP. Micelles from lipid derivatives of water-soluble polymers as delivery systems for poorly soluble drugs. *Adv Drug Deliv Rev* 2004, 56:1273-1289.
  18. Guo P, Coban O, Snead NM, Trebley J, Hoepflich S, Guo S, Shu Y. Engineering RNA for targeted siRNA delivery and medical application. *Adv Drug Deliv Rev* 2010, 62:650-666.
  19. Guo M, Mao H, Li Y, Zhu A, He H, Yang H, Wang Y, Tian X, Ge C, Peng Q, et al. Dual imaging-guided photothermal/photodynamic therapy using micelles. *Biomaterials* 2014, 35:4656-4666
  20. Maria Rosa Aguilar, J.S. Román, *Smart Polymers and their Applications*, Woodhead publications, Cambridge UK, 1st, 2014, 171.