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Nanomicelles as Versatile Nanocarriers: Advances in Drug Delivery, Diagnostics, Theranostics, and Industrial Applications

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ABSTRACT:
Nanomicelles are tiny droplets formed by the self-assembly of amphiphilic material that have a hydrophobic and hydrophilic component and offer limitless possibilities with respect to the use of nanomaterials for drug delivery in biomedical applications. In this review, we will provide an overview of the current state of the art in nanomicellar systems by systematically reviewing all of the literature and reviewing and evaluating nanomicellar systems regarding their structure, physicochemical properties, classification, methods of preparation, biomedical uses, recent advances, and disadvantages of each type of nanomicellar system. The nanomicelles are identified as a specific category consisting of polymeric, surfactant-based, mixed, stimuli-responsive, functionalized, reverse, and polyplex nanomicelles, which demonstrate a significant ability to increase the solubility, stability, bioavailability, and targeted delivery of poorly soluble drugs. In addition, nanomicellar systems have the potential to be utilized in cancer treatment, ocular and neurological delivery of drugs, antimicrobial treatment, diagnostic applications, and nutraceutical applications. The use of ligand-functionalization, stimuli-responsive, multidrug delivery, and hybrid nanomicellar systems demonstrate that the ability of nanomicelles to improve drug efficacy and achieve maximum target specificity makes them an excellent alternative to conventional methods of drug delivery. However, the continued use of nanomicelles in clinical applications is constrained by various limitations, including issues related to in vivo instability, toxicity, scale-up, and regulatory approval; hence, it is critical that further research be carried out to evaluate the safety of nanomicelles and develop standardised methods for large-scale manufacturing and clinical evaluation to maximize the use of nanomicelles to improve personalised medicine.

KEY WORDS: Nanomicelles; Drug Delivery Systems; Nanomedicine; Targeted Drug Delivery; Polymeric Micelles; Therapeutics.

I. INTRODUCTION

Nano micelles play a key role in nanotechnology by solving major challenges in delivering hydrophobic drugs, which make up about 40% of new pharmaceutical compounds[1]. These Amphiphilic assemblies create a hydrophobic core for lipophilic agents and a hydrophilic shell for solubility and stability in water[2]. Their nanoscale size (10–100 nm), biocompatibility, and adjustable surface properties make them suitable for drug delivery, imaging, diagnostics, and industrial applications[3]. For example, nanomicelles improve the bioavailability of anticancer drugs like paclitaxel and doxorubicin, while reducing systemic toxicity[4]. This article reviews nanomicelles, highlighting their synthesis, properties, and various applications. It also examines advancements such as pH-responsive and targeted nanomicelles, and addresses limitations like regulatory challenges and in vivo stability[5]. By integrating recent literature, the review aims to emphasize their potential in transforming healthcare and beyond[2].

Nanomicelles usually consist of Amphiphilic polymers that self-assemble in water into structures with a hydrophobic core and a hydrophilic shell, typically ranging from 20 to 200 nm in size. This assembly occurs at concentrations above the critical micellar concentration (CMC). The lipophilic core improves the solubility of poorly water-soluble molecules and allows for controlled drug release. The hydrophilic shell protects the encapsulated drug from the external environment, preventing interactions with plasma components and contributing to prolonged circulation in the body. Additionally, the small particle size helps avoid filtration by the liver and spleen, along with glomerular elimination. It also enhances cellular uptake and allows for crossing epithelial barriers. Together, these features result in increased drug bioavailability[7].

Over the last two decades, polymeric micelles have gained significant attention as a multifunctional delivery system for poorly water-soluble drugs. Typically, they form through the self-assembly of Amphiphilic polymers, with

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hydrophobic segments creating the inner core and hydrophilic segments forming the outer shell. This core-shell structure provides two main advantages for drug delivery: the hydrophobic core serves as a reservoir for solubilizing poorly water-soluble drugs, while the hydrophilic shell helps prevent opsonin adsorption, enhancing blood stability and extending circulation time. The small size of polymeric micelles also assists in evading clearance by the immune system in the liver and bypassing filtration through the spleen. Extended circulation time leads to better accumulation of micelles at tissue sites with abnormal blood vessels. This is a major reason to use polymeric micelles for delivering anticancer drugs, many of which have low water solubility[15].

