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Review Article

An Insight into Polymeric Micelles Preparation Methods and Applications as Drug Delivery Approach: A Review

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ABSTRACT

Polymeric micelles which are formed by the self-assembly of amphiphilic copolymers, are distinguished among the other forms of nanostructured carriers due to their restricted size distribution, conformation, and surface features that promote their accumulation in the tumor region. Their distinctive architecture enables them to dissolve hydrophobic medications, extends their circulation half-life, and ultimately results in improved therapeutic effectiveness. Their synthesis process is contingent upon the physicochemical properties of the block copolymers, which subsequently have a substantial impact on the efficacy of drug encapsulation. Owing to the increasing prevalence of compounds with solubility problems, the pharmaceutical industry is currently faced with a significant challenge in improving the solubility of medications. This paper delves into the basics of polymeric micelles by reviewing copolymers, technique of manufacture, and potential uses of polymeric micelles.

Keywords: Polymeric micelles, Block copolymers, Methods of preparation, Pharmaceutical applications, Drug delivery.

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INTRODUCTION

Polymeric Micelles (PMs) are nano-sized drug delivery devices with a core-shell structure formed by self-assembly of amphiphilic block copolymers in aqueous solution as shown in Figure 1. In diluted aqueous solutions, amphiphilic molecules exist independently and function as surfactants to reduce surface tension at the air-water interface (Owen *et al*., 2012; Pepić *et al*., 2013).

The self-assembly above Critical Micelle Concentration (CMC) is an entropically favored phenomenon. During the process, the hydrophobic compartment of the copolymer forms the core of polymeric micelles, whereas the hydrophilic compartment forms the shell (Wei *et al*., 2009).

Polymeric micelles possess several characteristics that make them well-suited for therapeutic drug delivery purposes. The hydrophobic core of polymeric micelles can serve as a storage site for non-polar pharmaceutical compounds. By incorporating these medications into polymeric micelles, the need for formulation vehicles and the consequent toxicity are avoided (Oerlemans *et al*., 2010; Hanafy *et al*., 2018).

At or above their Critical Micelle Concentration (CMC), amphiphilic block copolymers adopt nano-sized, self-assembling polymeric micelles with core-shell architectures in aqueous fluids. The hydrophilic shells of these drug carrier systems provide a stable suspension of micelles in the circulatory system. However, the hydrophobic core improves the solubility of the medication by confining the poorly soluble portion within, hence enhancing its bioavailability (Lu *et al*., 2020; Kahraman *et al*., 2015). A hydrophobic core can bind to weakly water-soluble medicines by either physical trapping or chemical adhesion, while a hydrophilic shell maintains colloidal stability (Wang *et al*., 2022).

As opposed to the usual free drug diffusion, polymeric micelles are delivered into cells by receptor-mediated endocytosis, therefore bypassing the P-glycoprotein (P-gp) efflux. P-gp is a potent drug efflux protein that obstructs the delivery of many medications to the brain, gut, and Multidrug-Resistant (MDR) tumors (Razzaq *et al*., 2021). Nevertheless, these systems have the disadvantages of generating large-sized aggregates that are beyond the desired size range for drug delivery systems utilizing nanoscale particles, as well as their instability in aqueous dispersion resulting in phase separated states (Lu *et al*., 2013; Noure*t al*., 2016).

Unlike micellar structures made of traditional surfactant molecules, which are tiny molar mass molecules, polymeric micelles are generated at lower Critical Micelle Concentration (CMC) values. They are more persistent in vitro and *in vivo* because they dissociate at a slower rate and accumulate drugs more effectively at the target surface (Zhou *et al*., 2016). A critical

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and major aspect in determining the body arrangement of micelles when an Enhanced Permeation Retention effect (EPR) is involved is their restricted size range, which is comparable to that of viruses and lipoproteins (Bose *et al*., 2021). Significantly, polymeric micelles often exhibit a consistent particle size, exceptional thermal stability, compatibility with biological systems, and the capacity to encapsulate both hydrophilic and hydrophobic medications (Sohail *et al*., 2022).

Therefore, polymeric micelles are extensively employed in research as nanocarrier systems to transport drugs and other therapeutic agents, including anticancer drugs, proteins, nucleic acids, contrast/imaging agents, and antibiotics, to overcome antibiotic resistance and improve therapeutic effectiveness (Sinani *et al*., 2023). Furthermore, these systems can exhibit intelligence and responsiveness to many environmental stimuli, including pH, electric and magnetic fields, and ultraviolet electromagnetic radiation (Mohammadi *et al*., 2023). Over a hundred polymeric micelle-based drug delivery formulations have progressed to different phases of clinical and preclinical studies in several countries (Cai *et al*., 2023). Mixed Polymeric Micelles (MPMs) are achieved by combining two or more distinct amphiphilic copolymers to enhance their characteristics and address the drawbacks of simple PMs, such as disaggregation/dissociation upon dissolution (Chen *et al*., 2016). In general, MPMs consistently demonstrate superior stability and encapsulation efficiency compared to basic PMs (Ferreira *et al*., 2023; Senthilkumar *et al*., 2022).

Several parameters influence the size of polymeric micelles, including the molecular weight of the amphiphilic block copolymer, the number of amphiphiles that aggregate, the relative proportion of hydrophilic and hydrophobic chains, and the method of synthesis (Neal *et al*., 2021).

Types of polymers or copolymers employed in the production of polymeric micelles

Amphiphilic block copolymers consist of two or more polymer blocks of varying sizes, which are preferably incompatible, chemically connected in a linear or branching arrangement. The units may consist of a neutral polymer (either hydrophilic or hydrophobic) or a polyelectrolyte (anionic, cationic, or zwitterionic) (Kuperkar *et al*., 2022; Wang *et al*., 2023). These copolymers, especially diblock and occasionally triblock copolymers have been intensively studied. The hydrophilic blocking component in these copolymers consists of nonionic surfactants of the Polyethyleneoxide (PEO) or Polyethylene Glycol (PEG) condensate type. Some of these surfactants may not be polymeric because of the low molecular weight PEO. These surfactants are commercially available and highly beneficial, such as Tweens®, Tritons®, Soluplus®, Cremophor EL®, Solutol HS15®, TPGS®, and others (Chaudhari *et al*., 2020). Poly (N-isopropylacrylamide) (PNIPAM), Polyvinyl Caprolactam (PVCL), Polyvinyl Pyrrolidone (PVP), Polyvinyl Alcohol (PVA), as well as some polyacids and poly bases, are well recognized hydrophilic blocking compounds (Atanase *et al*., 2022). Polypropylene Oxide (PPO), Polylactic Acid (PAA), Polycaprolactone (PCL), Polybutylene Oxide (PBO), Polystyrene Oxide (PSO), Polybutadiene (PB), Polystyrene (PS), and Polymethylacrylate (PMA) are examples of hydrophobic blocks (Haladjova *et al*., 2024). L-amino acid polymers, polyesters, and pluronic can also be used. These acids are extensively utilized as poly (L-aspartate) and poly (L-glutamate) and undergo derivatization based on their functional structures (Mehan *et al*., 2022).

