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MICELLAR NANOTECHNOLOGY: POLYMERIC MICELLES FOR ENHANCED DRUG DELIVERY

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ABSTRACT

Polymeric micelles have emerged as a versatile and effective platform for drug delivery, particularly in the treatment of cancer and other diseases requiring targeted therapeutic interventions. These nanocarriers are formed by the self-assembly of amphiphilic block copolymers in aqueous solutions, resulting in a core-shell structure. The hydrophobic core acts as a reservoir for poorly water-soluble drugs, while the hydrophilic shell provides stability in the biological environment and prevents premature clearance from the bloodstream. This dual functionality enhances the bioavailability of encapsulated drugs, improves their solubility, and reduces systemic side effects by enabling controlled and site-specific drug release. Polymeric micelles can also be engineered for stimuli-responsive drug release, triggered by changes in pH, temperature, or enzymatic activity, making them suitable for precision medicine. Furthermore, surface modifications of micelles, such as the attachment of targeting ligands, improve their selectivity toward specific cells or tissues, such as tumor sites, enhancing therapeutic efficacy. Despite the promising preclinical results, challenges remain in clinical translation, including stability issues, large-scale production, and the need for thorough understanding of in vivo interactions. This review explores the latest advancements in polymeric micelle design, drug loading mechanisms, stimuli-responsive systems, addressing the barriers that need to be overcome for successful clinical implementation. Along with their uses in oral, parenteral, transdermal, intranasal, and other drug delivery systems, PMs varieties, preparation techniques, and characterisation are described.

KEYWORDS: Polymeric micelles, Drug delivery system, Amphiphilic block copolymer, hydrophobic drugs, Targeted drug delivery, Solubility Enhancement.

1. INTRODUCTION

The landscape of conventional drug delivery techniques has changed due to the substantial breakthroughs and quick evolution of polymer-based drug delivery technologies. Smart drug delivery techniques are the main emphasis of modern systems, whereas prior systems mostly used polymers for diffusion control. Improved bioavailability, stimulus-responsive release, feedback mechanisms, and tailored distribution to specific areas are some of these sophisticated systems' main advantages. Various biocompatible polymers have been developed in response to concerns about the biocompatibility of specific polymers in drug delivery applications. Furthermore, new developments in chemical engineering have made it easier to create new polymers and alter old ones to better suit the requirements of intelligent drug delivery systems.[1]

The introduction of high-throughput drug discovery technology made the challenge of improving some existing medications through chemical alterations even more apparent. Due to their poor water solubility, over half of the lead drug candidates found through high-throughput screening are dropped before the formulation development phase. Furthermore, poorly produced drug candidates frequently fail because of poor metabolism, bioavailability, and/or unfavorable side effects, all of which lower the molecules' therapeutic index.[2]

The non-specific distribution of medications throughout the body and the development of harmful effects in healthy organs unrelated to the diseased process are two of the main issues with safe and efficient pharmacotherapy. Furthermore, medications may be removed, metabolized, or inactivated soon after administration before they reach their site of action. Rapid clearance and uncontrolled distribution will lower

the overall concentration of medications at their site of action, decreasing the likelihood of a successful and effective course of therapy without unintended hazardous side effects.[3]

One efficient method of getting medications to their targets is by employing micellar solutions of amphiphiles. Water-insoluble medications can be readily dissolved and loaded for distribution to the desired locations because of the hydrophobic environment of the micelle core. The development of targeted drug delivery systems aims to minimize drug loss and degradation, avoid negative side effects, boost medication bioavailability, and raise the quantity of pharmaceuticals in the desired zone of interest. Numerous drug carriers are widely employed, including soluble polymers, insoluble natural and synthetic polymers, microparticles, cells, cell ghosts, lipoproteins, liposomes, and micellar systems based on amphiphilic polymers. There are benefits and drawbacks to these drug delivery methods.[4]

Although there may be some concerns about their stability in plasma, polymeric micelles now appear to be among the most beneficial delivery systems for water-insoluble medications. The production, characterisation, and possible uses of polymeric micelles as drug carriers are briefly reviewed in this paper.[5]

1.1 Advantages of polymeric micelles in drug delivery

1. Improved solubility of poorly water-soluble drugs.
2. Controlled and sustained drug release.
3. Targeted drug delivery to specific sites (e.g., tumors).
4. Reduced systemic toxicity.
5. Biocompatibility with minimal adverse reactions.
6. Reduced immunogenicity due to PEGylation.

