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Polymeric Nanoparticles for Targeted Drug Delivery: An Updated Review

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Abstract

Targeted drug delivery via Polymeric Nanoparticles (PNPs) has emerged as a highly promising strategy to improve therapeutic outcomes while minimizing systemic toxicity. Owing to their unique physicochemical characteristics, such as biocompatibility, biodegradability, and tunable surface properties, PNPs can efficiently encapsulate a wide range of therapeutic agents and deliver them selectively to pathological sites. This review provides a comprehensive analysis of the design principles, classification, synthesis methodologies, and surface functionalization strategies of PNPs. Their applications in cancer therapy, gene delivery, and other biomedical domains are critically evaluated. Key challenges, including potential toxicity, production scalability, and regulatory considerations, are discussed. Finally, future directions emphasizing stimuli-responsive polymers and personalized nanomedicine approaches are highlighted.

Keywords: Polymeric nanoparticles, Targeted drug delivery, Nanomedicine, Biocompatibility, Cancer therapy.

1 | Introduction

Drug Delivery Systems (DDSs) play a critical role in modern medicine by enabling precise, controlled, and targeted administration of therapeutic agents. Traditional delivery routes, including oral and intravenous administration, face several limitations, such as degradation and nonspecific biodistribution, which can reduce therapeutic efficacy and increase systemic toxicity [1], [2]. These challenges have motivated the development of advanced drug delivery platforms that can overcome biological barriers, such as poor solubility and rapid systemic clearance, and improve clinical outcomes.

Nanotechnology has revolutionized drug delivery by enabling nanoscale carriers for controlled, targeted therapy. Among these, Polymeric Nanoparticles (PNPs) have attracted considerable attention due to their

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unique physicochemical properties, including biocompatibility, biodegradability, mechanical stability, and tunable surface chemistry [1], [3]. PNPs typically range from 10 to 1000 nm and can encapsulate a wide range of therapeutic agents, including small-molecule drugs, peptides, proteins, and nucleic acids. Encapsulation protects cargo from premature degradation, enhances solubility, prolongs circulation time, and enables controlled release in the target tissue [2], [4], [5].

A key advantage of PNPs is their ability to be functionally modified for enhanced targeting. Surface modifications, including PEGylation, ligand conjugation, and incorporation of stimuli-responsive polymers, enable active targeting to specific cell types or tissues. In contrast, passive targeting relies on the Enhanced Permeability and Retention (EPR) effect observed in tumors and inflamed tissues [4], [5]. This dual targeting strategy significantly improves therapeutic efficacy while reducing off-target side effects.

PNPs have been widely explored for applications in cancer therapy, gene delivery, vaccine development, the treatment of infectious diseases, and the crossing of physiological barriers, such as the blood-brain barrier [6], [7]. Despite their promise, several challenges remain, including large-scale production, reproducibility, potential polymer toxicity, storage stability, and regulatory approval [8], [9].

In recent years, the field has witnessed remarkable innovations, including the development of stimuli-responsive PNPs that release drugs in response to pH, temperature, or enzymatic activity, as well as approaches integrating PNPs with personalized medicine strategies. These advances highlight the potential of PNPs to transform therapeutics and enable exact, patient-specific interventions.

This review aims to provide a comprehensive overview of PNPs, covering their design principles, classification, synthesis methods, surface functionalization strategies, biomedical applications, current challenges, and future perspectives, with a particular focus on recent innovations and emerging trends in targeted drug delivery [1], [2], [5].

2 | Classification of Polymeric Nanoparticles

PNPs can be classified by structural characteristics, polymer type, and biodegradability, which are critical factors for selecting appropriate nanoparticles for specific drug-delivery applications [3], [4]. Understanding these classifications enables optimization of key properties, including stability, biocompatibility, drug release profiles, and interactions with biological systems *(Fig. 1)* [1], [5].

