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Review Article

Polymeric Micelles for Targeted Drug Delivery: Recent Advances and Challenges

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ABSTRACT

To improve drug delivery systems and to enhance the solubility and Minimizing side effects.to improve stability, and bioavailability of poorly water-soluble drugs. Polymeric micelles (PM) are revolutionising the field of medicine by improving the delivery of poorly soluble drugs, increasing their effectiveness, and lowering their side effects. This results in better gene therapies, targeted drug delivery, and more effective cancer treatments. To put it simply, PM make treatments more accurate and efficient, revolutionising patient care and personalised medicine. Polymeric micelles are paving the way for a future in which medications are safer, more effective. Polymeric micelles typically have a core-shell structure, with a hydrophobic core and a hydrophilic shell. This configuration allows them to encapsulate hydrophobic drugs within the core, enhancing their solubility and stability. Size: They usually range from 10 to 100 nm in size, which is ideal for drug delivery applications as it allows them to circulate in the bloodstream for extended periods and accumulate in target tissues through the enhanced permeability and retention (EPR) effect. Methods for development of micelles: Direct Dissolution, Precipitation/evaporation, Oil/water emulsion, Thin Film Hydration.

INTRODUCTION

Many drug development failures are attributed to the water insolubility of drug. Challenges related to low solubility can lead to suboptimal drug delivery and reduced bioavailability. Approximately 35% of approved drugs and nearly 90% of molecules in the discovery process exhibit poor water solubility, low bioavailability, high toxicity. This review is based on the recent advance and challenges in polymeric micelles for targeted drug delivery. The polymeric micelles are modern technique to improve the solubility of poorly water-soluble drugs and issue related to the administration of drugs. Polymeric micelles are nothing but supramolecular structure i.e. aggregation of colloids formed in solution by self- constructed amphipathic polymer and particle size is between 10nm to 100nm. Polymeric micelles, in comparison to other nanocarriers, typically exhibit smaller size, simpler manufacturing and sterilization procedures and strong solubilization capabilities. However, these advantages are sadly correlated with a reduced stability in blood and plasma fluids and more difficult evaluation. Polymeric micelles are widely applicable to the chemotherapeutic agent and other antibiotics. In this review, different pharmaceutical application of polymeric micelles and their method of preparation and evaluation parameter are discussed.

It can be difficult to find novel medication for treating illnesses without sacrificing efficacy and safety. Despite notable progress in development of novel medications, several medical diseases remain untreated and require efficient treatment. The progress of finding and developing new drugs has been accelerated by the market potential, current market competition, and dry pipeline of developmental candidates. Because of this, many medications that receive approvals have subpolar biopharmaceutical qualities. It is 90% of medication in development pipeline and 40% of marketed drugs are comprised of poorly soluble compounds [1]. Numerous commercially available medications have issues with poor safety and

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Table 1: Historical development in nanotechnology [4]

Sr.	Year	Development
1	1959	Nanotechnology first time discussed by R. Feynman
2	1974	The concept of nanotechnology trail by Taniguchi for the first time.
3	1981	Scanning probe microscope developed by J.RES DEV
4	1985	Fullerenes by R. Smalley
5	1986	First book on nanotechnology the coming era of nanotech published by K. Eric Drexler.
6	1991	Evaluation of Carbon Nanotube for first time by S. Ijima
7	1999	1st nano medicine book by Freitas Jr. "Nanomedicine: Basic Capabilities" was published
8	2001	A number of researchers have received awards for their work on the development and evaluation of carbon nanotubes and wires, as well as their theoretical contributions to nano-meter-scale electrical devices.
9	2003	The first advanced nanotechnology policy conference took place. The Feynman Prize in nanotechnology was given for creating novel enzymes with altered functions and for engineering stable protein structures and the first centre for nano mechanical systems was founded.
10	2004	There was the first advanced nanotechnology policy conference. The first centre for nanomechanical systems was founded, and the Feynman Prize in nanotechnology was given for creating novel enzymes with modified functions and for creating stable protein structures.
11	2005-10	Prepared 3D nano systems include automation, 3D networking, nano-formulation and active nano items that alter their state while being used.
12	2011-24	Binging of advance molecular nanotechnology