1.2 Disadvantages of polymeric micelles in drug delivery

1. Limited drug loading capacity.
2. Instability in dilute conditions, causing premature drug release.
3. Rapid clearance by the body's immune system.
4. Potential toxicity from degradation products or non-degradable polymers.
5. Complex manufacturing and scalability.
6. Difficulty in achieving precise targeting.
7. Risk of premature drug leakage.

2. Polymeric micelle

The ability of polymeric micelles to self-assemble into the micellar system in aqueous solutions at concentrations higher than their CMC makes them a nanoscale colloidal drug delivery platform made of amphiphilic block copolymers. When a hydrophobic and a hydrophilic segment are present in the same molecule at or above the CMC, they self-assemble to produce a core-shell dynamic micellar structure, which is a characteristic of amphiphilic copolymers. Such micelles have a hydrophilic component that creates the shell or corona and a hydrophobic piece of copolymer that forms the micelle's core. These two segments have distinct characteristics and behave differently in relation to the solvent. The core of polymeric micelles can include hydrophobic moieties, and the corona shields it from these harmful substances.[6]

For carriers of drug delivery, the characteristics of PMs offer several advantages. The RES and macrophages cannot see PMs because of their small size and hydrophilic shells. As a result, their drug cargos have longer circulation periods. Encapsulating poorly soluble medications into PM cores increases their bioavailability, which can lower the dosage needed and decrease negative effects. The EPR effect and passive targeting are further improved by PMs' tiny size and longer blood circulation periods. Additionally, by adding ligands, the hydrophilic block that makes up the corona or shell can be altered to improve targeted therapy and efficacy while lowering adverse effects.[7]

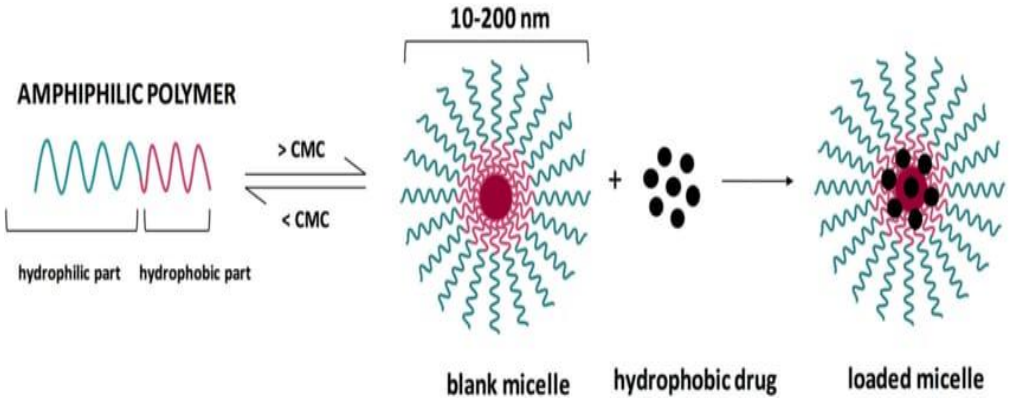


Fig. 1: Polymeric micelle.

3. Methods of preparation

The physicochemical properties of the block copolymers used for the PM manufacture serve as the basis for the PM preparation technique. The drug encapsulation efficiency and physicochemical properties are highly influenced by the technique selected. The stability, size,

and polydispersity index are influenced by the concentration of the copolymers, the ratio of aqueous to organic, and the sequence of addition. To create a standard recipe for creating PMs with appropriate physicochemical and functional features, it is therefore advantageous to optimize these parameters.[1] Several methods have been developed for the preparation of polymeric micelles, each with its specific advantages depending on the application and properties of the desired formulation. Here is an overview of the primary methods used to prepare polymeric micelles.

3.1 Direct dissolution method

The solvent casting process is another name for the solvent evaporation method. It makes use of a volatile organic solvent that can dissolve both the medication and the polymer. This technique was used to successfully insert the anticancer drug camptothecin (CPT) into a PEG poly(aspartate) block copolymeric micelle. The lengthy and extremely hydrophobic core-forming blocks cannot be used with this procedure, just like with the direct dissolution method. The direct dissolution approach is mostly utilized to create PMs from copolymers with high aqueous solubility. This approach, which is rather straightforward, entails combining copolymers and medications in aqueous solvents while encasing the medications using mechanical techniques like heating, sonication, and stirring. The core-forming blocks' dehydration results in PM.[1,6]

3.2 Ultrasonication method

This method involves the use of high-frequency ultrasonic waves to break up large polymer aggregates in solution. The copolymers are initially dissolved in an organic solvent, and upon sonication, the solvent evaporates, leaving behind polymer micelles. This technique is especially useful for forming micelles with smaller sizes and narrower size distributions.