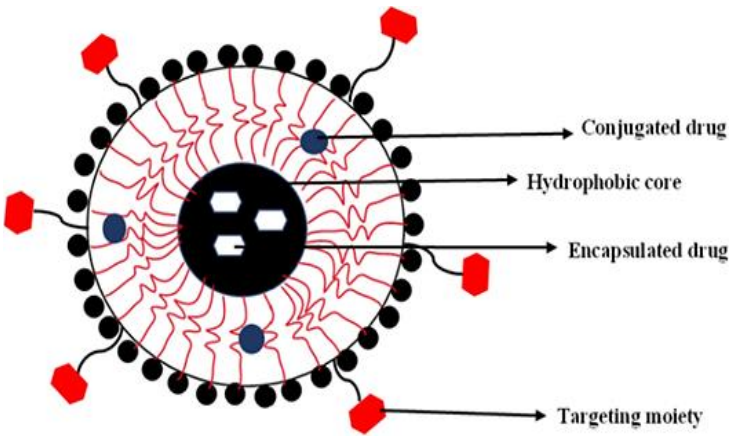

Fig. 1. Schematics of polymeric nanoparticles [6].

2.1 | Structural Classification

Structurally, PNPs are broadly categorized into nanospheres and nanocapsules:

I. Nanospheres: solid matrix systems in which therapeutic agents are uniformly dispersed. Nanospheres provide sustained drug release, mechanical stability, and protection for both hydrophilic and hydrophobic drugs [3], [4].

II. Nanocapsules: core–shell structures comprising a liquid or oily core surrounded by a polymeric shell. Nanocapsules offer enhanced encapsulation efficiency, protection of labile drugs, and controlled release through polymer degradation or diffusion [5], [10].

2.2|Classification Based on Polymer Type

PNPs can be fabricated from natural or synthetic polymers:

I. Natural polymers: examples include chitosan, alginate, gelatin, and dextran. These polymers are generally biocompatible, biodegradable, and minimally toxic. However, they may exhibit batch-to-batch variability and lower mechanical stability [6], [7].

II. Synthetic polymers: examples include Polylactic Acid (PLA), Poly(Lactic-co-Glycolic Acid) (PLGA), Polyethylene Glycol (PEG), and Polycaprolactone (PCL). Synthetic polymers allow tunable degradation rates, reproducible manufacturing, and surface modifications (e.g., PEGylation) to prolong circulation time. PLA and PLGA degrade into non-toxic metabolites, making them ideal for biomedical applications [4], [8].

2.3|Biodegradability

Biodegradable polymers, such as PLA and PLGA, degrade into safe monomers and are suitable for transient drug delivery [5], [6].

Non-biodegradable polymers: these materials persist in the body for extended periods and may accumulate, but they are helpful for long-term drug release or imaging applications (*Table 1*) [7].

Table 1. Classification of polymeric nanoparticles.

Type of Nanoparticle	Structure	Common Polymers	Applications	References
Nanocapsules	Core–shell	PLGA, PCL, PEG	Targeted drug delivery, protection of sensitive drugs	[1], [3], [10]
Nanospheres	Solid matrix	PLA, PCL, PEG	Controlled drug release, high mechanical stability	[1], [3]
Dendrimers	Branched structure	PAMAM, PPI	Gene delivery, targeted drug delivery	[3], [10]
Micelles	Amphiphilic structure	PEG–PLA	Solubilization of hydrophobic drugs, controlled drug delivery	[2], [3]
Polymersomes	Vesicular structure	PEG–PBD	Drug and protein transport, crossing biological barriers	[1], [2]

3|Properties of Polymeric Nanoparticles: Critical Factors Affecting Drug Delivery Performance

The physicochemical characteristics of PNPs, including particle size, surface charge, morphology, surface modification, and drug loading/release behavior, play a pivotal role in determining their biological interactions, biodistribution, and therapeutic efficacy [1], [11]. Optimizing these parameters enables the development of stable, biocompatible, and targeted nanocarriers with improved drug delivery performance [3], [4].

