



**INTERNATIONAL JOURNAL OF  
PHARMACEUTICAL SCIENCES**  
[ISSN: 0975-4725; CODEN(USA): IJPS00]  
Journal Homepage: <https://www.ijpsjournal.com>



## Review Paper

# Polymeric Micelles as Advanced Nanocarriers

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### ARTICLE INFO

Published: 18 Mar 2026

**Keywords:**

Polymeric micelles;  
Nanocarriers; Amphiphilic  
block copolymers; Targeted  
drug delivery; Controlled  
drug release

**DOI:**

10.5281/zenodo.19087477

### ABSTRACT

Polymeric micelles have emerged as one of the most versatile and effective nanocarrier systems for improving the delivery of poorly water-soluble drugs. These nanoscale, core-shell structures are formed through the self-assembly of amphiphilic block copolymers, enabling the encapsulation of hydrophobic therapeutics within a stable and biocompatible architecture. Their small size, enhanced solubility, prolonged circulation time, and ability to selectively accumulate in diseased tissues—particularly tumors—position them as a highly promising platform in modern drug-delivery research. This review provides a comprehensive overview of polymeric micelles, beginning with their fundamental principles, structural features, and mechanisms of self-assembly. Various micelle morphologies—including spherical, cylindrical, reverse, disk-shaped, vesicular, worm-like, mixed, and cross-linked systems—are discussed in relation to their influence on drug-loading capacity, stability, biodistribution, and therapeutic performance. Methods of micelle preparation, critical micelle concentration (CMC), formation kinetics, and factors governing micelle stability are also highlighted. Furthermore, the review explores recent advancements in stimuli-responsive micelles, uni-molecular and cross-linked systems, and applications ranging from cancer therapy and gene delivery to dermal, ocular, and diagnostic uses. While polymeric micelles offer significant advantages such as improved solubility, controlled release, and reduced systemic toxicity, limitations including premature drug release, scale-up challenges, and biological instability remain areas of ongoing investigation. Overall, recent progress from 2020–2025 demonstrates that polymeric micelles continue to evolve into increasingly sophisticated, multifunctional nanocarriers. Their adaptability, biocompatibility, and tunability reflect a strong potential for future clinical translation across diverse therapeutic fields.

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**Relevant conflicts of interest/financial disclosures:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



## INTRODUCTION

The safe, efficient, and targeted distribution of poorly water-soluble medications is one of the most fascinating difficulties in the field today's drug delivery. A lot of appealing medicinal compounds fall short of their full potential just because they are challenging to dissolve, are quickly eliminated, or have undesirable side effects. Polymeric micelles have shown themselves to be a promising answer in this regard. Polymeric micelles are core-shell nanoparticles formed when block and graft copolymers self-assemble in a specified solvent. Polymeric micelles have a spherical shape and range in size from 10 to 100 nanometers. Surfactant micelles have much worse thermodynamic and kinetic stability than polymeric micelles. Medicinal substances and drugs used to treat diseases are less soluble in watery medium. Consequently, a great focus has been placed on creating extremely effective and site-specific drug delivery devices.<sup>1</sup> For medications that are amphiphilic and poorly soluble in water, polymeric micelles have emerged as a unique and promising colloidal delivery mechanism. Since they can dissolve large amounts of hydrophobic substances in their inner core, they are thought to be more stable than surfactant micelles. These particles' small size and hydrophilic coating may allow them to impact tumor tissues and exhibit prolonged circulation durations *in vivo*.<sup>2</sup> The structural features, drug loading capabilities, pharmacokinetics, and biodistribution of different formulations are reviewed, as are clinical trials and the techniques used to describe these features in connection to drug delivery systems. It examines the many functions of polymer micelles in drug delivery, emphasizing their special qualities such as biocompatibility, stability, and adjustable drug release kinetics. Solutions containing amphiphilic molecules or surfactant monomers with a polar