3.3 Dialysis method

The dialysis process is used when the selected amphiphilic copolymers are not very soluble in water. To encourage the formation of micelles, an aqueous solvent is added after the drug and copolymer have been dissolved in a common solvent. The mixture is dialyzed against water for a long time in order to remove the organic solvents. Because it influences the micelle's physical properties and the effectiveness of drug encapsulation, the solvent selection is crucial for this process. Additionally important is the proper ratio of organic to aqueous solvent. Tetrahydrofuran, acetone, acetonitrile, N,N-dimethylformamide, and dimethyl sulfoxide are typical solvents for this process.[1]

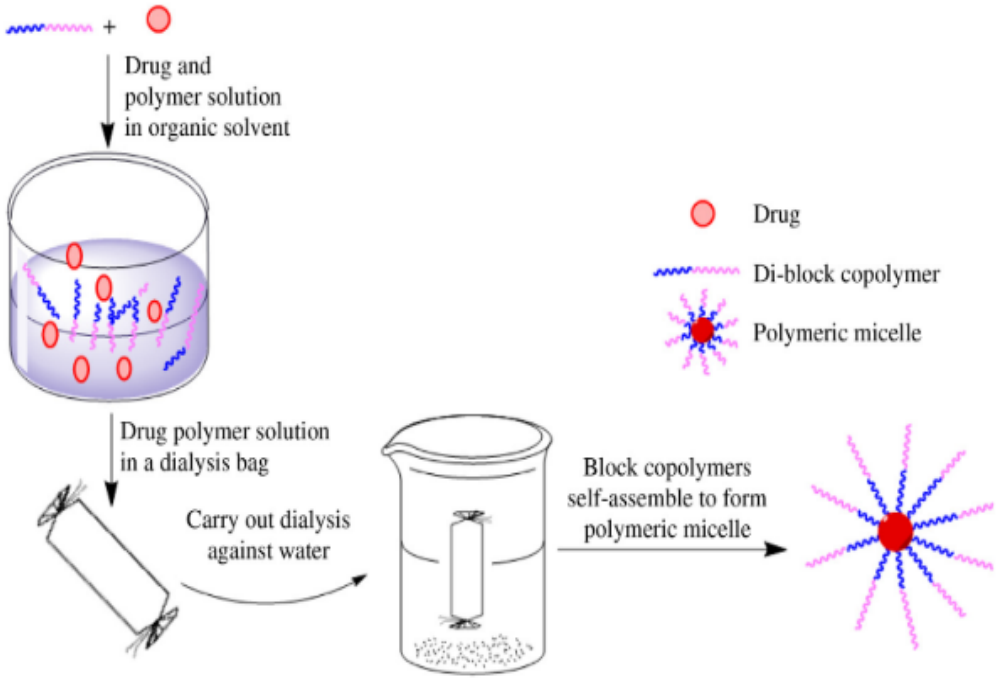
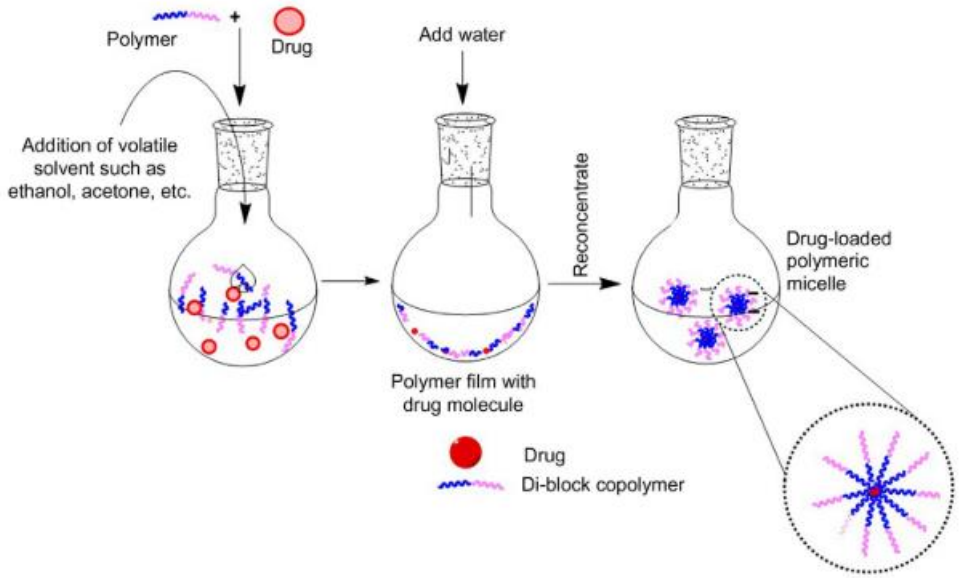


Fig. 2: Dialysis method.