3.1|Particle Size

Particle size is a critical determinant of biodistribution, clearance, and tumor accumulation. PNPs in the 10–200 nm range can efficiently exploit the EPR effect for passive tumor targeting [7], [9]. Particles smaller than

10 nm are rapidly excreted via renal filtration, whereas those larger than 200 nm are cleared by the Mononuclear Phagocyte System (MPS) [12]. Techniques such as nanoprecipitation or solvent evaporation allow precise control over nanoparticle size [3], [13].

3.2 | Surface Charge

The zeta potential influences nanoparticle colloidal stability, circulation time, and cellular uptake [11], [14]. Positively charged nanoparticles exhibit enhanced interaction with cell membranes but may induce higher cytotoxicity. In contrast, neutral or slightly negatively charged PNPs exhibit greater stability and reduced immune clearance, thereby supporting prolonged circulation and improved tumor targeting [8], [12].

3.3 | Morphology

Nanoparticle shape affects tissue penetration, cellular internalization, and biodistribution [9]. Spherical PNPs are commonly used due to their uniformity and predictable drug release, whereas non-spherical shapes, such as rods or ellipsoids, have shown enhanced uptake in certain tumor models [13], [15]. Morphology can be fine-tuned through polymer composition and fabrication methods [7].

3.4 | Surface Modification

Surface functionalization enhances the specificity, stability, and circulation time of PNPs [11], [16]. PEGylation reduces immune recognition and prolongs systemic circulation [12], [13]. Additionally, conjugation of targeting ligands, including antibodies, folate, or peptides, enables active targeting to pathological sites, thereby improving therapeutic selectivity [8], [17]. These strategies facilitate the design of multifunctional nanoparticles for both therapy and imaging applications.

3.5 | Drug Loading and Release

The efficiency of drug encapsulation and release is influenced by polymer–drug compatibility, nanoparticle architecture, and surface chemistry [7], [10]. Hydrophobic drugs are typically entrapped in the nanoparticle core, whereas hydrophilic drugs are distributed throughout the polymer matrix [5], [9]. Moreover, stimuli-responsive polymers ,such as pH- or enzyme-sensitive PLA or PEG systems, enable controlled drug release in response to pathological microenvironments, thereby enhancing therapeutic precision [14], [18].

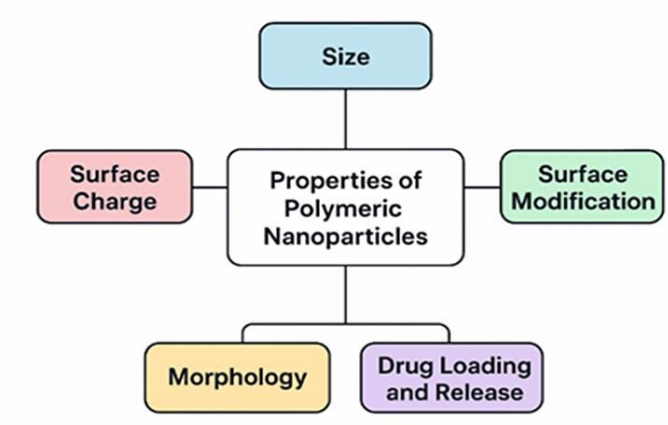

Fig. 2. Properties of polymeric nanoparticles and key factors affecting drug delivery.

4 | Methods of Preparation of Polymeric Nanoparticles

The fabrication method of PNPs is a critical determinant of their size, morphology, drug-loading capacity, and release behavior. Selection of an appropriate technique depends on the polymer type, drug solubility, and desired delivery profile [1], [5]. Commonly employed preparation methods are summarized below.

4.1 | Emulsion Polymerization

In emulsion polymerization, monomers are polymerized within an oil-in-water or water-in-oil emulsion stabilized by surfactants [3], [8]. This approach allows precise control over particle size and uniformity, making it suitable for hydrophobic drugs incorporated in the oil phase. While scalable, residual surfactants may remain, raising potential toxicity concerns and limiting their use for hydrophilic compounds [7], [10], [11].