Multiple studies have documented the importance of certain block polymers authorized by the Food and Drug Administration (FDA), including Poly (E-caprolactone) (PCL), Polylactic Acid (PLA), Polyglycolic Acid (PGA), and Polylactic acid-co-Glycolic Acid (PLGA), because of their biocompatibility, affordability, and biodegradability (Bartnikowski *et al*., 2019). PEG is the most commonly used hydrophilic block due to its exceptional solubility in aqueous solutions and various organic solvents, so enabling versatile preparation methods. Additionally, PEG is non-toxic and has low immunogenicity. Lastly, PEG typically does not interact with biological components, hence facilitating its biodistribution after administration (Miyata *et al*., 2011). Although many co-polymers have a lower solubilization capability, they can simultaneously improve permeability more effectively than traditional solubilizers. D-α-Tocopheryl Polyethylene Glycol 1000 Succinate (TPGS) is a hydrophilic compound classified as a fat-soluble form of vitamin E (Yang *et al*., 2018).

TPGS has lipophilic alkyl tail and hydrophilic polar head with Hydrophilic/Lipophilic Balance (HLB) value of 13.2 and Critical Micelle Concentration (CMC) of 0.02% w/w. It has been commonly utilized in solubilization, emulsification and wetting process (Guo *et al*., 2013). The solubility, absorption, and bioavailability of drugs can be improved with the help of TPGS, which also inhibits intestinal P-gp drug efflux and increases P-gp expression (Eedara *et al*., 2014). The graft copolymer Soluplus® consists of a Polyethylene Glycol (PEG 6000) backbone with one or two side chains comprising of vinyl acetate unsystematically copolymerized with vinyl caprolactam (57% polyvinyl caprolactam, 30% polyvinyl acetate and 13% polyethylene glycol).

As it is hydrophilic and nonionic, its solubility does not change along with the gastrointestinal tract. It is slightly surface active, a property which could be useful to maintain supersaturation of poorly soluble drugs in the gastrointestinal tract (Rani *et al*., 2020). It can produce 80 nm-sized polymeric micelles in liquid media and improves passive diffusion across many routes of administration and has shown to be a flexible excipient for passive targeting (Pignatello *et al*., 2022).

Another popular micellar carrier for the delivery of medicinal medicines with low solubility is poloxamer-188 block copolymer (Islam *et al*., 2021).

One type of amphiphilic copolymer is the graft copolymer, which consists of two polymer chains-one serving as the backbone and the other as the side grafted portion. In most cases, the copolymers exhibit characteristics shared by the grafts and the polymeric backbones (Kulthe *et al*., 2012).

Types of polymeric micelles

One way to categorize polymeric micelles is according to the intermolecular forces that separate the core segment from the water around it. They are categorized into three distinct sets (Nagaich *et al*., 2013).

Conventional

Core and shell interact hydrophobically in water, generating micelles. Hydrophobic interactions can generate amphiphilic block co-polymers, such as poly (ethylene oxide). The compound is a blend of ethylene oxide and propylene oxide (Shukla *et al*., 2021; Maboudi *et al*., 2024).

Polyion Complex Micelles (PICMs)

Micelles of this nature form when two or more ionic polymers with opposing charges, such as polyelectrolytes, bind electrostatically. The addition of these polymers to the solution enables them to permeate the micelle's shell and generate specific PMs. The configuration and dimensions of the charged micelle coronas were governed by the Van-der Waals interaction forces and the electrostatic force (Luo *et al*., 2009).

These micelles readily form themselves in an aqueous solution, maintain their structural integrity, and possess a remarkably high capacity to transport drugs. The central region of the PICMs is utilized for encapsulating several therapeutic agents, including hydrophobic drug molecules, charged macromolecules, and metal complexation via hydrogen bonding, as well as hydrophobic and electrostatic interactions (Reddy *et al*., 2015). Methoxy polyethylene glycol-grafted chitosan is an example of a copolymer used to prepare polyion complex micelle (Jeong*et al*., 2009).

Non-covalently connected polymeric micelles

An innovative method that does not need block copolymers can also be employed to synthesize polymeric micelles. Polymeric micelles are formed by the self-assembly of homopolymer, random copolymer, graft copolymer, or oligomer particles, driven by interpolymer hydrogen bonding complexation. Non-covalently integrated micelles are formed when the core and shell of a homopolymer chain are joined at their end by certain intermolecular interactions, such as H-bonding or metal-ligand interactions (Mourya *et al*., 2011).

Methods of Preparation of polymeric micelles

Physicochemical properties of the block copolymers chosen for PMs synthesis determine the technique of preparation. The selected approach exerts a substantial influence on the physicochemical characteristics and the efficiency of drug encapsulation (Gaucher *et al*., 2005). The size, polydispersity index, and stability of copolymers are influenced by the sequence of addition, the ratio of aqueous to organic phases, and the concentration of the copolymers. Hence, it is beneficial to optimize these factors in order to determine a standard formula for producing PMs with favorable physicochemical and functional properties (Simões *et al*., 2015).

Direct Dissolution Method

Primarily, copolymers with excellent water solubility are employed in the direct dissolving technique for the production of PMs. This technique is quite straightforward and entails the combination of copolymers and pharmaceuticals in water-based solvents, along by mechanical processes such as agitation, sonication, and heating, to enclose the medications (Sotoudegan *et al*., 2016). Formation of PMs occurs as a result of the dehydration of the core-forming blocks. The copolymers and medicines are individually dissolved in aqueous solvents and then combined to produce Polymer Materials (PMs) (Cholkar *et al*., 2012).

Simple Mixing

Polymeric micelles are formed by the self-assembly of block copolymers with opposing charges in an aqueous solution. After undergoing multivalent electrostatic complexation, charged macromolecules like nucleic acids, proteins, and oligonucleotides are enclosed inside the core compartment. The PEG chains that surround the core constitute the protective shell compartment (Florinas *et al*., 2016).

Polyion Complex (PIC) micelles comprising positively charged PEG-b-poly (L-lysine) and negatively charged PEG-b-poly (aspartic acid) are composed of polymeric micelles formed by electrostatic interactions. Nevertheless, PIC micelles generated using this approach can be delicate under physiological circumstances and may detach and separate due to neutralization by salts and interactions with naturally existing polyelectrolytes or charged proteins. Therefore, it is necessary to stabilize PIC micelles in order to enhance their usefulness in biological settings (Nakamura *et al*., 2020).

Solvent Evaporation Method

The solvent evaporation technique entails the disintegration of copolymers and pharmaceuticals in a shared solvent or chemically compatible solvents. When both polymers are dissolved in the solvent and are soluble in water, this is the preferred technique for producing polymeric micelles. A drug-copolymer thin film is produced via solvent evaporation. The introduction of water

or buffers results in the spontaneous generation of polymeric micelles charged with drugs. In addition, the micelles are uniformly distributed in size whether processed using a sonicator or high-pressure extruder (Makhmalzade *et al*., 2018; Rajablou *et al*., 2023; Zhai *et al*., 2013).