head and a lipophilic tail exhibit abrupt changes in a variety of physicochemical characteristics. The orientation and association of amphiphilic molecules in solution, which results in the creation of structures known as micelles, is linked to the change in physicochemical qualities. The micelles inside contain a hydrophobic core and outwardly a hydrophilic surface. Micelles typically consist of 50–200 monomers; the aggregation number is the average number of monomers that form a micelle at any particular moment. Since a spherical micelle's radius is about equal to the length of a fully extended surfactant monomer, which is typically 1-3 nm, micelles are classified as colloidal.<sup>3</sup> In pharmaceutical research, biocompatible polymers have been widely used as excipients for conventional pharmaceutical formulations and, more recently, in nanomedicines to improve the therapeutic effects of powerful medications. Micelles created by amphiphilic block copolymers in aqueous solution were thought to be carriers for medicinal chemicals that were poorly soluble and either covalently bonded to polymer chains or noncovalently integrated.<sup>4</sup> into the micelles some thirty years ago. Since then, a great deal of research has been done on the use of amphiphilic block copolymers in the creation of polymeric micelles for medicinal purposes. Numerous innovative block copolymers have been put up to create delivery methods based on micelles as possible human nanomedicines. Numerous noteworthy developments in polymeric micelles have been produced to maximize the delivery of medicinal compounds.<sup>4</sup> The self-assembly of amphiphilic block copolymers in aqueous solution creates the core-shell structure of polymeric micelles (PMs), which are nanoscale drug delivery vehicles. An entropically favored phenomenon is the independent existence of amphiphilic molecules in diluted aqueous solutions, which serve as surfactants to lower surface tension at the air-water interface.



Throughout the process, the copolymer's hydrophilic and hydrophobic compartments produce the shell and core of the polymeric micelles, respectively. Polymeric micelles are ideal for therapeutic medication administration because of a number of their properties. Non-polar medicinal substances can be stored in the hydrophobic core of polymeric micelles. These drugs can be incorporated into polymeric micelles to eliminate the requirement for formulation vehicles and the toxicity that results.<sup>5</sup>

### **Micelles:**

Changes in physicochemical characteristics brought on by the orientation and aggregation of amphiphilic molecules in solution are linked to the formation of micelles. Depending on their composition, micelles can have a diameter of 2 to 20 nm and are typically spherical in shape. Micelles have attracted a lot of attention due to their potential to deliver drugs that aren't very soluble in water. Micelles are made up of self-assembling amphiphilic molecules. The structures consist of a hydrophobic/nonpolar section (tail) and a hydrophilic/polar segment (head). Micelles are created in an aqueous solution, with the nonpolar region forming the micelle's core and the polar region facing the micelle's outer surface. Micelles have the ability to administer both hydrophilic and hydrophobic agents.<sup>1</sup>

### **Types Of Micelles:**

Micelles can adopt a variety of morphologies depending on the molecular structure of amphiphilic polymers, their packing parameter, and the surrounding environment. These structural variations significantly influence drug-loading efficiency, stability, biodistribution, and therapeutic performance. Understanding the diversity in micellar shapes is essential for designing optimized polymeric micelle systems

for drug delivery. The major micelle morphologies are described below.

#### **1. Spherical Micelles**

Spherical micelles are the most classical and widely reported morphology in polymeric micelle research. They form when the hydrophobic segments of amphiphilic polymers aggregate to create a compact core, while hydrophilic chains extend outward to form a stabilizing corona. This geometry provides high colloidal stability, low critical micelle concentration, and excellent capacity for loading hydrophobic molecules. Spherical micelles remain the most clinically explored micellar systems, especially for delivering poorly water-soluble anticancer drugs.<sup>6</sup>

#### **2. Reverse Micelles**

Reverse micelles typically form in nonpolar environments, where the hydrophilic blocks orient toward the interior and the hydrophobic blocks face outward. Although more common in traditional surfactant chemistry, reverse polymeric micelles are gaining attention for specialized applications such as enzyme encapsulation, biocatalysis, and solubilization of hydrophilic molecules in organic media. Their unique architecture allows the creation of nanoscale aqueous microenvironments in nonpolar phases.<sup>7</sup>