Nanoparticles (NPs) that can encapsulate and deliver thousands of drug molecules per particle hold great promise for treating diseases like cancer, inflammation, and infections[1]. Despite years of research and development in NP therapeutics, very few formulations have reached clinical use and made a real impact on patients. While numerous proof-of-concept studies showcase novel NPs that target and kill cancer cells, significantly fewer have been engineered and optimized for clinical translation. A key challenge is the complexity of NP optimization, as each disease type requires finding the best combination of biophysical and chemical parameters (e.g., size, charge, surface composition) that allow for molecular targeting, immune evasion, and controlled drug release. Additionally, technology platforms for rapidly synthesizing NPs with a variety of properties in a consistent manner are just beginning to emerge[17].

II. STRUCTURE AND PROPERTIES OF NANOMICELLES

Nanomicelles represent supramolecular ag gregates of amphiphilic molecules, including surfactants or block copolymers, with hydrophobic interior and hydrophilic corona [1](figure 1).
Their most important characteristics are:

Size and Morphology
With diameters between 10–100nm,nanomicelles cross biological barriers and avoid being rapidly cleared by the reticuloendothelial system[3]. Their morphology (spherical, rod-like, or worm-like) is controlled by surfactant architecture, solvent conditions, and external parameters such as pH or temperature [6].

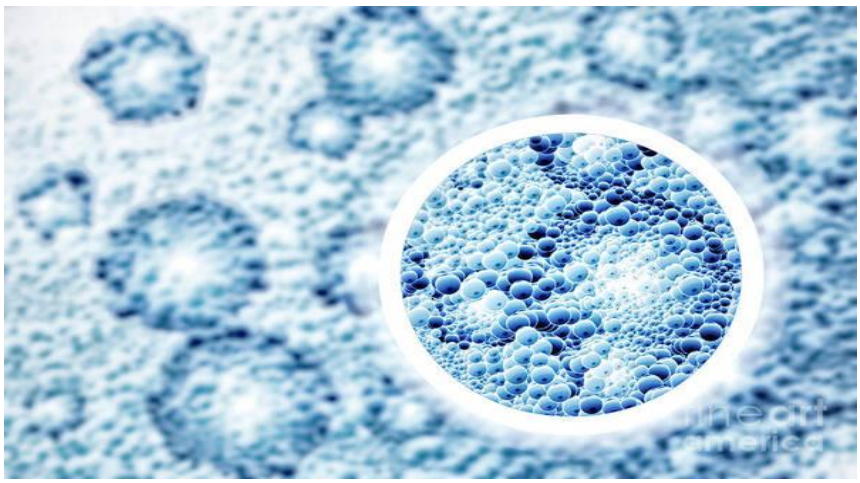

Figure 1 : Structure of Nanomicelles

Critical Micelle Concentration (CMC) :

The critical micelle concentration is the lowest concentration of surfactants in a solution above which micelles start forming of their own. In general, before arriving at this concentration, surfactants normally adsorb at the surface, thereby lowering surface tension. Surface tension either remains nearly constant or changes less dramatically if the CMC is exceeded because more surfactants form micelles instead of accumulating at the surface[2]. The factors that affect the CMC are temperature, pressure, the presence of electrolytes, and other surface-active materials. It is an important physicochemical characteristic that manifests when surfactants start to develop micelles, affecting their effectiveness in various

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processes such as medication administration, emulsification, and cleaning. For example, the CMC of sodium dodecyl sulfate in water is approximately 8x10^-3 mol/L at 25°C. Micelle production lowers the free energy of the system by shielding hydrophobic components from water and lowering interfacial energy[7].

Core-Shell Structure:

Core-shell nanomicelles are nanoscale drug delivery vehicles that have a distinct core-shell structure produced by the self-assembly of amphiphilic block copolymers[1]. The hydrophobic core serves as a reservoir to increase the solubility and durability of poorly water-soluble (hydrophobic) drugs. The micelle's hydrophilic outer shell stabilizes it in aqueous conditions, inhibits aggregation, prolongs circulation time by avoiding reticuloendothelial system identification and clearance, and facilitates controlled drug release[8].