Dialysis Method

The dialysis technique is employed when the chosen amphiphilic copolymers exhibit limited solubility in water. After dissolving the copolymer and drug in a shared solvent, an aqueous solvent is added to induce the production of micelles. The solution is subjected to prolonged dialyzation against water in order to eliminate the organic solvents. Choosing the appropriate solvent is crucial for this technique, as it directly impacts the physical properties of the micelles and the effectiveness of drug encapsulation (Vinchurkar *et al*., 2021).

Achieving an optimal ratio of aqueous and organic solvent is crucial. Typical solvents employed in this technique include N,N-dimethylformamide, dimethylsulfoxide, acetone, acetonitrile, tetrahydrofuran, and others (Pignatello *et al*., 2022; Islam *et al*., 2021; Kulthe *et al*., 2012; Nagaich *et al*., 2013; Shukla *et al*., 2021; Maboudi *et al*., 2024; Luo *et al*., 2009; Reddy *et al*., 2015; Jeong *et al*., 2009; Mourya *et al*., 2011; Gaucher *et al*., 2005; Simões *et al*., 2015; Sotoudegan *et al*., 2016; Cholkar *et al*., 2012; Florinas *et al*., 2016; Nakamura *et al*., 2020; Makhmalzade *et al*., 2018; Rajablou *et al*., 2023; Zhai *et al*.,2013; Vinchurkar *et al*., 2021; Fesenmeier *et al*., 2024).

Continuous Processing

A novel co-axial turbulent jet with co-flow continuous technology has been recently developed for the synthesis of polymeric micelles. Previous studies have shown the use of this technology for the synthesis of liposomes, enabling continuous processing. The approach was demonstrated using a block copolymer of mPEG (5 kD)-PCL as the polymer for drug loading curcumin (Gupta *et al*., 2020).

Micelles exhibiting low polydispersity indices and high drug loading were generated using the technique. Another benefit of this procedure over the traditional preparation method is the control it provides over the processing settings (Bauer *et al*., 2023).

In situ Charge-Neutralization-Controlled Particle Coagulation Mechanism

An *in situ* charge-neutralization-controlled particle coagulation method has recently been developed for the creation of monodisperse polymeric particles. The anionic surfactant molecules adsorbed on the surface of particles are protected from cationic radicals produced during the breakdown of the initiator, which aid in particle coagulation. Through the use of *in situ* charge neutralization, both the particle number and the rate of micelle capture for initiator radicals are improved. By streamlining the emulsion polymerization process, the nucleation time of the particles is reduced, and monodisperse particles ranging in size from 200 to 300 nm are produced (Liu *et al*., 2016).

Spiropyran-Initiated Atom Transfer Polymerization

Another relatively new method for producing polymeric micelles that are sensitive to changes in light intensity and temperature is spiropyran-initiated atom transfer polymerization. With its reversibility, high sensitivity to light, and excellent photo fatigue resistance, spiropyran is among the most useful photochromic chemicals. This approach successfully synthesized various types of multi-responsive polymeric micelles. These micelles include spirogyra chain end groups, PNIPAM blocks, and PMMA (Fagan *et al*., 2021; Chen *et al*., 2016).

Pharmaceutical application of polymeric micelles

Polymeric micelles are primarily developed to enhance three key aspects of drug performance: (1) the solubilization of hydrophobic or water-insoluble pharmaceuticals, (2) the modulated or prolonged release of a drug, and (3) the selective targeting of a certain cell type or organ (Movassaghian *et al*., 2015) which will be further elaborated upon below:

Solubilization of hydrophobic or water-insoluble drugs

The incorporation of the drug into the hydrophobic core of polymeric micelles is the method by which inadequately water-soluble pharmaceuticals are solubilized (González-Iñiguez *et al*., 2024). The increased permeability and retention (EPR) effect of polymeric micelles can enable the improvement of aqueous formulations of hydrophobic medications, extension of their circulation time *in vivo*, enhancement of cellular absorption, and passive targeting at tumor sites (Yang *et al*., 2015).

Numerous studies have previously established that polymeric micelles may greatly improve the water solubility of medicines with low water solubility (Zlotnikov *et al*., 2023).

Controlled or sustained release of a drug

Polymeric Micelles (PMs) are of certain interest due to the protection of the hydrophobic drug contained in the micellar hydrophobic core by the outer hydrophilic corona. This corona helps to prevent the elimination of micelles by the mononuclear phagocytic system (MPS) in physical circulation, hence extending the *in vivo* circulation time owing to its brush-like nanostructure (Sang *et al*., 2019; Feng *et al*., 2021).

Targeting a certain cell type or organ

Micelles as medication carriers can provide several distinct advantages. They have the capacity to enhance the bioavailability of medications with limited solubility and prolong their presence

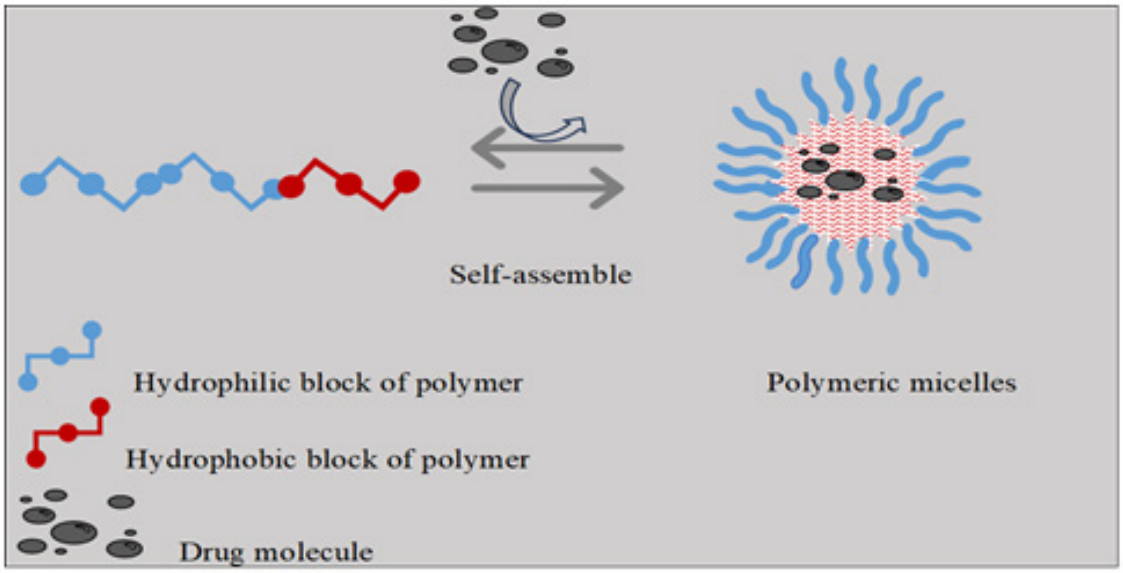

Figure 1: Formation and drug loading of polymeric micelles by self-assemble of amphiphilic block copolymers in aqueous solution.

in the bloodstream, therefore facilitating a gradual buildup in the specific area where effects are required. Micelles' size enables them to gather in regions of the body with bleeding blood vessels and they may be selectively targeted by attaching a particular ligand to their outer surface (Fei *et al*., 2021).