#### **3. Cylindrical (Rod-like) Micelles**

Cylindrical micelles emerge when amphiphilic polymers pack in a manner that favors axial elongation instead of forming a closed spherical structure. Their elongated, anisotropic shape improves margination along vascular walls, enhances tumor penetration, and reduces renal clearance. These benefits make rod-like micelles promising candidates for cancer nanomedicine where prolonged systemic exposure and deep tissue penetration are desired.<sup>8</sup>

#### **4. Disk-Shaped Micelles**

Disk-like micelles represent a less common but scientifically significant morphology. They form from lamellar or sheet-like assemblies that do not close into vesicles. Due to their large interfacial area, disk micelles are useful for membrane-mimicking studies and can facilitate the delivery of drugs that benefit from planar or interfacial alignment. Their unique shape also helps in understanding intermediate structures in micelle-to-vesicle transitions.<sup>9</sup>

### 5. Vesicles (Polymersomes)

Vesicles, also known as polymersomes are bilayered structures enclosing an aqueous core. Unlike simple micelles, vesicles can encapsulate both hydrophilic drugs (inside the core) and hydrophobic drugs (within the bilayer). Polymersomes exhibit superior mechanical stability and tunable membrane thickness compared to conventional liposomes. These features make polymeric vesicles suitable for complex delivery strategies, including combination therapies and controlled release applications.<sup>10</sup>

### 6. Worm-Like Micelles (Filomicelles)

Worm-like or filamentous micelles possess long, flexible, chain-like structures. Their unique morphology provides remarkably long circulation times due to reduced renal clearance and distinct flow behavior in the bloodstream. These micelles gradually permeate biological tissues, enabling

sustained and controlled drug release. Their extended systemic presence makes them particularly valuable for chronic or long-term therapies.<sup>8</sup>

### 7. Mixed Micelles

Mixed micelles form through the co-assembly of two or more amphiphilic polymers or polymer-surfactant combinations. This approach allows fine control over micelle size, surface charge, stability, and drug-loading capacity. Mixed micelles also overcome limitations of single-polymer micelles, such as premature disassembly or low solubilization of ultra-hydrophobic drugs. They represent a versatile platform for enhancing therapeutic performance through synergistic polymer interactions.<sup>4</sup>

### 8. Polymeric Micelles (General Architecture)

Polymeric micelles form the overarching category encompassing all the morphologies described above. They arise from the self-assembly of amphiphilic block copolymers into core-shell nanostructures with high stability and tunable functionality. Polymeric micelles can be engineered for targeted delivery, stimuli-responsive behavior, controlled release, and improved pharmacokinetics. Their structural versatility and functional adaptability have made them one of the most promising nanocarrier platforms in modern drug delivery research.<sup>6</sup>

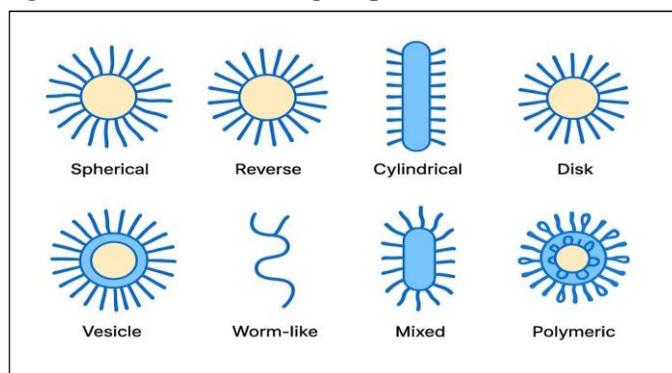


Fig.2.1.1 Types of Micelles

## Polymeric Micelles:

Polymeric micelles are a known auto-assembly that is created in a liquid and is made up of amphiphilic macromolecules in general amphiphilic di- or tri-block copolymers composed of blocks that are solvophilic and solvophobic. Amphiphilic block copolymers are useful for the creation of polymeric micelles. A new and promising colloidal delivery method for medications that are amphiphilic and poorly soluble in water is polymeric micelles.<sup>1</sup> Micelle morphologies include spheres, tubules, inverse micelles, bottle-brush shapes, and more, depending on the solvent conditions and hydrophobic and hydrophilic segments. A variety of techniques, including dilution, lyophilization solution, evaporation, dialysis, and oil-in-water emulsion, are used to prepare micelles.<sup>11</sup>