4.2 | Solvent Evaporation

In this widely used method, the polymer and drug are dissolved in a volatile organic solvent and emulsified in an aqueous stabilizer solution. As the solvent evaporates, drug-loaded nanoparticles are formed [4], [6]. This technique accommodates both hydrophilic and hydrophobic drugs and provides high encapsulation efficiency. However, residual solvents and limited control over particle size remain challenges [5], [8].

4.3 | Nanoprecipitation

Nanoprecipitation is a simple, low-energy technique ideal for biodegradable polymers such as PLA, PLGA, and PCL [6], [13]. A polymer–drug solution in an organic solvent is added to a miscible non-solvent (typically water), causing instantaneous nanoparticle formation by precipitation [1], [2], [9]. It produces particles with narrow size distributions (50–300 nm), although achieving high drug-loading capacity may be limited [7].

4.4 | Self-Assembly

Amphiphilic block copolymers can spontaneously self-assemble into nanoparticles or micelles in aqueous media. The resulting structure has hydrophobic cores that entrap poorly soluble drugs and hydrophilic shells that enhance colloidal stability [12], [14]. This method yields small, uniform, and biocompatible nanoparticles but requires careful polymer design and may pose challenges for long-term stability and scalability [15].

4.5 | Supercritical Fluid Technology

This environmentally friendly technique employs supercritical carbon dioxide as a green solvent to form nanoparticles without leaving organic residues. Upon depressurization, nanoparticles precipitate from the polymer–drug mixture [13], [16]. This approach enables clean processing and precise size control, though high operational costs and limited polymer compatibility restrict its widespread application (*Fig. 3*) [7], [17].

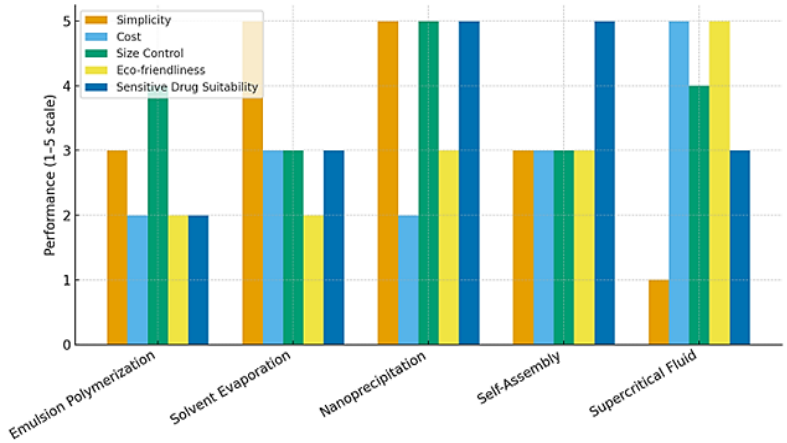

Fig. 3. Comparison of preparation methods in nanoparticles.

5 | Targeted Drug Delivery Using Polymeric Nanoparticles

Targeted drug delivery aims to direct therapeutic agents specifically to diseased tissues while minimizing systemic toxicity. PNPs are ideal carriers due to their tunable size, surface chemistry, and drug-encapsulation capacity, enabling enhanced bioavailability and precise site-specific delivery [8], [18]. Targeting is generally achieved through passive or active mechanisms [11], [19].

5.1 | Passive Targeting

Passive targeting exploits the EPR effect, where nanoparticles (10–200 nm) preferentially accumulate in tumors or inflamed tissues due to leaky vasculature and impaired lymphatic drainage [7], [9]. Surface modification with PEGylation prolongs circulation and reduces rapid MPS clearance [4], [12]. EPR effectiveness, however, varies among tumor types, and limited vascularization may restrict drug accumulation [18].