In the aqueous medium, the micelles are structured in a manner where their outer surface consists of components that exhibit minimal reactivity towards tissue components or blood. This structural characteristic enables micelles to persist in the bloodstream for an extended period without being detected by phagocytic cells or dedicated proteins. A crucial characteristic of micelles as drug carriers is their long-lasting nature (Khan *et al*., 2024; Serras *et al*., 2020).

Methods of drug loading in polymeric micelles

Overall, there are three primary approaches for incorporating medicines into polymer micelle cores; these will be further upon in the subsequent sections:

Chemical conjugation

Through a well-engineered pH or enzyme sensitive linker, a drug is chemically linked to the core, forming a block of co-polymer that may be cleaved to release the drug in its active form inside a cell (Zhou *et al*., 2017). The conjugate functions as a polymer prodrug that spontaneously structures itself into a core-shell configuration, the structure of the polymer-drug bond and its stability are entirely determined by the pace at which the medication is released. The rate of drug release and the efficacy of the prodrug can be influenced by controlling the type of the polymer-drug linkage and the stability of the drug conjugate linkage (Zhang *et al*., 2020).

Physical entrapment

For hydrophobic drug compounds, the physical incorporation or dissolution of pharmaceuticals within block copolymer micelles is often more desirable than micelle-forming polymer-drug conjugates (Iurciuc-Tincu *et al*., 2021). Indeed, many polymers and drug molecules do not container active functional groups for chemical conjugation, and therefore, specific block copolymers must be designed for a given type of drug. Drugs can be physically incorporated into the fundamental structure of micelles using one of two approaches: (i) by the interaction with the hydrophobic core-forming section of the polymer, or (ii) by conjugating them to the polymer backbone utilizing labile bonds that may be broken under certain conditions to retrieve the active medicament (Ghosh *et al*., 2022; Perumal *et al*., 2018).

Polyionic complexation

Micelles may enclose charged macromolecules like nucleic acids and proteins by means of electrostatic interactions, also known as charge neutralization, with block ionomers that have opposing charges. The generation of persistent PIC micelles, which can withstand physiological salt concentrations even in diluted circumstances, is facilitated by the multivalent complexation of charged groups on the core-forming segment of the block copolymer with numerous charged moieties on the payloads (Cabral *et al*., 2024).

Applications of Polymeric micelles in Drug Delivery

Oral route

The modulation of gastrointestinal transit time is a problem that can be addressed by extending the duration of medication presence within the gastrointestinal system. Polymeric nanocarriers have

become important oral delivery vehicles due to their remarkable bioavailability, excellent drug trapping, controlled release, and low toxicity (El-Helaly *et al*., 2024; Alsafar *et al*., 2023).

Drug-loaded micelles in the systemic circulation exhibit extended retention duration and very efficient tissue permeability, enabling them to accumulate in sick tissue for passive targeting. In addition, polymeric micelles with stable, biocompatible, and solubilizing characteristics have attracted significant interest for oral delivery. Moreover, the encapsulated medication can be shielded not only from interaction with the gastrointestinal contents that are likely to cause breakdown and metabolism but also endowed with the properties of sustained-release and direct cellular absorption (Dian *et al*., 2014).

Intranasal route

Drug administration via the intranasal route is the administration of drug formulations through the nose to produce a specific pharmacological effect. The intranasal route offers a non-invasive means of delivering pharmacological substances for target effects on the local, systemic, and Central Nervous System (CNS) (Lamptey *et al*., 2022). Intranasal administration should improve the drug's brain bioavailability by overcoming first-pass metabolism, achieving the desired concentration at the target location, reducing undesirable side effects, and bypassing the blood-brain barrier through the olfactory area of the nasal orifice (Bothiraja *et al*., 2022).

Polymeric micelles are highly favored nanocarriers for brain delivery due to their optimal particle size, which allows them to easily penetrate the blood brain barrier and enhance the Encapsulation Efficiency (EE%) (Elezaby *et al*., 2017).

Using a nose-to-brain delivery system utilizing PEG-PCL-Tat micelles containing anti-cancer medicines and siRNA to rats with a brain tumor model, we successfully shown the remarkable suppression of brain tumor development and a significant extension of lifespan. Post-entry into the brain, the drug-loaded polymeric micelle should ideally exhibit selectivity towards tumor cells (Kanazawa *et al*., 2020).

Pulmonary route

To enhance drug targeting and minimize the side effects of traditional cancer chemotherapy, polymeric micelles have been extensively researched for the treatment of lung cancer. The objective is to investigate the enhanced targeting of micelles by modifying their surface to interact with tumor microenvironment conditions, such as pH or peptide targeting (Ibarra-Sánchez *et al*., 2022). The effectiveness of these micelles has been tested in a model of pulmonary melanoma metastasis. We investigated the loading of micelles with various drugs, such as antifungal agents for treating lung fungal infections with minimal side effects, and loading peptide-modified micelles with fasudil for pulmonary arterial hypertension to enhance the retention time of micelles in affected arterial cells (Rezazadeh *et al*., 2018).

Ocular route

Ocular medication administration via the formation of multiblock polymers that enhance the solubility, stability, and bioavailability of drugs. Micelles have evolved as highly promising drug delivery systems for the treatment of diverse ocular disorders that impact distinct parts of the eye (Assiri *et al*., 2024).

Characterized by their amphiphilic properties, these polymers can create micelles in water, therefore facilitating the dissolution of pharmaceuticals that are not easily soluble in water. Micelle production enables the encapsulation of medicinal compounds within the hydrophobic core of the micelle, therefore safeguarding them from degradation and improving their transportation to the intended location within the eye (Safwat *et al*., 2020).

CONCLUSION

Polymeric micelles have become important pharmaceutical carriers due to their practical preparation methods, adaptable drug-loading protocols, and ability to host poorly soluble drugs in a dynamic manner. Specifically, adjusting the assembly/disassembly equilibrium of block copolymers controls drug loading/release.