### Structure Of Polymeric Micells:

Polymeric micelles are tiny, nanoscale assemblies formed when amphiphilic block copolymers organize themselves in water. These micelles generally exhibit a core-shell structure, which is essential for their stability and functionality.<sup>11</sup>

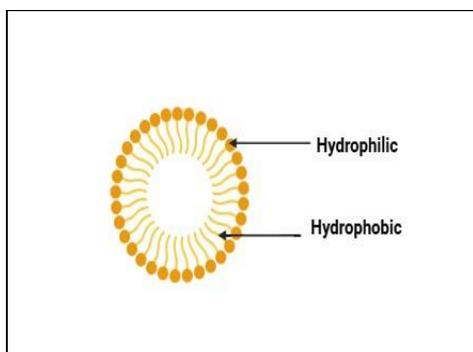


Fig.3.1.1 Structure of Micelle

- **Hydrophobic Core:**
- The inner part of the micelle is composed of the hydrophobic segments of the polymer.

- This region can trap hydrophobic molecules, such as certain drugs, making micelles useful in drug delivery.
- The size and density of the core depend on factors like the length of the
- **Hydrophilic Shell (Corona):**
- The outer layer consists of hydrophilic polymer chains.
- It interacts with water, which prevents micelles from sticking together and enhances their stability in solution.
- The shell also influences biocompatibility and circulation time in the body<sup>13</sup>
- **Shape and Morphology:**
- While many polymeric micelles are spherical, other forms like rod-shaped, wormlike, or vesicle-like micelles can occur depending on the balance between the hydrophilic and hydrophobic blocks.<sup>11</sup>
- This flexibility in structure allows researchers to fine-tune the micelles for specific drug delivery requirements.

## Formation Of Polymeric Micells

### 1 Self assembly:

Self-assembly is the process by which a structured organization forms on its own. The human brain, spider webs, fingerprints, DNA patterns, phospholipids in cell walls, honeycombs, butterfly wings, zebra stripes, desert dunes, and more are examples of self-organized structures found in nature. Small molecules, either in bulk or in solution, self-assemble or aggregate into particular systems in science. Because of its mechanical and physical characteristics, this arrangement is more stable. The self-assembly of polymers and surfactants has been the subject of numerous reports. Specifically, polymers with different

architectures include graft polymers, cyclic polymers, and amphiphilic block copolymers<sup>11</sup>.

## 2 CMC :

The main topic here is polymeric micelles, and CMC is very important when developing the micelle. So, the focus is on finding CMC, and then the formation of micelles is talked about in depth. Self-assembling nanoparticles known as polymeric micelles are composed of amphiphilic block polymers, which are polymers with both hydrophilic and hydrophobic blocks. Amphiphilic block polymers behave similarly to regular amphiphiles and form polymeric micelles above CMC in aqueous solution<sup>14</sup>.

### Formation Mechanism:

Polymeric micelles form spontaneously when amphiphilic block copolymers are placed in an aqueous solution. The driving force behind this self-assembly is the hydrophobic effect, where the water-fearing (hydrophobic) blocks cluster together to minimize contact with water, while the hydrophilic blocks interact with the surrounding water, forming a stabilizing shell.<sup>15,11</sup>

#### • **Critical Micelle Concentration (CMC):**

- The formation of micelles occurs only when the polymer concentration exceeds a threshold called the critical micelle concentration (CMC).
- Below this concentration, the polymers exist as individual chains (unimers). Once the CMC is reached, micelles start forming spontaneously.<sup>1,13</sup>

#### • **Factors Affecting Formation:**

- **Polymer composition:** The ratio of hydrophobic to hydrophilic blocks determines the size, shape, and stability of micelles.
- **Solvent conditions:** Temperature, pH, and ionic strength can influence micelle formation.