tolerability as well as poor solubility, low permeability, fast metabolism and rapid excretion from body. To overcome this type problems by creating nanocarrier that can either passively or actively target on the site of the action, which gives results in a more effective treatment and therapeutic effect, reduced dose of administration and decrease toxicity. Nanomedicine is an emerging field of study that combines nanotechnology and medicine [2].

History of Nanotechnology

Nanotechnology development has been a journey of scientific discovery and technological innovation, spanning several decades. For Historical development pipelines in nanotechnology refer to Table 1.

The primary goal of creating novel medication for the last decade has been the construction of an appropriate drug carrier [3]. The most significant nanocarrier for above regard the Polymeric micelles is fit to the above all problems occur in new drug development e.g. poor solubility, high toxicity, frequent drug administration. The polymeric micelles are self-constructed Microscopic colloidal dispersion having a Aquaphobic core and a Aquaphilic shell, typically with particle sizes between less than 100 nm. Polymeric micelles are exhibit unique or original qualities due to their size, solubility, customized surface or exposure to the environment. These characteristics render them multipurpose and indispensable in different domains, including pharmaceuticals, biomedical science and other applications [5].

Ideal Characteristics of Polymeric Micelles

- Structural stabilityMicelles have a core made of polymer chains that are entangled, giving them both kinetic and thermodynamic stability [6].
- Specific binding ability: Using the increase permeability retention (EPR) effect, forming micelles of stimuli-responsive amphipathicDi block copolymers, or adding a particular targeted ligand molecule to the micelle surface. Immuno-micelles, which are produced by affixing p-nitrophenyl carbinyl groups from monoclonal antibody molecules on the water-exposed terminal of micelle corona forming blocks, exhibit high binding selectivity and targeted ability [7].
- Ability to solubilize water insoluble drugs: Solubility of medications in water Polymeric micelles is thought to be the most effective pharmacological carriers for solubilising drugs in water. One of the key components that can create a transparent aqueous solution with a medication concentration adequate to reach therapeutic levels is Aquaphobic. Polymeric micelles possess the ability to cause a decrease in the drug's bioavailability [8].
- Increased bioavailability: While less permeable tumours are only penetrated by

micelles with a dimension of 25 nm, which conforms to the role of size, larger tumours are more easily accumulated in highly permeability areas near the site of action.
- Sustain release of drug on basis of polymer or surfactant [9].
- Increasing solubility of sparingly soluble drug.
- Mucoadhesive properties [10].

Types of Polymeric Micelles

Simple Micelles

In an aqueous medium, regular micelles are amphipathic co-polymer structures that self-assemble. They are created in an aqueous solution, or the aqueous environment, which has an external Aquaphilic region and an internal Aquaphobic zone. PEG-polylactic acid, PEG-PLGA, and poloxamers are a few examples.

These are the amphiphilic copolymer self-assembled structures in a non-aqueous medium. They have an interior Aquaphilic zone and an exterior Aquaphobic region, and they are manufactured in an organic medium. For instance, PCL-P2VP micelles in oleic acid and Phosphazene micelles in chloroform [11].

Inverted Micelles

These are the amphipathic co polymer structures that self- constructed in an aqueous solution. They have an interior Aquaphilic zone and an exterior Aquaphobic zone, and they are created in an organic medium.

Single Molecular Micelles

These polymers allow a single molecule to self-assemble into a micelle because they have numerous Aquaphilic and Aquaphobic areas in one molecule. These are created by amphipathic molecules in an aqueous media, such as Core (Laur) PEG micelles. They have special single-molecule structures that allow them to remain stable in the face of drastic changes in temperature, pH, ionic strength, and other environmental factors. Examples of these alterations include severe dilution [12].