The versatility of PMs formulations offers significant potential and opportunities for further investigation into their utility in medication delivery. The assumption is that PMs have the potential to make substantial contributions to forthcoming oral drug-delivery systems. Currently, research on PMs mostly concentrates on anti-cancer applications. Nevertheless, the effective extension of the uses of PMs in the treatment of various disorders is possible. Significant progress in the delivery of nucleic acids and proteins can also be accomplished via (PMs). Therefore, PMs are now being thoroughly researched and have the potential to be valuable instruments in addressing several outstanding challenges in pharmacological medication delivery.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PMs: Polymeric micelles; **CMC:** Critical micelle concentration; **EPR:** Enhanced permeation retention effect; **MPMs:** Mixed polymeric micelles; **PEO:** Polyethyleneoxide; **PEG:** Polyethylene

glycol; **PNIPAM:** Poly (N-isopropylacrylamide); **PVCL:** Polyvinyl caprolactam; **PVP:** Polyvinyl pyrrolidone; **PVA:** Polyvinyl alcohol; **PPO:** Polypropylene oxide; **PAA:** Polylactic acid; **PCL:** Polycaprolactone; **PBO:** Polybutylene oxide; **PSO:** Polystyrene oxide; **FDA:** Food and Drug Administration; **PLGA:** Polylactic acid-co-glycolic acid; **HLB:** Hydrophilic/lipophilic balance; **PICMs:** Polyion complex micelles.

REFERENCES

Al Alsafar, Z. F. (2023). Formulation, Characterization, and Evaluation of Ticagrelor-loaded Nano Micelles Enhance Intestinal Absorption. lami, M.S., & Haroon, Z. Bahrain Medical Bulletin, 45(2).

Assiri, A. A., Glover, K., Mishra, D., Waite, D., Vora, L. K., & Thakur, R. R. S. (2024). Block copolymer micelles as ocular drug delivery systems. Drug Discovery Today, 29(8), Article 104098. https://doi.org/10.1016/j.drudis.2024.104098

Atanase, L. I., Salhi, S., Cucoveica, O., Ponjavic, M., Nikodinovic-Runic, J., & Delaite, C. (2022). Biodegradability Assessment of Polyester Copolymers Based on poly (ethylene adipate) and poly(ε-caprolactone). Polymers, 14(18), 3736. https://doi.org/10.3390/polym14183736

Bartnikowski, M., Dargaville, T. R., Ivanovski, S., & Hutmacher, D. W. (2019). Degradation mechanisms of polycaprolactone in the context of chemistry, geometry and environment. Progress in Polymer Science, 96, 1–20. https://doi.org/10.1016/j.progpolymsci.2019.05.004

Bauer, T. A., Schramm, J., Fenaroli, F., Siemer, S., Seidl, C. I., Rosenauer, C., Bleul, R., Stauber, R. H., Koynov, K., Maskos, M., & Barz, M. (2023). Complex structures made simple–continuous flow production of core cross-linked polymeric micelles for paclitaxel prodrug-delivery. Advanced Materials, 35(21), Article e2210704. https://doi.org/10.1002/adma.202210704

Bose, A., Roy Burman, D., Sikdar, B., & Patra, P. (2021). Nanomicelles: Types, properties and applications in drug delivery. IET Nanobiotechnology, 15(1), 19–27. https://doi.org/10.1049/nbt2.12018

Bothiraja, C., Dhage, K., & Kamble, R. (2022). D-α-Tocopherol polyethylene glycol succinate and stearoylmacrogol glycerides biomaterial based nanostructured mixed micelles as nose-to-brain targeting drug delivery system. Materials Technology, 37(6), 397–410.

Cabral, H., Miyata, K., Osada, K., & Kataoka, K. (2018). Block copolymer micelles in nanomedicine applications. Chemical Reviews, 118(14), 6844–6892. https://doi.org/10.1021/acs.chemrev.8b00199

Cai, R., Zhang, L., & Chi, H. (2023). Recent development of polymer nanomicelles in the treatment of eye diseases. Frontiers in Bioengineering and Biotechnology, 11, Article 1246974. https://doi.org/10.3389/fbioe.2023.1246974

Chaudhari, S. P., & Handge, N. M. (2020). Formulation, development and evaluation of lopinavir loaded polymeric micelles. Journal of Science and Technology (JST), 5(4), 173–187.

Chen, L.-C., Chen, Y.-C., Su, C.-Y., Wong, W.-P., Sheu, M.-T., & Ho, H.-O. (2016). Development and characterization of lecithin-based self-assembling mixed polymeric micellar (saMPMs) Drug Delivery Systems for Curcumin [sa MPMs]. Scientific Reports, 6(1), Article 37122. https://doi.org/10.1038/srep37122

Chen, S., Liu, H., Hu, J., Zou, H., & He, Y. (2016). Self-assembly and morphology transition of amphipathic spiropyran-based random copolymers to control drug release. Designed Monomers and Polymers, 19(8), 730–739.

Cholkar, K., Patel, A., Vadlapudi, A. D., & Mitra, A. K. (2012). Novel nanomicellar formulation approaches for anterior and posterior segment ocular drug delivery. Recent Patents on Nanomedicine, 2(2), 82–95. https://doi.org/10.2174/1877912311202020082

Dian, L., Yu, E., Chen, X., Wen, X., Zhang, Z., Qin, L., Wang, Q., Li, G., & Wu, C. (2014). Enhancing oral bioavailability of quercetin using novel soluplus polymeric micelles. Nanoscale Research Letters, 9(1), 2406. https://doi.org/10.1186/1556-276X-9-684

Eedara, B. B., Veerareddy, P. R., Jukanti, R., & Bandari, S. (2014). Improved oral bioavailability of fexofenadine hydrochloride using lipid surfactants: *Ex vivo, in situ* and *in vivo* studies. Drug Development and Industrial Pharmacy, 40(8), 1030–1043. https://doi.org/10.3109/03639045.2013.801984

Elezaby, R. S., Gad, H. A., Metwally, A. A., Geneidi, A. S., & Awad, G. A. (2017). Self-assembled amphiphilic core-shell nanocarriers in line with the modern strategies for brain delivery. Journal of Controlled Release, 261, 43–61. https://doi.org/10.1016/j.jconrel.2017.06.019

El-Helaly, S. N., & Rashad, A. A. (2024). Mirtazapine loaded polymeric micelles for rapid release tablet: A novel formulation-*in vitro* and *in vivo* studies. Drug Delivery and Translational Research, 14(9), 2488–2498. https://doi.org/10.1007/s13346-024-01525-w

Fagan, A., Bartkowski, M., & Giordani, S. (2021). Spiropyran-based drug delivery systems. Frontiers in Chemistry, 9, Article 720087. https://doi.org/10.3389/fchem.2021.720087

Fei, Z., & Yoosefian, M. (2021). Design and development of polymeric micelles as nanocarriers for anticancer Ribociclib drug. Journal of Molecular Liquids, 329, Article 115574.

Feng, X., Ding, J., Gref, R., & Chen, X. (2017). Poly(β-cyclodextrin)-mediated polylactide-cholesterol stereocomplex micelles for controlled drug delivery. Chinese Journal of Polymer Science, 35(6), 693–699.