3.4 Solvent evaporation method

Thin-film hydration and solvent evaporation procedures are employed when the copolymers are soluble in a volatile and water-miscible organic solvent. The synthesis of polymeric micelles and solvent evaporation occur at somewhat different times in thin-film hydration and evaporation. Copolymers are dissolved in an organic solvent, the solvent is evaporated to form a thin polymer film, a water phase is added to hydrate the film, and stirring is done to make the micelle. Furthermore, according to the solvent evaporation strategy, the copolymer is dissolved in an organic solvent, water is added to the mixture to form the micelle, and the solvent is then evaporated.[8]



3.5 Film hydration method

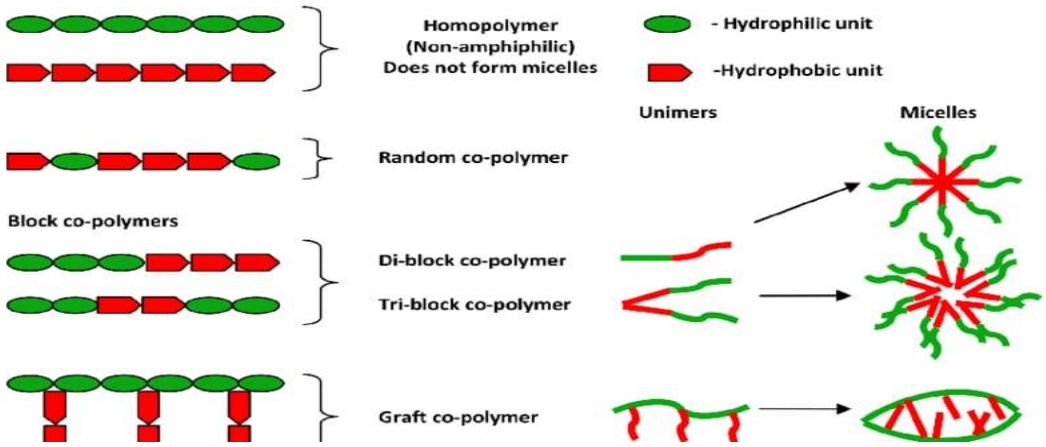
In this technique, the block copolymer is first dissolved in an organic solvent and then spread as a thin film on the surface of a container by evaporating the solvent under vacuum. The dried film is then hydrated with an aqueous solution, leading to the formation of micelles. This method is commonly used when hydrophobic drugs are involved, as it allows for drug loading during film formation.

3.6 Emulsion method

In this micelle preparation technique, a water-immiscible volatile organic solvent (chloroform, dichloromethane, ethyl acetate, and methylene chloride) is added slowly to the aqueous medium, forming an emulsion. The copolymer and medicine are present in this aqueous media, and micelle production occurs following agitation and solvent evaporation.[8],[9]

4. Types of polymer used

Graft copolymers and block copolymers (di, tri, or tetra) are two types of micelle-forming amphiphilic copolymers. One polymer chain serves as the backbone of a graft copolymer, while additional polymer chains serve as the side "grafted" portions. These copolymers typically exhibit both the graft's and the polymeric backbone's characteristics. In order to create well-defined 22 graft copolymers, "click" reactions have become a popular method for adding polymer chains to polymeric backbones. Typically, amphiphilic di block AB-type or triblock ABA-type copolymers self-assemble to produce spherical micelles in aqueous solutions. The length of a hydrophilic block is somewhat more than that of a hydrophobic block.[10] A variety of methods can be used to create diblock copolymers. Successful routes to block copolymers include ring-opening polymerization, polycondensation, free radical polymerization, anionic polymerization, cationic polymerization, living/controlled radical polymerization (including atom transfer radical polymerization (ATRP), nitroxide mediated polymerization (NMP), and reversible addition fragmentation chain transfer (RAFT)), and additional innovative techniques.[11]