Current Advance of Polymeric Micelles

- Easy loading of water insoluble drug and drug release control by polymers structure, need of surface functionalization
- Easy and cost-effective preparation
- Enhanced Bioavailability
- Tumour Targeting
- Decrease toxicity
- Minimum drug degradation and loss
- High drug loading capacity
- Increase water solubility of drug
- Sustained drug release
- Solubilizing the insoluble drugs
- Controlled drug-releasing properties
- Increasing drug stability
- Versatility in monomer species
- Surface modification
- Relatively scalable of preparation method [13-16].

Current Challenges in Developments of Polymeric Micelles

- Complex characterization
- Deformation and Disassembly
- Chance of accumulation on healthy cells
- High cost of preparation of micelles
- Low stability
- Low drug loading
- Low colloidal stability [17].

Method of Drug Targeting

Passive Targeting:

Drug delivery techniques, known as "passive delivery systems," aim to affect systemic circulation. A passive hepatic drug target can be made of specific colloid due to its capacity to be absorbed by Reticulo Endothelial System (RES), particularly in the kidney and GI [18, 19].

Reverse Targeting:

Because the strategy aims to prevent passive uptake of colloid carrier by RES, it is referred as reverse targeting. reverse targeting is achieved by pre-injection large volumes of blank colloidal carrier or macromolecule such as dextran sulphate, which inhibit the normal function of the RES. RES saturation and defence mechanism inhibition are the outcome of this tactic. It is quite effective to target drugs to non-RES organ using this strategy [18-21].

Actively Targeting

This way of surface modification supplies a drug-carrying carrier system to a specific region instead of spontaneous RES absorption. Technique for altering the surface include applying an albumin protein coating, a bio-adhesive non-ionic surfactant or monoclonal antibodies that target particular cells or tissues.

There are several ways to alter active targeting including following:

Table 2: Polymers used in formulation of micelles

Name of polymer	Ideal Properties	Method of preparation	Advantages	References
Polyesters e.g., POLLA, PLGA, PCL	Clinically approved drug clinically it is biodegradable.	Ring-opening polymerization of cyclic monomers.	Biodegradable, High loading capacity.	[24,25]
Polyether E.g., PPO, poly (butylene oxide)	PPO is a part of tri Di block copolymers (poloxamers PEO-PPO-PEO)	Anionic Ring-opening polymerization of alkylene oxides	Di block copolymers are commercially available e.g., poloxamers	[26,27]
Poly amino aide e.g., PBLA, PBLO	Biodegradable. Aquaphobicity is increased because of the benzyl pendant group.	Polymerization of á-amino acid	High loading capacity[poly(glutamic acid)] tested clinically, with greater affinity	[28,29,30]
Poly(2-oxazine)	Water insoluble drugs can be highly loaded e.g., curcumin	LCRP(2-oxazine monomer)	The ultra-high capacity of drug loading.	[31,32,33]
Poly(2-oxazoline) e.g., PBuOx, PiPrOx, PPrO.	The flexibility of the polymeric structure.	LCRP (2-oxazoline monomers)	Ultra-high capacity for loading of water insoluble drugs e.g., paclitaxel	[34,35,36]
PEG e.g., mPEG, OH-PEG	It has stealth property, shell-forming Di block copolymers	Living anionic ROP of ethylene oxide	PEG has a Aquaphilic shell which reduce the Internalization process. Used in Genexol® PM (clinically approved)	[37,38]
Poly(sarcosine)	Used as PEG replacement	á-aminoacid-N-carboxy-anhydrides living polymerization	Biodegradability.	[39,40]

First Level Targeting: It targeting of medicine nano carrier systems to reach a specific towel or organ. For case, delivery of medicine medicines to a specifically blocked roadway from a medicine- eluting stent or medicine into the peritoneal depression, cerebral ventricles, eyes, or joint. Micelles could be used for adding the particularity to reach the diseased organs after intravenous administration. These micelles have 10nm to 100nm size in periphery and were suitable to reach the body organ and order.