Ferreira, M. D., Duarte, J., Veiga, F., Paiva-Santos, A. C., & Pires, P. C. (2023). Nanosystems for brain targeting of antipsychotic drugs: An update on the most promising nanocarriers for increased bioavailability and therapeutic efficacy. Pharmaceutics, 15(2), 678. https://doi.org/10.3390/pharmaceutics15020678

Fesenmeier, D. J., Cooper, E. S., & Won, Y.-Y. (2024). Overcoming limitations of conventional solvent exchange methods: Achieving monodisperse non-equilibrium polymer micelles through equilibration-nanoprecipitation (ENP). Journal of Colloid and Interface Science, 661, 861–869. https://doi.org/10.1016/j.jcis.2024.01.167

Florinas, S., Liu, M., Fleming, R., Van Vlerken-Ysla, L., Ayriss, J., Gilbreth, R., Dimasi, N., Gao, C., Wu, H., Xu, Z.-Q., Chen, S., Dirisala, A., Kataoka, K., Cabral, H., & Christie, R. J. (2016). A nanoparticle platform to evaluate bioconjugation and receptor-mediated cell uptake using cross-linked polyion complex micelles bearing antibody fragments. Biomacromolecules, 17(5), 1818–1833. https://doi.org/10.1021/acs.biomac.6b00239

Gaucher, G., Dufresne, M.-H., Sant, V. P., Kang, N., Maysinger, D., & Leroux, J.-C. (2005). Block copolymer micelles: Preparation, characterization and application in drug delivery. Journal of Controlled Release, 109 (1–3), 169–188. https://doi.org/10.1016/j.jconrel.2005.09.034

Ghosh, B., & Biswas, S. (2021). Polymeric micelles in cancer therapy: State of the art. Journal of Controlled Release, 332, 127–147. https://doi.org/10.1016/j.jconrel.2021.02.016

González-Iñiguez, K. J., Figueroa-Ochoa, E. B., Martínez-Richa, A., Cajero-Zul, L. R., & Nuño-Donlucas, S. M. (2024). Synthesis of poly (L–lactide)-poly (ε–caprolactone)–poly (ethylene glycol) Terpolymer Grafted onto Partially Oxidized Carbon Nanotube nanocomposites for Drug Delivery. Polymers, 16(18), 2580. https://doi.org/10.3390/polym16182580

Guo, Y., Luo, J., Tan, S., Otieno, B. O., & Zhang, Z. (2013). The applications of vitamin E TPGS in drug delivery. European Journal of Pharmaceutical Sciences, 49(2), 175–186. https://doi.org/10.1016/j.ejps.2013.02.006

Gupta, A., Costa, A. P., Xu, X., Lee, S.-L., Cruz, C. N., Bao, Q., & Burgess, D. J. (2020). Formulation and characterization of curcumin loaded polymeric micelles produced via continuous processing. International Journal of Pharmaceutics, 583, Article 119340. https://doi.org/10.1016/j.ijpharm.2020.119340

Haladjova, E., & Rangelov, S. (2024). Application of Polymeric Micelles for Drug and Gene Delivery. Pharmaceutics, 16(5), 646. https://doi.org/10.3390/pharmaceutics16050646

Hanafy, N. A. N., El-Kemary, M., & Leporatti, S. (2018). Micelles structure development as a strategy to improve smart cancer therapy. Cancers, 10(7), 238. https://doi.org/10.3390/cancers10070238

Ibarra-Sánchez, L. Á., Gámez-Méndez, A., Martínez-Ruiz, M., Nájera-Martínez, E. F., Morales-Flores, B. A., Melchor-Martínez, E. M., Sosa-Hernández, J. E., Parra-Saldívar, R., & Iqbal, H. M. N. (2022). Nanostructures for drug delivery in respiratory diseases therapeutics: Revision of current trends and its comparative analysis. Journal of Drug Delivery Science and Technology, 70, Article 103219. https://doi.org/10.1016/j.jddst.2022.103219

Islam, N., Irfan, M., Khan, S.-U.-D., Syed, H. K., Iqbal, M. S., Khan, I. U., Mahdy, A., Raafat, M., Hossain, M. A., Inam, S., Munir, R., & Ishtiaq, M. (2021). Poloxamer-188 and d-α-tocopheryl polyethylene glycol succinate (TPGS-1000) mixed micelles integrated orodispersible sublingual films to improve oral bioavailability of ebastine; *in vitro* and *in vivo* characterization. Pharmaceutics, 13(1), 54. https://doi.org/10.3390/pharmaceutics13010054

Iurciuc-Tincu, C.-E., Cretan, M. S., Purcar, V., Popa, M., Daraba, O. M., Atanase, L. I., & Ochiuz, L. (2020). Drug delivery system based on pH-sensitive biocompatible poly (2-vinyl pyridine)-b-poly (ethylene oxide) nanomicelles loaded with curcumin and 5-fluorouracil. Polymers, 12(7), 1450. https://doi.org/10.3390/polym12071450

Jeong, Y. I., Seo, D. H., Kim, D. G., Choi, C., Jang, M. K., Nah, J. W., & Park, Y. (2009). Methotrexate-incorporated polymeric micelles composed of methoxy poly (ethylene glycol)-grafted chitosan. Macromolecular Research, 17, 538–543.

Kahraman, E., Karagö, E., Dinçer, S., & Ozsoy, Y. (2015). Polyethylenimine modified and non-modified polymeric micelles used for nasal administration of carvedilol. Journal of Biomedical Nanotechnology, 11(5), 890–899. https://doi.org/10.1166/jbn.2015.1915

Kanazawa, T., Taki, H., & Okada, H. (2020). Nose-to-brain drug delivery system with ligand/cell-penetrating peptide-modified polymeric nano-micelles for intracerebral gliomas. European Journal of Pharmaceutics and Biopharmaceutics, 152, 85–94. https://doi.org/10.1016/j.ejpb.2020.05.001

Khan, S., Vahdani, Y., Hussain, A., Haghighat, S., Heidari, F., Nouri, M., & Falahati, M. (2021). Polymeric micelles functionalized with cell penetrating peptides as potential pH-sensitive platforms in drug delivery for cancer therapy: A review. Arabian Journal of Chemistry, 14(8), Article 103264.

Kulthe, S. S., Choudhari, Y. M., Inamdar, N. N., & Mourya, V. (2012). Polymeric micelles: Authoritative aspects for drug delivery. Designed Monomers and Polymers, 15(5), 465–521. https://doi.org/10.1080/1385772X.2012.688328

Kuperkar, K., Patel, D., Atanase, L. I., & Bahadur, P. (2022). Amphiphilic block copolymers: Their structures, and self-assembly to polymeric micelles and polymersomes as drug delivery vehicles. Polymers, 14(21), 4702. https://doi.org/10.3390/polym14214702

Lamptey, R. N. L., Gothwal, A., Trivedi, R., Arora, S., & Singh, J. (2022). Synthesis and characterization of fatty acid grafted chitosan polymeric micelles for improved gene delivery of VGF to the brain through intranasal route. Biomedicines, 10(2), 493. https://doi.org/10.3390/biomedicines10020493

Liu, B., Meng, W., Wang, P., Zhang, M., & Zhang, H. (2016). *In situ* charge neutralization-controlled particle coagulation and its effects on the particle size distribution in the one-step emulsion polymerization. European Polymer Journal, 83, 278–287.