Stability

Thermodynamic stability at CMC and kinetic stability below CMC provide structure integrity during circulation[2]. Physiological conditions (e.g., pH, enzymes) can break up stability[5].

Biocompatibility and Biodegradability

PEG, polylactide (PLA), poly(ε-caprolactone) (PCL), and chitosan provide low toxicity and safe in vivo degradation[9].

Surface Modifiability

Surface modifiability is the ability to alter a nanomicelle's hydrophilic shell chemically or physically to tailor its properties for specific applications, especially drug delivery[4]. Its versatility allows it to be functionalized with various ligands, polymers, or compounds to offer enhanced biocompatibility, targeted distribution, increased interaction with biological environments, and stealth characteristics[10].

3. TYPES OF NANOMICELLES:

Nanomicelles
are categorized according to their composition, structure, and functionality, each of which presents distinct benefits:

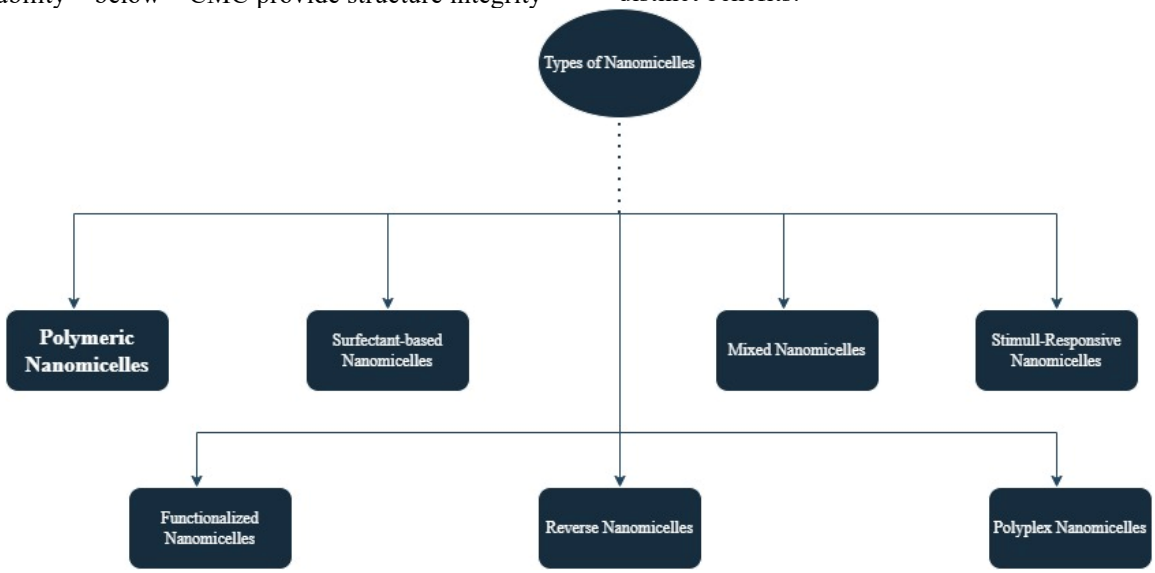

Figure 2: Types of Nanomicelles

Polymeric Nanomicelles

Prepared using block copolymers (e.g., PEG-PLA, PEG-PCL, Pluronic F127), they deliver high stability, controllable drug release, and high drug-loading capacity[2].
They find extensive application in the delivery of anticancer drugs such as paclitaxel[11].

Surfactant-Based Nanomicelles

Made up of ionic (e.g., sodium dodecyl sulfate), non-ionic (e.g., vitamin E TPGS), or zwitterion surfactants, these are inexpensive but less stable with higher CMC[3]. Vitamin E TPGS increases the solubility of drugs and prevents P-glycoprotein efflux[12].

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Mixed Nanomicelles
Blending more than one surfactant or polymer (e.g., Soluplus and vitamin E TPGS), these maximize drug encapsulation, stability, and bioavailability[7]. These are useful in oral delivery of silymarin[10].

Stimuli-Responsive Nanomicelles
They release drugs upon environmental stimuli such as pH, temperature, light, or redox conditions[5]. pH-responsive chitosan-based nanomicelles release drugs within acidic tumor microenvironments (pH ~5.5)[9]. Light-responsive micelles based on azobenzene groups allow for targeted drug release[13].