Second Level of Targeting: It is also known as cellular targeting, is the precise delivery of a medication to a particularly cell type, such as tumours cells, avoiding normal cells in the process. In second-order targeting, a particular cell internalises the medication or drug carrier. To enter the cell, the carrier is supposed to bind to a particular antigen on the cell surface.

Third Level of Targeting: Targeting intercellular organelles is also referred to as third level targeting or third-level targeting medication distribution to the target cells. Delivering medications to a cell's nexus is an example of organelle-position targeting in gene therapy. The carrier system must break free from the lysosomal declination following endocytosis and discharge intracellularly into the nexus. For example, the third place in medicine targeting is organelle targeting. Cystic fibrosis and endoplasmic reticulum storage problems are linked to endoplasmic reticulum complaints. Natural disorders of the glycosylation pattern and dementia are linked to the Golgi outfit complaint [20-23].

Polymer Used In Formulation of Micelles

In development of polymeric micelles formulators require the different type of polymers and co-polymers for more details and example to refer Table 2.

Mechanism of Micelles Formation

The production of micelles is influenced by two different forces. There are repelling and attractive forces. Molecules are associated with each other by force, but polymeric micelles expansion is limited by repulsive force. When amphiphilic copolymers are dissolved in specific solvent and they are self-assembled. For

polymers that are Aquaphilic or Aquaphobic minors amounts of polymers only from single chain it focus-on the increase in concentration. It approaches what is known as the critical micelles- concentration, at which polymers chains started to bind together, further assembling to create micelles that are structured so that the chain is formed by the Aquaphilic portion, while the Aquaphobic compound forms the core at the centre of the structure [41].

Methods of Preparation

Many techniques are used for developing micellar solutions; primarily depend on the Di block copolymers' physicochemical characteristics. The solubility of a Di block copolymers of the micelle in the aqueous solution determines the optimum approach to be used. The following are the methods of production of polymeric micelles:

Direct Dissolution

It is the technique for producing micelles that is most frequently used. Di block copolymers, which are very soluble in water, are used in it. Both the polymer and the API dissolve in an aqueous solution. For the drug to load into the micelle, stirring and heating are necessary. Micelle formation is initiated by the dehydration of core-forming blocks. This method produces micelles by combining a medication with a polymer, usually (poly(propylene oxide)). They are all dissolved in an aqueous solution separately. When the two solutions are mixed at the proper drug-polymer ratio, micelles are created. The benefit of water-soluble copolymers is their ease of dissolution in water or their ability to function as a buffer for drugs and other copolymers. One problem is low encapsulation efficiency [42, 43].

Precipitation/Evaporation

The method includes selecting a suitable Evaporative solvent to dissolve the polymer and the API ingredient. A steady aqueous phase is added to the mixture after dissolution. After then, it is constantly agitated to get rid of the organic media. The micelle production process is started when the organic solvent is removed. The fundamental benefit of precipitation is that it produces material that is homogeneous and pure. Among its many drawbacks are the requirement to separate the product after precipitation and the high volume of solutions containing salt that are produced. Additionally, it is challenging to maintain a constant product quality if the precipitation is done intermittently. To understand more in details to refer Fig. 1 [44, 45].