Lu, A. (2020). Amphiphilic and thermoresponsive block copolymers based on hydroxypropyl methyl cellulose as nano-carrier of hydrophobic drugs (Doctoral dissertation, Université Montpellier).

Lu, Y., & Park, K. (2013). Polymeric micelles and alternative nanonized delivery vehicles for poorly soluble drugs. International Journal of Pharmaceutics, 453(1), 198–214. https://doi.org/10.1016/j.ijpharm.2012.08.042

Luo, Y., Yao, X., Yuan, J., Ding, T., & Gao, Q. (2009). Preparation and drug controlled-release of polyion complex micelles as drug delivery systems. Colloids and Surfaces. B, Biointerfaces, 68(2), 218–224. https://doi.org/10.1016/j.colsurfb.2008.10.014

Maboudi, A. H., Lotfipour, M. H., Rasouli, M., Azhdari, M. H., MacLoughlin, R., Bekeschus, S., & Doroudian, M. (2024). Micelle-based nanoparticles with stimuli-responsive properties for drug delivery. Nanotechnology Reviews, 13(1), Article 20230218.

Makhmalzade, B. S., & Chavoshy, F. (2018). Polymeric micelles as cutaneous drug delivery system in normal skin and dermatological disorders. Journal of Advanced Pharmaceutical Technology and Research, 9(1), 2–8. https://doi.org/10.4103/japtr.JAPTR_314_17

Mehan, N., Kumar, M., Bhatt, S., Shankar, R., Kumari, B., Pahwa, R., & Kaushik, D. (2022). Self-Assembly polymeric nano micelles for the futuristic treatment of skin cancer and phototoxicity: Therapeutic and clinical advancement. Critical Reviews in Therapeutic Drug Carrier Systems, 39(2), 79–95. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2021035589

Miyata, K., Christie, R. J., & Kataoka, K. (2011). Polymeric micelles for nano-scale drug delivery. Reactive and Functional Polymers, 71(3), 227–234. https://doi.org/10.1016/j.reactfunctpolym.2010.10.009

Mohammadi, F., Moradi, A., Tavakoli, F., Rahmati, S., Giti, R., & Ramezani, V. (2023). Development and characterization of a copolymeric micelle containing soluble and insoluble model drugs. PLOS One, 18(5), Article e0286251. https://doi.org/10.1371/journal.pone.0286251

Mourya, V. K., Inamdar, N., Nawale, R. B., & Kulthe, S. S. (2011). Polymeric micelles: General considerations and their applications. Indian Journal of Pharmaceutical Education and Research, 45(2), 128–138.

Movassaghian, S., Merkel, O. M., & Torchilin, V. P. (2015). Applications of polymer micelles for imaging and drug delivery. Wiley Interdisciplinary Reviews. Nanomedicine and Nanobiotechnology, 7(5), 691–707. https://doi.org/10.1002/wnan.1332

Nagaich, U., Deepak, P., Sharma, A., Gulati, N., & Chaudhary, A. (2013). Polymeric micelles: Potential drug delivery devices. Indonesian Journal of Pharmacy/Majalah Farmasi Indonesia, 24(4).

Nakamura, N., Mochida, Y., Toh, K., Fukushima, S., Anraku, Y., & Cabral, H. (2020). Effect of mixing ratio of oppositely charged block copolymers on polyion complex micelles for *in vivo* application. Polymers, 13(1), 5. https://doi.org/10.3390/polym13010005

Neal, T. J., Parnell, A. J., King, S. M., Beattie, D. L., Murray, M. W., Williams, N. S. J., Emmett, S. N., Armes, S. P., Spain, S. G., & Mykhaylyk, O. O. (2021). Control of particle size in the self-assembly of amphiphilic statistical copolymers. Macromolecules, 54(3), 1425–1440. https://doi.org/10.1021/acs.macromol.0c02341

Nour, S. A., Abdelmalak, N. S., Naguib, M. J., Rashed, H. M., & Ibrahim, A. B. (2016). Intranasal brain-targeted clonazepam polymeric micelles for immediate control of status epilepticus: *In vitro* optimization, *ex vivo* determination of cytotoxicity, *in vivo* biodistribution and pharmacodynamics studies. Drug Delivery, 23(9), 3681–3695. https://doi.org/10.1080/10717544.2016.1223216

Oerlemans, C., Bult, W., Bos, M., Storm, G., Nijsen, J. F. W., & Hennink, W. E. (2010). Polymeric micelles in anticancer therapy: Targeting, imaging and triggered release. Pharmaceutical Research, 27(12), 2569–2589. https://doi.org/10.1007/s11095-010-0233-4

Owen, S. C., Chan, D. P. Y., & Shoichet, M. S. (2012). Polymeric micelle stability. Nano Today, 7(1), 53–65. https://doi.org/10.1016/j.nantod.2012.01.002

Pepić, I., Lovrić, J., & Filipović-Grčić, J. (2013). How do polymeric micelles cross epithelial barriers? European Journal of Pharmaceutical Sciences, 50(1), 42–55. https://doi.org/10.1016/j.ejps.2013.04.012

Perumal, S., Atchudan, R., & Lee, W. (2022). A review of polymeric micelles and their applications. Polymers, 14(12), 2510. https://doi.org/10.3390/polym14122510

Pignatello, R., Corsaro, R., Bonaccorso, A., Zingale, E., Carbone, C., & Musumeci, T. (2022). Soluplus® polymeric nanomicelles improve solubility of BCS-class II drugs. Drug Delivery and Translational Research, 12(8), 1991–2006. https://doi.org/10.1007/s13346-022-01182-x

Rajablou, K., Attar, H., Sadjady, S. K., & Heydarinasab, A. (2023). DSPC based polymeric micelles loaded with amphotericin B: Synthesis, characterization, and *in vitro* study. Nanomedicine Research Journal, 8(1), 37–49.

Rani, S., Mishra, S., Sharma, M., Nandy, A., & Mozumdar, S. (2020). Solubility and stability enhancement of curcumin in Soluplus® polymeric micelles: A spectroscopic study. Journal of Dispersion Science and Technology, 41(4), 523–536. https://doi.org/10.1080/01932691.2019.1592687

Razzaq, S., Rauf, A., Raza, A., Akhtar, S., Tabish, T. A., Sandhu, M. A., Zaman, M., Ibrahim, I. M., Shahnaz, G., Rahdar, A., & Díez-Pascual, A. M. (2021). A multifunctional polymeric micelle for targeted delivery of paclitaxel by the inhibition of the P-glycoprotein transporters. Nanomaterials, 11(11), 2858. https://doi.org/10.3390/nano11112858

Reddy, B. P. K., Yadav, H. K. S., Nagesha, D. K., Raizaday, A., & Karim, A. (2015). Polymeric micelles as novel carriers for poorly soluble drugs–A Review. Journal of Nanoscience and Nanotechnology, 15(6), 4009–4018. https://doi.org/10.1166/jnn.2015.9713