5.2 | Active Targeting

Active targeting involves conjugating ligands such as antibodies, peptides, or small molecules to nanoparticle surfaces to recognize overexpressed receptors on target cells [8] specifically, [17]. Examples include:

I. Antibodies binding to tumor antigens (e.g., HER2 in breast cancer) [9].

II. RGD peptides targeting integrins on tumor vasculature [1].

III. Folic acid binds to folate receptors, which are frequently overexpressed in cancers [7].

This approach enhances receptor-mediated uptake and minimizes systemic exposure, though it requires optimized ligand synthesis, stability, and receptor specificity [6], [16].

5.3 | Benefits and Challenges

Combining passive and active targeting mechanisms improves overall efficiency: nanoparticles first accumulate at diseased sites via EPR and then undergo ligand-mediated internalization [14], [18]. Achieving immune evasion and maintaining ligand stability remain significant challenges. PEGylation prolongs circulation but may induce mild immunogenicity if not adequately controlled [4], [12].

5.4 | Combined Targeting Strategies

Integrating EPR-based passive accumulation with ligand-mediated active targeting yields synergistic effects in cancer therapy. Such hybrid systems enhance tumor localization, receptor-specific uptake, and controlled intracellular release, improving therapeutic response and reducing resistance. These strategies underscore the importance of rational nanoparticle design for precise and effective cancer therapy [17], [19].

6 | Biomedical Applications of Polymeric Nanoparticles

PNPs are versatile carriers in biomedical research due to their ability to encapsulate diverse therapeutic agents and control drug release. Their tunable physicochemical properties make them ideal for applications in cancer therapy, genetic and inflammatory diseases, and vaccine delivery (*Fig. 4*) [1], [5–7].

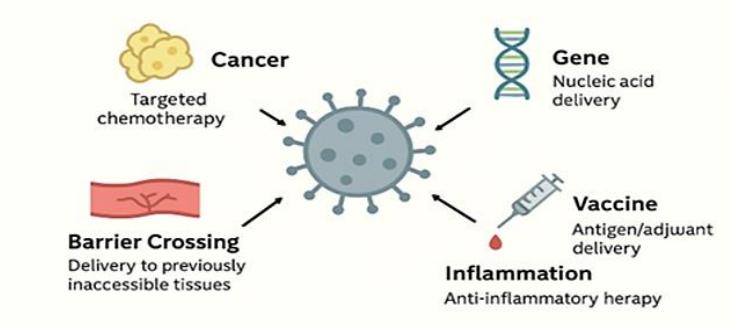

Fig. 4. Biomedical applications of polymeric nanoparticles.

6.1 | Cancer Therapy

Cancer treatment is the most extensively studied application of PNPs. Conventional chemotherapy often causes systemic toxicity due to poor drug selectivity, whereas PNPs improve tumor localization via passive (EPR effect) and active (ligand-mediated) targeting [8], [9]. Drugs such as doxorubicin and paclitaxel can thus be delivered directly to tumors, enhancing therapeutic efficacy while minimizing side effects [12]. In addition, PNPs support gene and immunotherapy by delivering siRNA, mRNA, or immune modulators, helping to overcome Multidrug Resistance (MDR) [7], [13].

6.2 | Gene Delivery

PNPs act as efficient non-viral vectors for gene transfer, protecting nucleic acids (DNA, RNA, siRNA) and facilitating cellular uptake [14], [15]. Cationic polymers such as Polyethyleneimine (PEI) can form complexes with nucleic acids, while copolymers like PLGA-PEG reduce toxicity and enhance transfection efficiency [5]. Their ability to cross biological barriers, such as the Blood–Brain Barrier (BBB), offers significant potential for genetic and neurological therapies [17], [18].

6.3 | Inflammatory Diseases

For chronic inflammatory conditions, including rheumatoid arthritis and inflammatory bowel disease, PNPs enable localized and sustained release of anti-inflammatory drugs, reducing systemic exposure [4], [7]. Surface ligand modifications enhance drug accumulation at inflamed tissues, while controlled release prolongs therapeutic duration [15], [19].