4.1 Polymeric micelles drug delivery systems that have been clinically approved or under clinical trials

Drug Delivery System	Polymer	Drug	Indication	Status	Reference
Genexol-PM	Poly(D,L-lactic acid)-b-poly(ethylene glycol)	Paclitaxel	Breast, lung, ovarian cancers	Clinically approved (Korea, US trials)	[15]
NK105	Poly(ethylene glycol)-b-poly(aspartic acid)	Paclitaxel	Advanced gastric cancer	Phase III (Japan)	[16]
SP1049C	Pluronic block copolymers	Doxorubicin	Gastrointestinal cancers	Phase II	[17]
NC-6004 (Nanoplatin™)	Poly(glutamic acid)-PEG	Cisplatin	Solid tumors	Phase III	[18]
CriPec® docetaxel	Methacrylate-based copolymer	Docetaxel	Prostate cancer	Phase I/II	[19]
Nanoxel-PM	Poly(D,L-lactic acid)-PEG	Docetaxel	Breast cancer, NSCLC	Phase II/III	[20]
Paxceed™	Poly(ethylene glycol)-b-poly(glutamic acid)	Paclitaxel	Various cancers	Phase I/II	[21]
PEG-PCL micelles	Poly(ethylene glycol)-b-poly(ε-caprolactone)	Doxorubicin	Breast cancer, Hepatocellular carcinoma	Preclinical	[22]

5. Characterization of micelles

The first and most important stage after micelle preparation is micelle characterization. This provides information about viscosity, stability, size and shape, CMC, and chemical structure. Physical, chemical, or a combination of physical and chemical processes can be used to manufacture polymeric micelles. Physical approaches are typically simpler, while chemical approaches that guarantee covalent bonding between the medication and the copolymer offer more stability in the systemic circulation. Creating stimuli-responsive micelles allows for more control over medication loading and release. To get the required effects, a mix of chemical and physical techniques can also be applied.[12]

5.1 Critical Micellar Concentration (CMC)

An essential component of PM characterisation is CMC determination. It primarily symbolizes the balance between hydrophilic and hydrophobic segments. The CMC is affected by the distribution of the hydrophilic portion in the amphiphilic polymer, the molecular weight of the hydrophilic portion, and the properties of hydrophobic groups. There are numerous techniques for calculating CMC. Electrical conductivity, surface tension, and light scattering are reporter-free techniques for determining CMC that rely on modifications in macroscopic factors. Other popular techniques for determining CMC with the use of appropriate optical probes are photometric and fluorometric methods.[1] One of the better methods for figuring out the CMC of polymeric micelles is pyrene fluorescence. Pyrene's fluorescence spectra are extremely sensitive to even slight variations in solution and probe microenvironment polarity. The apparent pyrene concentration stays constant while the polymer concentration rises, but upon CMC, its fluorescence intensity dramatically increases. The hydrophobic pyrene molecules efficiently separate from the aqueous surrounding phase upon micellization and accumulate at the micellar core. The CMC can be readily ascertained from the plot of fluorescence intensity and pluronic concentration based on this pyrene molecule partitioning phenomena. The CMC of the system is determined by the junction of the slope tangent and the lower horizontal.[4]

5.2 Particle size measurement

The micellar size can be determined via DLS, photon correlation spectroscopy, or quasielectric light scattering. When laser light strikes a particle that is continuously influenced by Brownian motion, Doppler shift takes place, changing the source radiation's wavelength based on the micelle's size. This method can therefore be used to determine size and size distribution; in addition, it can compute hydrodynamic radius using the Stokes-Einstein equation. Furthermore, micelle aggregation number and micelle surface area per single polymer chain can be measured using it.[6]

5.3 Stability of polymeric micelle

Micelle stability is indicated by thermodynamic and kinetic stability. If there is more polymer in the aqueous solution than the CMC, the micellar system can be regarded as thermodynamically stable. As the micelle is administered i.v., the system undergoes extreme dilution; hence, it is necessary to know the CMC of the system. It is necessary that the system remains in the micellar form in the systemic circulation until it reaches the targeted site. The rate at which the polymer chain exchanges

between the micelle and the bulk determines kinetic stability. To forecast when the physically confined medication will be released from the polymeric micelle, kinetic stability is crucial.

Block copolymers are discovered to generate a kinetically stable micellar system due to the increased number of hydrophobic sites available for interaction. A lack of kinetic stability could cause the medication to leak from the micellar system into the bloodstream before it reaches its intended location. In order to improve both the thermodynamic and kinetic stability, a number of techniques have been used, including methods to lower the CMC, core cross-linking, and heterocomplex micelle production. Aromatic groups have been shown to lower the CMC and improve the contacts, which increases the micelle's stability.[6]

6. Stimuli responsive micelle

Stimuli-responsive micelles are a class of self-assembled nanoparticles that can undergo significant changes in their properties in response to specific external stimuli. These micelles have gained considerable attention in drug delivery, diagnostics, and other biomedical applications due to their ability to release therapeutic agents in a controlled manner.