Functionalized Nanomicelles
These are conjugated with ligands (e.g., antibodies, folic acid, aptamers) and these result in active targeting of cancer cells expressing excess receptors[4]. Folate-conjugated nanomicelles improve doxorubicin delivery to breast cancer cells[4].

Reverse Nanomicelles
These are created in non-polar solvents with a hydrophobic shell and hydrophilic core and deliv er hydrophilic drugs such as peptides[3].

Polyplex Nanomicelles
Prepared from cationic polymers, these encapsulate nucleic acids (such as mRNA, siRNA) for gene therapy[14].Polymeric and stimuli-responsive nanomicelles are especially promising owing to their stability and accuracy, and functionalized nanomicelles improve therapeutic specificity[12].

4. PREPARATION METHODS

Nanomicelles are prepared using methods appropriate to their composition and use

Direct Dissolution:
Direct dissolution, which involves dissolving the amphiphilic block copolymers in an aqueous solvent and letting them spontaneously self-assemble into nanomicelles, is a straightforward method for producing nanomicelles[2]. Because it doesn't call for complex processing procedures or organic solvents, this method is simple, scalable, and suitable for hydrophilic polymers or copolymers[11].

Dialysis
Nanomicelles can be formed when polymer/medication are solubilized in a water-miscible organic solvent (examples: formamide or dimethylformamide) followed by self-assembly through dialysis against water to eliminate the organic solvent.

Film Hydration
A copolymer/drug thin film is created when a solvent evaporates and then hydrated to generate micelles for use as a delivery system for hydrophobic drugs (ex: curcumin).

Oil-in-Water Emulsion
Uniform micelles are created when a copolymer/drug mixture is emulsified in a water phase followed by the removal of the solvent through evaporation; this method provides high drug-loading efficiencies.

Ultrasonic Self-Assembly
Ultrasonic self-assembly preparation of nanomicelles is a technique that uses ultrasonic vibrations (sonication) to drive amphiphilic molecules to self-assemble into nanomicelles[16]. Cavitation, or the formation, growth, and collapse of microbubbles, is the result of applying ultrasonic energy to a solution containing the polymers or surfactants. This causes micro-mixing and strong local shear forces. This promotes the efficient and controlled aggregation of molecules into nanoscale micellar structures. Sonication improves homogeneity, reduces particle size, and increases micelle stability by preventing aggregation. The size of nanomicelles can be controlled by varying the sonication's intensity, duration, and temperature[6]. The technique is also used to load hydrophobic drugs or other materials into the nanomicelle cores during assembly to produce stable drug-loaded nanocarrier systems. Ultrasonic self-assembly is regarded as a rapid, scalable, and environmentally benign method for the creation of pharmaceutical and cosmetic nanomicelles[1].

Microfluidic Synthesis
Emerging as a precise method, microfluidics controls micelle size and polydispersity by manipulating flow rates in microchannels[17].Each method offers control over micelle size, drug loading, and release kinetics, but challenges include scalability, residual solvent removal, and reproducibility[2]. For instance, dialysis is time-consuming and costly for large-scale

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production[15]. Microfluidic synthesis shows promise for overcoming these limitations but requires specialized equipment[17].

5. APPLICATIONS OF NANOMICELLES.

Nanomicelles possess transformative uses in variou s sectors

5.1 Drug DeliveryCancer Therapy:

Ocular Delivery: Nanomicelles transport hydrophobic agents such as voclosporin or rapamycin to the posterior segment of the eye, crossing obstacles such as the stroma of the cornea and blood-retinal barrier[8]. They provide prolonged release, minimizing dosin g frequency[18].

Neurological Disorders: Polyplexnanomicelles administer mRN A coding for brain-derived neurotrophic factor (BDNF) intranasally for the treatment of olfactory dysfunction, avoiding the blood-brain barrier[14]. They administer siRNA for neurodegenerative diseases[19].

Oral Administration: Nanomicelles improve the bioavailability of poorly soluble drugs such as silymarin by increasing intestinal permeability and absorption[10]. They shield drugs from gastrointestinal breakdown[7].

Antimicrobial Therapy: Nanomicelles deliver antibiotics such as vancomycin to fight resistant bacteria, enhancing penetration into biofilms[20].