- **Preparation method:** Techniques such as dialysis, solvent evaporation, or microfluidics can control micelle size and morphology.

#### • **Kinetics vs Thermodynamics:**

- Micelle formation can be thermodynamically controlled, reaching the most stable configuration, or kinetically trapped, where the micelles form rapidly but are not in the lowest-energy state<sup>15,16</sup>
- This distinction is important for designing micelles for drug delivery, as the kinetics affect how the micelle behaves in biological environments.

#### • **Stimuli-Responsive Formation:**

- Some micelles are responsive to external stimuli such as pH, temperature, or light. These stimuli can trigger formation, disassembly, or drug release, making them useful for targeted delivery<sup>17</sup>

### Properties Of Polymeric Micelles

Polymeric micelles possess several unique properties that make them highly suitable for applications such as drug delivery, imaging, and biomedical use. These properties are closely related to their core-shell structure and the self-assembly behavior of amphiphilic block copolymers.<sup>11</sup>

#### • **Critical Micelle Concentration (CMC):**

- The CMC is the minimum polymer concentration required for micelle formation.
- Low CMC values indicate high stability, as micelles remain intact even upon dilution in the bloodstream.<sup>13</sup>

#### • **Size and Morphology:**

- Polymeric micelles are typically 10–100 nm in diameter.
- Size can be tuned by changing block lengths or preparation conditions.



- Morphology can be spherical, rod-like, or worm-like, which affects drug loading efficiency and circulation time.<sup>18</sup>
- **Stability:**
  - The hydrophilic corona stabilizes the micelle by steric repulsion, preventing aggregation.
  - Core-crosslinked micelles exhibit enhanced stability, resisting premature disassembly under physiological conditions.<sup>15</sup>
- **Drug Loading and Release:**
  - The hydrophobic core allows encapsulation of poorly water-soluble drugs, while the hydrophilic shell ensures dispersibility.
  - Drug release can be controlled by stimuli such as pH, temperature, or enzymes, which makes micelles responsive carriers<sup>17</sup>
- **Biocompatibility and Circulation:**
  - Hydrophilic shells, often composed of polyethylene glycol (PEG) or other biocompatible polymers, enhance blood circulation time and reduce recognition by the immune system.<sup>11</sup>

### Applications Of Polymeric Micelles

Polymeric micelles have attracted significant attention in nanomedicine and pharmaceutical research due to their unique core-shell structure, stability, and tunable properties. Their applications are largely related to drug delivery, diagnostics, and therapeutic targeting.<sup>11</sup>

- **Drug Delivery:**
  - Polymeric micelles are used to encapsulate poorly water-soluble drugs, increasing solubility and bioavailability.
  - The hydrophilic shell enhances blood circulation time, while the hydrophobic core protects the drug until release at the target site.<sup>13</sup>

- Stimuli-responsive micelles can release drugs in response to pH, temperature, or enzymes, allowing targeted therapy.<sup>17</sup>
- **Cancer Therapy:**
  - Micelles can preferentially accumulate in tumor tissues via the enhanced permeability and retention (EPR) effect.
  - This enables delivery of anticancer drugs with reduced side effects compared to conventional formulations.
- **Gene Delivery:**
  - Cationic block copolymer micelles can bind and protect nucleic acids, allowing safe gene or RNA delivery for therapeutic purposes.
  - The micelle structure protects genetic material from enzymatic degradation in the bloodstream.<sup>11</sup>
- **Imaging and Diagnostics:**
  - Polymeric micelles can carry contrast agents for MRI, CT, or fluorescence imaging.
  - Stimuli-responsive micelles improve signal localization, enhancing diagnostic accuracy.