Types of Stimuli Stimuli-responsive micelles can be triggered by various environmental factors

1. **pH-Responsive micelles:** These micelles are designed to release their payload in response to pH changes, often taking advantage of the acidic microenvironment of tumors or specific organelles like lysosomes.
2. **Temperature-Responsive micelles:** Polymers with lower critical solution temperatures (LCST) can change solubility with temperature variations, allowing for controlled drug release when exposed to physiological temperature shifts.
3. **Redox-Responsive micelles:** Utilizing the difference in redox potential between healthy and diseased tissues, these micelles can release drugs in the presence of specific reductive environments.
4. **Light-Responsive micelles:** Incorporating photo-responsive materials allows micelles to release their cargo upon exposure to specific wavelengths of light, providing spatial and temporal control.
5. **Magnetic Field-Responsive micelles:** By embedding magnetic nanoparticles, these micelles can be manipulated and targeted using external magnetic fields.[8]

7. Mechanism of drug Encapsulation and Release

7.1 Drug encapsulation

The insoluble medications can be physically trapped through emulsification or dialysis, or they can be chemically conjugated and encapsulated in the micellar core. High quantities of integrated drug may not be obtained by simply equilibrating the drug and micelles in water. In the chemical conjugation process, the hydrophobic drug is incorporated into the polymeric micelle core when a covalent link is formed between the drug's particular group and the micelle's hydrophobic core. Steric hindrance and resistance to enzymatic cleavage are caused by such linkages. The physical method is more advantageous for drug integration than the chemical method. Drugs are typically physically trapped using the oil-in-water emulsion process or dialysis. The distribution of a drug within the micelle may be impacted by the drug loading process. The initial amount of medicine added determines the incorporation efficiency. The medication precipitates after the loading capacity is reached. The aggregation number of the polymeric micelles also affects the drug loading efficiency. The supplied medications are more soluble in the inner core of micelles with a high aggregation number.[4]

7.2 Drug release

The design used to prepare the polymeric micellar delivery system, the incorporated drug's location within the polymeric micelles, the physicochemical characteristics of the incorporated drug, and the chemical structure of the micelle-forming block copolymer all influence the mode of drug release from polymeric micelles.

Drug release from micelle-forming block copolymer drug conjugates can occur through two main pathways: either drug cleavage within the micellar structure and subsequent diffusion out of the micellar carrier, or micellar dissociation followed by drug cleavage from the polymeric unimers.[13]

8. Application in drug delivery

1. Enhanced Solubility and Stability of hydrophobic drugs

One of the primary applications of polymeric micelles is improving the solubility and stability of hydrophobic drugs. Drugs that are poorly soluble in water often exhibit low bioavailability. Polymeric micelles, with their hydrophobic core, can encapsulate such drugs, increasing their solubility in aqueous environments. This leads to improved therapeutic efficacy. For example, paclitaxel, a potent anticancer drug with poor water solubility, has been successfully delivered using polymeric micelles, leading to enhanced pharmacokinetics and tumor accumulation.[23]

2. Targeted drug delivery

Polymeric micelles can be functionalized with targeting ligands (e.g., antibodies, peptides) to achieve targeted drug delivery. This feature allows the drug-loaded micelles to accumulate in specific tissues or cells, such as cancerous tissues, while sparing healthy tissues. The enhanced permeability and retention (EPR) effect also contributes to the passive targeting of tumor tissues by polymeric micelles. Studies have shown that targeting ligands, when attached to polymeric micelles,

significantly improve drug accumulation in tumor tissues.[24]

3. Controlled and Sustained release of drugs

Polymeric micelles offer the capability for controlled and sustained release of drugs. By manipulating the polymer composition and structure, the release profile of the encapsulated drug can be tailored. This is particularly beneficial in maintaining therapeutic drug levels over extended periods, reducing dosing frequency, and minimizing side effects. For instance, micelles loaded with doxorubicin have been developed to provide sustained release, improving the drug's therapeutic window and reducing cardiotoxicity.[25]

4. Multifunctional drug delivery platforms

Polymeric micelles can serve as multifunctional platforms for combination therapy, allowing the co-delivery of multiple therapeutic agents. This can be especially beneficial in cancer therapy, where delivering both a chemotherapeutic agent and a gene therapy agent could provide a synergistic effect. Micelles have also been explored for the co-delivery of drugs and imaging agents, enabling real-time monitoring of drug distribution and therapeutic response.[14]