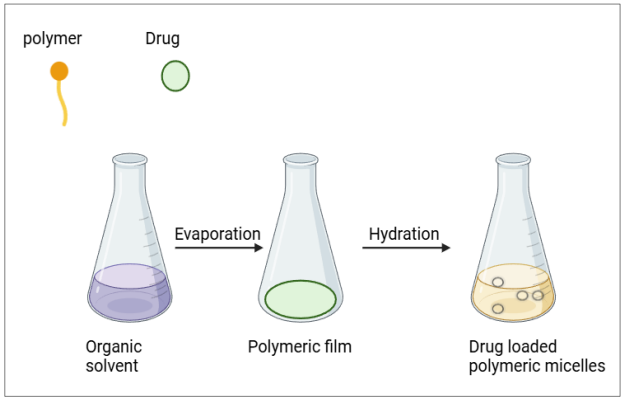

Figure 1: Solvent Evaporation Method

Oil/Water Emulsion

APIs that are lipophilic are soluble in water-immiscible solvents such as ethyl acetate, dichloromethane, or chloroform. To create an O/W emulsion, distilled water is added. Drug-loaded micelles are created by slowly evaporating the organic solvent. Polymeric micelles have the advantages of uniform size and ease of preparation. A significant drawback is the difficulty in getting rid of organic solvents and free medicines (Fig. 2) [46].

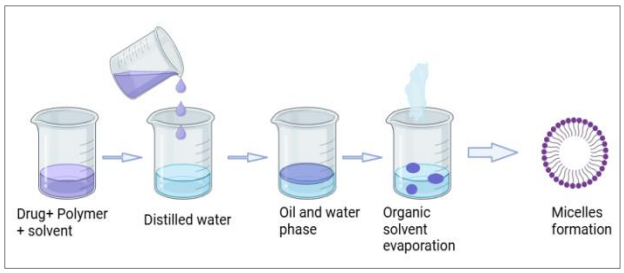

Figure 2: Oil in Water Emulsion Method

Thin Film Hydration

Drug compounds that are lipophilic dissolve the copolymer in an organic phase. A rotary evaporator is used to evaporate the solvent, creating a dry film in the process. After adding aqueous medium to the film, it is agitated and subjected to sonication, which forms drug-loaded micelles. Lipid film hydration is the simplest method for producing liposomes because it doesn't require the use of any sophisticated or costly equipment, nor does it require high pressure or temperature. The low encapsulation efficiency for micellar preparation is a drawback. For more details refer Fig. 3 [47].

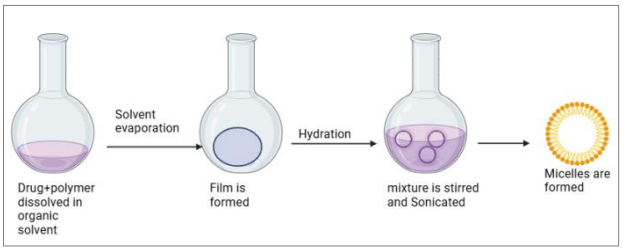

Figure 3: Thin Film Hydration

Ultrasonication

Amphiphilic polymers and Aquaphilic are dissolved in aqueous solutions, and the drug is extracted using the organic phase of a Aquaphobic rotating evaporator. To obtain drug-loaded micelles, the final product solution is subjected to sonication. According to research like that done by Nakabayashi et al., nano emulsions created by ultrasonication are transparent and stable even in the absence of surfactant. The method's drawback is that it can only produce modest amounts of nano emulsions. For more details refer Fig. 4 [48].

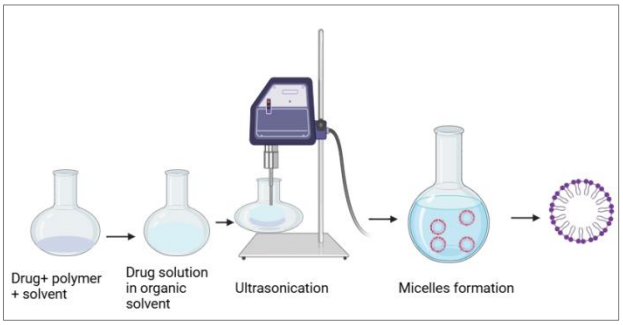

Figure 4: Ultrasonication Method

Dialysis

When an amphipathic copolymer has insoluble in water, this technique is applied. In the same organic solvent media that are used for solubilisation-dimethyl sulfoxide, N, N-Dimethyl formamide, acetonitrile, tetrahydrofuran, acetone, or dimethylacetamide-lipophilic medicines including copolymers are added and combined. After adding aqueous medium to the mixture to encourage the production of micelles, it is dialysed against water for a while to eliminate organic solvents. Drugs that are Aquaphobic and copolymers that are soluble in organic solvents can be treated using the dialysis technique. The inability to easily extract free pharmaceuticals and organic solvents from the Di block copolymers in organic solvents is a major drawback [49].