Rezazadeh, M., Davatsaz, Z., Emami, J., Hasanzadeh, F., & Jahanian-Najafabadi, A. (2018). Preparation and characterization of spray-dried inhalable powders containing polymeric micelles for pulmonary delivery of paclitaxel in lung cancer. Journal of Pharmacy and Pharmaceutical Sciences, 21(1s), 200s–214s. https://doi.org/10.18433/jpps30048

Safwat, M. A., Mansour, H. F., Hussein, A. K., Abdelwahab, S., & Soliman, G. M. (2020). Polymeric micelles for the ocular delivery of triamcinolone acetonide: Preparation and *in vivo* evaluation in a rabbit ocular inflammatory model. Drug Delivery, 27(1), 1115–1124. https://doi.org/10.1080/10717544.2020.1797241

Sang, X., Yang, Q., Wen, Q., Zhang, L., & Ni, C. (2019). Preparation and controlled drug release ability of the poly [N-isopropylacryamide-co-allyl poly (ethylene glycol)]-b-poly (γ-benzyl-l-glutamate) polymeric micelles. Materials Science and Engineering. C, Materials for Biological Applications, 98, 910–917. https://doi.org/10.1016/j.msec.2019.01.056

Senthilkumar, M., Dash, S., Vigneshwari, R., & Paulraj, E. (2022). Aceclofenac-loaded pluronic F108/L81 mixed polymeric micelles: Effect of HLB on solubilization. Designed Monomers and Polymers, 25(1), 1–11. https://doi.org/10.1080/15685551.2022.2028373

Serras, A., Faustino, C., & Pinheiro, L. (2024). Functionalized polymeric micelles for targeted cancer therapy: Steps from conceptualization to clinical trials. Pharmaceutics, 16(8), 1047. https://doi.org/10.3390/pharmaceutics16081047

Shukla, A., Tiwari, S., Singh, M. P., Singh, S., Singh, M. K., & Kumar, A. (2021). A comprehensive review on polymeric micelles: A promising drug delivery carrier. Journal of Analytical & Pharmaceutical Research, 10(3), 102–107. https://doi.org/10.15406/japlr.2021.10.00372

Simões, S. M. N., Figueiras, A. R., Veiga, F., Concheiro, A., & Alvarez-Lorenzo, C. (2015). Polymeric micelles for oral drug administration enabling locoregional and systemic treatments. Expert Opinion on Drug Delivery, 12(2), 297–318. https://doi.org/10.1517/17425247.2015.960841

Sinani, G., Durgun, M. E., Cevher, E., & Özsoy, Y. (2023). Polymeric-Micelle-Based delivery systems for nucleic acids. Pharmaceutics, 15(8), Article 2021. https://doi.org/10.3390/pharmaceutics15082021

Sohail, M., Yu, B., Sun, Z., Liu, J., Li, Y., Zhao, F., Chen, D., Yang, X., & Xu, H. (2022). Complex polymeric nanomicelles co-delivering doxorubicin and dimethoxycurcumin for cancer chemotherapy. Drug Delivery, 29(1), 1523–1535. https://doi.org/10.1080/10717544.2022.2073403

Sotoudegan, F., Amini, M., Faizi, M., & Aboofazeli, R. (2016). Nimodipine-loaded Pluronic® block copolymer micelles: Preparation, characterization, *in vitro* and *in vivo* studies. Iranian Journal of Pharmaceutical Research, 15(4), 641–661.

Vinchurkar, R. H., & Kuchekar, A. B. (2021). Polymeric micelles: A novel approach towards nano-drug delivery system. Biosciences Biotechnology Research Asia, 18(4), 629–649.

Wang, Q., Atluri, K., Tiwari, A. K., & Babu, R. J. (2023). Exploring the application of micellar drug delivery systems in cancer nanomedicine. Pharmaceuticals, 16(3), 433. https://doi.org/10.3390/ph16030433

Wang, Y., Thies-Weesie, D. M. E., Bosman, E. D. C., van Steenbergen, M. J., van den Dikkenberg, J., Shi, Y., Lammers, T., van Nostrum, C. F., & Hennink, W. E. (2022). Tuning the size of all-HPMA polymeric micelles fabricated by solvent extraction. Journal of Controlled Release, 343, 338–346. https://doi.org/10.1016/j.jconrel.2022.01.042

Wei, H., Cheng, S.-X., Zhang, X.-Z., & Zhuo, R.-X. (2009). Thermo-sensitive polymeric micelles based on poly (N-isopropylacrylamide) as drug carriers. Progress in Polymer Science, 34(9), 893–910. https://doi.org/10.1016/j.progpolymsci.2009.05.002

Yang, C., Wu, T., Qi, Y., & Zhang, Z. (2018). Recent advances in the application of vitamin E TPGS for drug delivery. Theranostics, 8(2), 464–485. https://doi.org/10.7150/thno.22711

Yang, X., Li, Z., Wang, N., Li, L., Song, L., He, T., Sun, L., Wang, Z., Wu, Q., Luo, N., Yi, C., & Gong, C. (2015). Curcumin-encapsulated polymeric micelles suppress the development of colon cancer *in vitro* and *in vivo*. Scientific Reports, 5(1), Article 10322. https://doi.org/10.1038/srep10322

Zhai, Y., Guo, S., Liu, C., Yang, C., Dou, J., Li, L., & Zhai, G. (2013). Preparation and *in vitro* evaluation of apigenin-loaded polymeric micelles. Colloids and Surfaces. Part A, Physicochemical and Engineering Aspects, 429, 24–30.

Zhang, Y., Ren, T., Gou, J., Zhang, L., Tao, X., Tian, B., Tian, P., Yu, D., Song, J., Liu, X., Chao, Y., Xiao, W., & Tang, X. (2017). Strategies for improving the payload of small molecular

drugs in polymeric micelles. Journal of Controlled Release, 261, 352–366. https://doi.org/10.1016/j.jconrel.2017.01.047

Zhou, W., Li, C., Wang, Z., Zhang, W., & Liu, J. (2016). Factors affecting the stability of drug-loaded polymeric micelles and strategies for improvement. Journal of Nanoparticle Research, 18, 1–18.

Zhou, Y., Zhou, C., Zou, Y., Jin, Y., Han, S., Liu, Q., Hu, X., Wang, L., Ma, Y., & Liu, Y. (2020). Multi pH-sensitive polymer–drug conjugate mixed micelles for efficient co-delivery of doxorubicin and curcumin to synergistically suppress tumor metastasis. Biomaterials Science, 8(18), 5029–5046. https://doi.org/10.1039/d0bm00840k

Zlotnikov, I. D., Ezhov, A. A., Ferberg, A. S., Krylov, S. S., Semenova, M. N., Semenov, V. V., & Kudryashova, E. V. (2023). Polymeric micelles formulation of combretastatin derivatives with enhanced solubility, cytostatic activity and selectivity against cancer cells. Pharmaceutics, 15(6), 1613. https://doi.org/10.3390/pharmaceutics15061613

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