5. Overcoming Multidrug Resistance (mdr)

One of the challenges in cancer therapy is the development of multidrug resistance (MDR). Polymeric micelles can help overcome this by delivering drugs that can bypass or inhibit the drug efflux pumps responsible for MDR. For example, micelles loaded with P-glycoprotein inhibitors and chemotherapeutic agents have shown potential in reversing MDR in cancer cells.[26]

9. Future prospective

9.1 Innovations in polymer chemistry

Advances in polymer chemistry will likely lead to the design of more sophisticated micellar structures. Researchers are developing novel polymers that can respond to multiple stimuli (e.g., pH, temperature, redox conditions) for even more precise drug release. Furthermore, biodegradable and biocompatible polymers are gaining attention, as they minimize toxicity and degradation concerns in the body. These innovations could lead to micelles that are more stable, efficient, and customizable for specific drugs or disease types, enhancing their therapeutic potential.

9.2 Clinical translation

While polymeric micelles have demonstrated success in preclinical studies, the pathway to clinical translation remains challenging. Overcoming hurdles such as large-scale production, reproducibility, and regulatory approval is essential for the technology to move into widespread clinical use. However, as production techniques improve and more clinical trials are conducted, micellar drug delivery systems could soon become a standard in pharmaceutical development. Collaboration between academia, industry, and regulatory bodies will be key to accelerating this transition.

9.3 Personalized medicine

Polymeric micelles also hold great potential in the field of personalized medicine. By modifying the surface of micelles with specific ligands, it's possible to create drug delivery systems tailored to an individual's unique disease profile, allowing for targeted therapy that is more effective and has fewer side effects. In the future, personalized micellar systems could be developed based on a patient's genetic, molecular, or cellular characteristics, providing a highly individualized treatment approach.

In summary, the future of polymeric micelles in drug delivery is likely to be shaped by cutting-edge innovations in polymer chemistry, the successful transition of this technology into clinical settings, and the growing demand for personalized, precision-based therapies.

10. CONCLUSION

In conclusion, polymeric micelles offer a versatile platform for drug delivery, especially for hydrophobic drugs that are otherwise challenging to administer due to poor solubility. These nanocarriers enhance drug circulation time, improve bioavailability, and provide the potential for targeted delivery, reducing systemic toxicity. Their core-shell structure allows for the encapsulation of drugs, while surface modifications can be made to enhance targeting to specific tissues or cells, such as tumors, through ligand-receptor interactions.

Moreover, stimulus-responsive micelles—those that respond to pH, temperature, or specific enzymes—allow for controlled release in response to the disease environment, offering more precise therapeutic outcomes. Polymeric micelles are especially promising in cancer treatment, where they can accumulate in tumor tissues via the enhanced permeability and retention (EPR) effect.

Despite the significant advancements, challenges remain in translating micellar nanotechnology from research to clinical application. Issues such as large-scale production, stability during storage and circulation, and potential immunogenicity need to be addressed. Nevertheless, the continued evolution of this technology, supported by ongoing research, positions polymeric micelles as a promising tool for the future of drug delivery, with the potential to revolutionize the way many therapies are administered.

REFERENCES

1. Kotta S, Aldawsari HM, Badr-Eldin SM, Nair AB, YT K. Progress in Polymeric Micelles for Drug Delivery Applications. Pharmaceutics. MDPI, 2022; 14.