Freeze Drying

Copolymer is dissolved in an aqueous-organic solvent mixture (water, ter-butanol, etc.) and then lyophilised along with medicinal medicines. Drug-loaded micelles are spontaneously formed in an injectable vehicle, which is added to the resulting freeze-dried combination to reconstitute it. It is useful that drugs and copolymers dissolve in a blend of organic solvent and water. One drawback is the possibility of organic solvent residues [50].

Characterization of Polymeric Micelles

Characterizations of polymeric micelles by different instruments are listed in Table 3 [50-54].

Marketed Products

Table 4 listed marketed products.

Application of Micelles

Currently the pharmaceutical drug development over 92% of medications with poor water solubility. The potency of anti-cancer medications will be significantly diminished if taken orally; nevertheless, the precise formulation of organic solvent and surfactants makes intravenous delivery of these drugs difficult. Despite possessing the desired pharmacological qualities, this problem leads to their low solubility, which prevents them from reaching the market. However, recent studies on polymeric micelles offer a different, cutting-edge method of delivering these medications. Traps can be used to load drugs [50].

Cancer Treatment

For targeted anticancer drug delivery, polymeric micelles self-assembled from amphiphilic Di block copolymers have attracted considerable interest due to their numerous physical and biological advantages over other nanocarriers. These nanoparticles have an Aquaphobic core that facilitates efficient loading of poorly water-soluble drugs and a Aquaphilic shell that ensures colloidal stability and an inherent shell effect, and are 10–100 nm in size. Furthermore, targeted and controlled delivery of Aquaphobic anticancer drugs such as paclitaxel (PTX) and doxorubicin (DOX) has been made possible by biodegradable polymeric micelles. These nanocarriers: (i) increase the solubility of anticancer drugs in water; (ii) potentially increase the drug circulation period; (iii) passively target tumor tissues by utilizing the EPR effect; (iv) enhance bioavailability; and (v) have excellent biocompatibility and can be

Table 3: Characterization of polymeric micelles [50-54]

Characterization technique	Characteristics
Dynamic light scattering (DLS and SLS)	Size, polydispersity, aggregation numbers.
Atomic force microscopy (AFM), (SEM and TEM, cryo-TEM).	Size
Fluorescence and surface tension	Critical micellar and association concentrations (CAC and C.M.C.)
Electrophoretic Light Scattering (ELS)	Surface characterization (zeta potential ZP)
(DSC), X-ray, (FTIR), Nuclear magnetic resonance (NMR)	Characterization of Critical micellization concentration (CMC) Degree of crystallinity Drug/polymer interaction
UV spectroscopy(HPLC), (LCMS).	Drug loading efficiency (DLE)Drug encapsulation efficiency (DEE)Release kinetics
X-ray and neutron scattering(SANS)	characterization Structural properties
Encapsulation Efficiency (%)	EE= Entrapment drug /theoretical drug loaded X100
Loading capacity (%)	Loading capacity =entrapped drug /total weight of micelles testedX100