- **Dermal Drug Delivery :**

Polymeric micelles successfully promoting to overcome the various skin barriers and skin toxicity.

- Which enhance the various pathway to promote the cosmetic science and drug delivery by the route of administration as Skin.<sup>19</sup>

### Other Applications:

- They are also explored for ocular drug delivery, anti-inflammatory therapy, and antibacterial applications, highlighting their versatility in biomedical research.<sup>18</sup>

### Advantages Of Polymeric Micelles



- **Enhanced Solubility of Hydrophobic Drugs:**

- The hydrophobic core allows encapsulation of poorly water-soluble drugs, increasing their bioavailability.<sup>11</sup>

- **Controlled and Targeted Drug Release:**

- Stimuli-responsive micelles release drugs in response to pH, temperature, or enzymes, enabling site-specific therapy.<sup>13,17</sup> ➤ Improved Stability and Circulation:

- The hydrophilic corona prevents aggregation and reduces rapid clearance from the bloodstream, enhancing in vivo stability.

- **Versatility in Applications:**

- Polymeric micelles can deliver small molecules, genes, or imaging agents, making them highly adaptable in nanomedicine.

- **Reduced Side Effects:**

- Targeted delivery reduces drug accumulation in healthy tissues, minimizing toxicity and side effects, especially in cancer therapy.<sup>18</sup>

### Limitations Of Polymeric Micelles

- **Limited Drug Loading Capacity:**

- The hydrophobic core can only hold a finite amount of drug, limiting the dose that can be delivered.<sup>11</sup>

- **Potential Premature Drug Release:**

- Micelles may disassemble below the critical micelle concentration (CMC), causing early drug leakage.<sup>13</sup>

- **Scale-up Challenges:**

- Reproducibility and large-scale production of micelles with uniform size and morphology can be difficult.

- **Stability Issues in Biological Fluids:**

- Interaction with proteins or blood components can destabilize micelles, affecting circulation time and drug delivery efficiency.<sup>17</sup>

### FUTURE PERSPECTIVES:

- **Enhanced Stability and Drug Loading:**

- Researchers are developing core-crosslinked micelles and multi-block copolymer designs to improve stability and increase drug loading capacity.<sup>17</sup>

- **Stimuli-Responsive and Smart Systems:**

- Development of pH, temperature, enzyme, and light-responsive micelles will allow more precise and targeted drug delivery, especially for cancer therapy.<sup>13</sup>

- **Combination Therapies:**

- Polymeric micelles are being investigated for co-delivery of multiple drugs or drug– gene combinations, enhancing treatment efficacy while minimizing side effects.

- **Clinical Translation:**

- More research is needed on scaling up production, reproducibility, and long-term biocompatibility, which are critical for clinical applications.<sup>18</sup>

### CONCLUSION

Polymeric micelles continue to stand out as one of the most versatile and impactful nanocarrier systems in modern drug delivery. Their unique core–shell architecture, ability to solubilize poorly water-soluble drugs, and capacity for controlled and targeted release collectively make them a powerful tool in pharmaceutical research. Over the years, advancements in polymer chemistry and self-assembly technology have enabled the design of micelles that are more stable, more selective, and more responsive to physiological stimuli.

Despite their immense potential, challenges such as limited drug-loading capacity, premature disassembly, and scale-up complexities still need



careful attention. Encouragingly, recent innovations—including stimuli-responsive systems, corecrosslinked micelles, and multifunctional hybrid structures—indicate that these limitations are gradually being addressed.

In essence, polymeric micelles represent a promising bridge between nanotechnology and therapeutics, offering new possibilities for safer, more efficient, and more patientfriendly drug delivery. Continued interdisciplinary efforts are expected to further expand their applications, shaping the next generation of advanced nanomedicine

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**HOW TO CITE:** Manoj Warade, Madhuri Narode, Namrata Tambe, Priyanka Patil, Vaishnavi Shelke, Polymeric Micelles as Advanced Nanocarriers, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 3, 1994-2003. <https://doi.org/10.5281/zenodo.19087477>