2. Batrakova E V., Bronich TK, Vetro JA, Kabanov A. V. Polymer micelles as drug carriers. In: Nanoparticulates as Drug Carriers. Imperial College Press, 2006; 57–93.
3. Mahmud A, Xiong XB, Aliabadi HM, Lavasanifar A. Polymeric micelles for drug targeting. J Drug Target, 2007; 15(9): 553–84.
4. Ahmad Z, Shah A, Siddiq M, Kraatz HB. Polymeric micelles as drug delivery vehicles.
5. Jones MC, Leroux JC. Polymeric micelles ± a new generation of colloidal drug carriers [Internet]. Available from: www.elsevier.nl/locate/ejphabio
6. Kapse A, Anup N, Patel V, Saraogi GK, Mishra DK, Tekade RK. Polymeric micelles: A ray of hope among new drug delivery systems. In: Drug Delivery Systems. Elsevier, 2019; 235–89.
7. Jasim A, Abdelghany S, Greish K. Current Update on the Role of Enhanced Permeability and Retention Effect in Cancer Nanomedicine. In: Nanotechnology-Based Approaches for Targeting and Delivery of Drugs and Genes. Elsevier Inc, 2017; 62–109.
8. Negut I, Bita B. Polymeric Micellar Systems—A Special Emphasis on "Smart" Drug Delivery. Pharmaceutics. MDPI, 2023; 15.
9. Parra A, Jarak I, Santos A, Veiga F, Figueiras A. Polymeric micelles: A promising pathway for dermal drug delivery. Materials. MDPI, 2021; 14.
10. V.K. Mourya*, Nazma Inamdar, R.B. Nawale, S.S. Kulthe, Polymeric Micelles: General Considerations and their Applications Ind J Pharm Edu Res, 2011; 45(2): 128-138.
11. Stenzel MH. RAFT polymerization: An avenue to functional polymeric micelles for drug delivery. Chemical Communications. Royal Society of Chemistry, 2008; 3486–503.
12. Deshmukh AS, Chauhan PN, Noolvi MN, Chaturvedi K, Ganguly K, Shukla SS, et al. Polymeric micelles: Basic research to clinical practice. International Journal of Pharmaceutics. Elsevier B.V, 2017; 532: 249–68.
13. Aliabadi HM, Lavasanifar A. Polymeric micelles for drug delivery. Vol. 3, Expert Opinion on Drug Delivery, 2006; 139–62.
14. Paprikar A, Soni A, Kaushal N, Lin S. Polymeric Micelles for Drug Delivery. In: Nanotechnology in the Life Sciences. Springer Science and Business Media B.V, 2021; 345–72.
15. Bae JW, Kim SY, Kim SM, Kim MS, Cho SH, Lee JM. Development of Genexol-PM, a polymeric micelle formulation for paclitaxel. J Control Release, 2005; 101(1-3): 59-68.
16. Matsumura Y, Hamaguchi T, Ura T, Muro K, Yamada Y, Shimada Y, et al. Phase I clinical trial and pharmacokinetic evaluation of NK105, a paclitaxel-incorporating micellar nanoparticle formulation. Cancer Sci, 2004; 95(5): 379-84.
17. Venne A, Li S, Mandeville R, Kabanov A, Alakhov V. Hypersensitizing effect of Pluronic L61 on cytotoxic activity, transport, and subcellular distribution of doxorubicin in multiple drug-resistant cells. Cancer Res, 1996; 56(8): 1906-11.
18. Cabral H, Nishiyama N, Kataoka K. Optimization of (polyethylene glycol)-poly(glutamic acid) block copolymer micelles for enhanced in vivo antitumor efficacy. J Control Release, 2005; 101(1-3): 223-32.
19. Rijcken CJ, Snel CJ, Schiffelers RM, van Nostrum CF, Hennink WE. Hydrolysable core-crosslinked thermosensitive polymeric micelles: synthesis, characterisation and in vivo studies. J Control Release, 2007; 120(1-2): 131-48.
20. Hwang C, Kim H, Choi S, Kim K, Kim T, Shin S. A phase II study of Nanoxel-PM, a novel polymeric micellar formulation of docetaxel, in advanced non-small-cell lung cancer. Nanomedicine, 2008; 4(2): 127-34.
21. Cho HJ, Yoon IS, Yoon HY, Koo H, Jin YJ, Ko SH, et al. Polymeric micelles for paclitaxel delivery with acid-labile linkages: Improved in vivo antitumor efficacy. J Control Release, 2006; 115(2): 160-7.
22. Xie H, Li Z, Zhang S, Wang Z, Zhang Y. PEG-PCL micelles for encapsulation and delivery of doxorubicin in breast cancer treatment: Preclinical studies. J Biomed Mater Res, 2010; 94(1): 141-9.
23. Kwon GS, Kataoka K. Block copolymer micelles as long-circulating drug vehicles. Adv Drug Deliv Rev, 1995; 16(2-3): 295-309.
24. Oerlemans C, Bult W, Bos M, Storm G, Nijsen JF, Hennink WE. Polymeric micelles in anticancer therapy: Targeting, imaging and triggered release. Pharm Res, 2010; 27(12): 2569-89.
25. Rana S, Yeh YC, Rotello VM. Engineering the nanoparticle-protein interface: Applications and possibilities. Curr Opin Chem Biol, 2016; 34: 112-8. Zhang H, Wu LP, Wu XL, Chen CH, Li X. Polymeric micelles for overcoming multidrug resistance in cancer. J Nanosci Nanotechnol, 2011; 11(4): 3546-54.