Table 4: Marketed products

Product	drug	Uses	Company
Genexol PM	Palcitaxel	Mammary Carcinoma, non-small cell lung cancer, pancreatic cancer.	Samyang
Estrasorb	Estrogen	Hypoestrogenism	Novavax
Medicelle	DACH-platin-PEG polyglutamic acid	Colon carcinoma	Nanocarrier
NK-911	Doxorubicin	Ovarian cancer and mammary carcinoma	Nipon Kayaku Co.
NK-105	Palcitaxel	Pancreatic cancer	Nipon Kayaku Co.
NC-6300	Epirubicin	Soft tissue sarcoma	Nanocarrier
NC-6004	Cisplatin	Head and neck cancer	Nanocarrier

degraded *in vivo* into non-toxic products that can be further absorbed and excreted from the human body. Due to their biodegradable nature, micellar solutions provide a useful tool to control drug release and prevent long-term toxicity caused by drug accumulation in human tissues. For example, Genexol PM, a PTX formulation based on biodegradable poly (ethylene glycol)-b-poly(D,L-lactide)(PEG-PLA) copolymer micelles, has been approved in various countries for the treatment of breast, ovarian, and other cancers, including Japan, Korea, the UK, and the US, as well as lung malignancies. Chemotherapy, radiation therapy, and surgical removal of tumors are traditional cancer treatments. Due to their cytotoxicity and non-specificity, chemotherapy drugs attack both healthy and cancer cells non-specifically. Therefore, they have significant side effects.

Polymer micelles, due to their low molecular weight, have proven to be effective drug carriers that promote indiscriminate biodistribution in normal and tumor tissues. Additionally, most anticancer drugs are water insoluble, resulting in poor absorption and low bioavailability; therefore, a carrier is required to transport the drug to the tumor [55-57].

Eye Treatment

Polymer micellar formulation-based ocular medication delivery technology has advanced significantly. Among their benefits are their compact size, easy to manufacture, Aquaphilic polymer micellar corona that generates aqueous solution, and excellent drug encapsulation capacity. Micellar formulations increase the bioavailability of medications in ocular tissues [58].

Fungal Infection

More than 25% of people worldwide suffer from mycoses and other fungal infections. These infections mainly affect patients with compromised immune systems due to age, clinical condition, comorbidities, and associated bacterial, viral, and fungal infections. Approximately 1,500,000 people die each year from these opportunistic mycoses, which are frequently brought on by Candida SPP., Crypto

coccus Normans, Pneumonitis, Aspergillus SPP., and Trichophytons SPP. Antifungal medications can be applied topically or taken orally to treat fungal infections. Despite their increased efficacy, alternative oral treatments increase the risk of potential drug interactions and can cause a number of adverse side effects [59].

Gene Delivery

Because of their potential, PMs have also been used in gene delivery applications. A common cationic polymer for gene delivery applications is polyethylenimine. A hydrophobic peptide's polyethyleneimine conjugate was made in a published study. In an aqueous solution, the amphiphilic conjugate created a core-shell-type micelle. Because cationic polyethyleneimine was present, the resulting core-shell micelle gave the micelles a positive surface charge. This made it easier for negatively charged plasmid DNA to be loaded. Good transfection efficiency was observed when evaluated in vitro. The technique has been suggested as an efficient way to transport genes [60].

Approaches to Overcome the Limitations Related to the Application of Polymeric Micelles

The use of polymeric micelles as drug delivery nano-systems has several benefits, but it's vital to consider any potential drawbacks. The polymeric micelles may occasionally exhibit specific drawbacks that need to be considered while assessing their potential limits, such as poor stability, poor drug loading, or excessive toxicity. For these reasons, scientists have designed a variety of procedures to mitigate the drawbacks of employing polymeric micelles (Table 5).

Recent Developments

Enhanced Targeting: Advances in polymeric micelles have improved their ability to target specific tissues or cells. This is achieved through the incorporation of ligands that bind to receptors overexpressed on target cells, enhancing the precision of drug delivery.

Stimuli-Responsive Systems: Newer polymeric micelles are designed to respond to specific stimuli such as pH, temperature, or enzymes. This allows for controlled drug release at the target site, minimizing side effects and improving therapeutic outcomes.

Multifunctional Micelles**:** Recent research has focused on developing multifunctional micelles that can deliver multiple drugs or combine therapeutic and diagnostic functions. This approach aims to provide comprehensive treatment and monitoring of diseases.