5.2 Diagnostics and Theranostics

Nanomicelles enclose imaging agents:

Diagnostics and Theranostics Nanomicelles encase imaging agents(e.g., gadolinium for MRI, fluorophores for near-infrared fluorescence) to increase diagnostic sensitivity[3]. Perfluorinatedamphiphilic copolymers allow 19F-MRI when they deliver therapeutic agents, providing imaging and therapy (theranostics)[11].Theranosticnanomicelles track dru g release in real-time, such as with quantum dot-loaded micelles for fluorescence imaging[21].

5.3 Nutraceutical Delivery

Nanomicelles enhance the bioavailability of bioactive compounds:

Nutraceutical Delivery Nanomicelles enhance the bioavailability of bioactives such as quercetin, curcumin, and silibinin against enzymatic degradation and increase absorption[12]. For instance, chitosan nanomicelles enhance quercetin solubility by 100-fold[5].

5.4 Industrial and Environmental ApplicationsPesticide Delivery:

Spinosad-loaded pH-responsive nanomicelles manage banana wilt by targeting fungal pathogens while minimizing environmental footpri nt[6]

Pesticide delivery

- Nanomicelles serve as effective delivery systems and increase the solubility and durability of pesticides by encasing hydrophobic pesticide molecules within their hydrophobic core[9].
- By permitting the controlled and extended release of pesticides that are triggered by environmental factors like temperature and humidity, they help to ensure the precise and efficient release of active ingredients. Hydrogen bonding cross-linked nanomicelles, for example, can expand and release pesticides at high temperatures and humidity levels, but they can also stop release at low temperatures and humidity levels[8].
- Nanomicelles can reduce environmental contamination and pesticide degradation by protecting active chemicals and lowering the amount of pesticide required[4].
- Combination delivery made possible by nanomicelles allows for the loading of two or more pesticides for synergistic pest control effects[3].

Cosmetics

- Boost the solubility and stability of the active ingredients
- Increase skin penetration and bioavailability
- Permit cosmetic agents to be released gradually and under control.
- Give molecules that are hydrophilic or lipophilic the ability to move in multiple ways.
- Improve a product's sensory attributes, texture, and appearance[2].
- Make it possible to remove oil and dirt effectively without sacrificing the skin's protective layer (e.g., micellar cleansers).
- Promote the targeted application of anti-aging, moisturizing, sunscreen, and pigmentation treatments.

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- They are widely used in commercial products due to their efficacy, affordability, and safety profile[22].

6. ADVANCEMENTS AND INNOVATIONS

Recent developments have broadened nanomicelle capabilities[2]:

Stimuli-Responsive Systems:

pH-, light-, temperature-, and redox-responsive nanomicelles achieve controlled release of drugs[5]. For instance, UV-responsive PEG-PCL micelles release doxorubicin in tumor microenvironments, reducing off-target effects[23]. Redox-responsive micelles take advantage of high glutathione concentrations in cancer cells for targeted release[24].

Targeted Delivery:

Ligand-functionalized nanomicelles improve specificity. Adenosine monophosphate-conjugated nanomicelles deliver to A1R receptors in lung cancer cells[25]. Peptide-conjugated micelles target drugs to brain tumour[26].

Multidrug Delivery:

Nanomicelles simultaneously deliver synergistic drugs (e.g., doxorubicin and magnolol) to counteract MDR, enhancing therapeutic efficacy [4]. Dual delivery of chemotherapeutics and immunotherapeutic promotes antitumor immunity[27].

Bio inspired Nanomicelles:

Nanomicelles from tyrosine integrate biocompatibility with catalytic properties for green chemistry use[13]. Enzyme-mimic micelles break down pollutants in environmental remediation[28].

Gene and mRNA Delivery:

Polyplex Nanomicelles shield nucleic acids and facilitate effective delivery. Intranasal mRNA delivery of neurological diseases represents a revol ution in gene therapy[14]. CRISPR/Cas9-loaded nanomicelles have potential in gene editing[29].