Advanced Drug Loading Techniques**:** Researchers are developing innovative methods to enhance drug loading efficiency in polymeric micelles. Techniques such as co-solvent evaporation and nanoprecipitation are being optimized to achieve higher drug encapsulation rates.

Limitations and Challenges

Stability: One of the primary challenges is maintaining the stability of polymeric micelles in the bloodstream. Premature disassembly can lead to drug leakage and reduced efficacy.

Scalability**:** Producing polymeric micelles on a large scale while maintaining consistency and quality is challenging. This is crucial for their commercial viability and widespread clinical use. Toxicity and Biocompatibility: Ensuring that the materials used in polymeric micelles are non-toxic and biocompatible is essential. Any adverse reactions can limit their clinical application.

Regulatory Hurdles**:** Navigating the regulatory landscape for approval of new drug delivery systems can be complex and time-consuming. Ensuring compliance with stringent regulations is necessary for bringing new polymeric micelle-based therapies to market.

Personalized Medicine**:** Polymeric micelles are being tailored for personalized medicine approaches. By customizing the polymer composition and drug payload, treatments can be more effectively matched to individual patient profiles, improving therapeutic outcomes.

Because polymeric micelles are effective and versatile drug delivery methods, they have been the focus of a lot of study over the last ten years. It is likely that micelles will be used in the future as medication nanocarriers, especially for ocular, fungal, and cancer therapies. In order to improve drug loading capacity, tumours-specific absorption, and anticancer activity, more intricate polymer architectures are being developed. Polymeric micelles drug delivery systems have a wide range of uses in medicine.

Table 5: Approaches to overcome the limitations

Limitation	Strategies	References
Toxicity and sensitivity	Using pH- sensitive micelles; targeting by using high affinity ligands a; Use Degradable PMs, linking PEG with Drug.	[60, 61]
Low stability	The PEGylation method and covalent cross-linked techniques: cross-linked micelles with a shell and a core. Covalent cross-bonding techniques: reversible boronated ester bond, clicks cross-linking method, di-function cross-linker, photo- and ultraviolet-induced dimerization; Strategies for non-covalent cross-linking: Micelle core complexation, macrocyclic host-guest complexation, modification of the Aquaphilic/Aquaphobic block ratios in micelles, elevation of the Aquaphobic segments' crystallinity, the addition of inorganic substances to the micelle's shell or core to stabilise its structure.	[62, 63]
Low drug encapsulation	Perfecting the comity between medicine and polymer; polymeric prodrugs; electrostatic relations; cross-linking of the shell of tone-assembled PMs; Host- guest complex micelles; Micelle- suchlike nanoparticles; integrated medicine attached polymers into lipids.	[64, 65]
High CMC	Increase chain length of the Aquaphobic group; Attaching colourful adipose acids with micelles with; addition of benzyl groups.	[66]
Rapid clearance	PEGylation approach; cross-linked with colourful stimulants-sensitive linkers for the rapid-fire concurrence.	[67]
Low selectivity	PEGylation -for the targeting to the high frequencies matched affinity.	[68]
Low permeability	High-affinity targeting ligands; Polymers with buffering capacity at endosomal pH; Aquaphobic halves and cationic groups.	[69]
Low efficiency in drug delivery	Intracellular redox-responsive drug release; high-affinity targeting ligands; cross-linked with stimulant-sensitive linkers.	[70]

CONCLUSION

Over the past ten years, polymeric micelles have been the subject of much research due to their versatility and efficiency as drug delivery systems. Future applications of micelles as drug nanocarriers, particularly for cancer therapy, fungal treatment, and ophthalmic therapy, appear promising. More complex polymer structures are being designed to enhance drug loading ability, tumors-specific absorption, and anticancer efficacy. Applications for polymeric micelles drug delivery systems in medicine are numerous.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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