Hybrid Nanomicelles:

Incorporating nanomicelles with liposomes or nanoparticles yields multifunctional systems for imaging, therapy, and diagnostics[3]. Liposome-nanomicelle hybrids, for instance, release hydrophobic and hydrophilic drugs concurrently[30].These advances overcome diff iculties such as non-specific delivery and poor stability, but extensive safety and efficacy studies are needed for clinical translation[2].

7. CHALLENGES AND LIMITATIONS

Even with great promise, nanomicelles encounter substantial challenges

In Vivo Stability:

Micelles can be diluted in biological fluids below their CMC, leading to premature drug release and decreased efficacy[2]. Micelles are destabilized by interactions with serum proteins[5].

Toxicity Issues:

Concerns about toxicity significantly restrict the use of nanomicelles, especially in the cosmetics and pharmaceutical sectors. Although nanomicelles improve drug solubility, stability, and targeted delivery, their large surface area and small size may lead to unexpected interactions with biological systems that could result in cytotoxicity, inflammation, or immunogenicity[3]. The substances used to make nanomicelles, such as polymers and surfactants, can themselves be hazardous or cause allergic reactions depending on their molecular weight, content, and biodegradability[9]. Additionally, residual solvents from the preparation process or surfactants may cause toxicity. The frequent absence of long-term safety data on nanomicelle accumulation and clearance in the body or environment raises concerns about bioaccumulation and off-target effects[6].

Scalability and Cost:

Sidelined synthesis processes such as dialysis and microfluidic synthesis are time and capital intensive, limiting mass production[15]. Trace levels of residual solvents in micelles present safety hazards[16].

Regulatory Barriers:

The absence of nanomaterial-specific regulations makes approval procedures complicate d, especially in the U.S. and Europe[13]. Global harmonized standards should be e stablished to promote safety and effectiveness[18].

Targeting Efficiency:

Non-specific uptake by healthy tissues diminishes therapeutic effectiveness and en hances side effects[4]. Active targeting approaches (e.g., ligand conjugation) are

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not invariably efficient because of receptor heterogeneity[10].

Clinical Translation:

Few nanomicellar formulations have reached clinical trials due to challenges in reproducibility, stability, and long-term safety[2]. For example, Genexol-PM (paclitaxel-loaded polymeric micelles) is approved in South Korea but faces scrutiny elsewhere[11].Addressing these challenges requires interdisciplinary collaboration in material science, pharmacology, and regulatory policy[6].

8. FUTURE DIRECTIONS

The future of nanomicelles lies in overcoming current limitations and expanding their applications

Personalized Medicine:

Designing nanomicelles to patient-specific biomarkers (e.g., tumor receptor profiles) will increase precision therapy[4]. Micelle design can be customized using machine learning for individual patients[24].

Hybrid Systems:

Merging nanomicelles with other nanocarriers (e.g., liposomes, dendrimers) will produce multifunctional platforms for simultaneous drug delivery, imaging, and diagnostics[3].

Clinical Translation:

Large-scale clinical trials to ensure safety, efficacy, and long-term consequences[1]. Academic-industry-regulatory collaboration will speed up approval[22].

Regulatory Frameworks:

Standardizing nanomaterial safety, toxicity, and efficacy at the global level will make approval processes more streamlined[29]. Efforts such as the EU's Nanomedicine Regulatory Framework are a step in the right direction[27].

Emerging Applications:

Nanomicelles hold potential for applications in immunotherapy, vaccine delivery, and tissue engineering. For instance, mRNA-loaded nanomicelles would boost COVID-19 vaccine efficacy[14].These approaches will make nanomicelle s an anchor for next-generation healthcare and industrial applications[2].

9. CONCLUSION

Nanomicelles are disruptive nanocarriers, solving key issues in drug delivery, diagnostics, theranostics, and industrial uses[1]. Their potential to encapsulate hydrophobic drugs, target specific tissues, and respond to environmental conditions makes them extremely useful in cancer treatment, ocular diseases, neurological disorders, and other applications[4,8,14]. Breakthroughs such as stimuli-responsive, ligand-functionalized, and bioinspired nanomicelles increase their precision and sustainability[5,13]. Yet, in vivo stability, scalability, toxicity, and regulatory issues must be overcome to achieve their full potential[31]. Further research, interdisciplinary work, and regulatory support will solidify nanomicelles as a foundation of personalized medicine and sustainable technology[2].

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