6.4 | Vaccine Delivery

PNPs serve as both antigen carriers and adjuvants, stabilizing antigens and enhancing immune responses [16], [17]. They facilitate antigen delivery to Antigen-Presenting Cells (APCs), promoting robust humoral and cellular immunity. Ligand modifications (e.g., mannose or lectins) enable targeted interaction with immune cells, reducing the required vaccine dose [6], [18]

6.5 | Crossing Biological Barriers

A key advantage of PNPs is their ability to traverse physiological barriers, such as the BBB and ocular membranes. Ligand-functionalized nanoparticles (e.g., transferrin- or insulin-conjugated) can cross the BBB via receptor-mediated transcytosis [13], [17], [18]. Similarly, in ocular diseases like glaucoma or Age-Related Macular Degeneration (AMD), PNPs improve local bioavailability and prolong therapeutic effects [7], [19].

7 | Challenges and Limitations of Polymeric Nanoparticles

Despite their broad biomedical potential, PNPs face several critical barriers to clinical translation. Significant limitations include potential toxicity, large-scale reproducibility, formulation stability, immune recognition, and complex regulatory pathways [15], [19].

7.1 | Toxicity and Biocompatibility

Although widely used polymers such as PLGA, PEG, and chitosan are considered biocompatible, residual monomers or degradation products can induce inflammation or organ-specific toxicity [4], [11]. Cationic polymers like PEI are particularly cytotoxic, prompting the development of modified and biodegradable variants with improved safety profiles [13], [15]. Additionally, nanoparticle accumulation in the liver and spleen necessitates comprehensive in vivo safety evaluations [7], [17].

7.2 | Scale-Up and Manufacturing

Achieving large-scale, reproducible production of PNPs with uniform size, composition, and drug loading remains a technical challenge [5], [18]. Conventional fabrication methods, such as emulsion polymerization or solvent evaporation, often lack the industrial-level control required. Recently, microfluidic and continuous-flow techniques have emerged as scalable, reproducible, and environmentally friendly alternatives [16], [20].

7.3 | Stability

The physicochemical stability of PNPs directly affects drug release and therapeutic efficacy. Instabilities such as particle aggregation or premature degradation can reduce drug effectiveness [6], [7]. Surface modification, particularly PEGylation, improves colloidal stability, minimizes premature drug leakage, and prolongs circulation time [12], [13], [17].

7.4 | Regulatory and Immune Barriers

Standardized regulatory frameworks for nanomedicines are still evolving, complicating approval processes due to the diversity of formulations [15], [19]. Rapid MPS clearance can also reduce therapeutic impact. Incorporating stealth coatings and targeting ligands has been shown to improve biodistribution and reduce immune recognition [4], [14].

8 | Future Perspectives of Polymeric Nanoparticles

PNPs continue to play a central role in nanomedicine due to their versatility in targeted therapy, gene delivery, and diagnostics [7], [17]. Future developments aim to improve precision, safety, and scalability through smart designs, green synthesis, and updated regulatory frameworks [18], [19].

8.1 | Stimuli-Responsive Polymers

Next-generation PNPs are being designed to respond to environmental stimuli, such as pH, temperature, or enzymes, enabling controlled, site-specific drug release [8], [14]. For example, pH-sensitive carriers release drugs preferentially in acidic tumor microenvironments, while enzyme-triggered systems activate in disease-specific sites. These "Smart" nanocarriers hold great potential for personalized therapies [5], [19–21].

8.2 | Personalized Medicine

Integration of PNPs into personalized medicine allows patient-specific targeting based on genetic or molecular profiles. Functionalization with ligands for biomarkers such as HER2 or EGFR facilitates precise drug delivery with minimal side effects [9], [18]. Additionally, theranostic nanoparticles combining diagnostic and therapeutic capabilities enable real-time monitoring and adaptive treatment strategies [16].

8.3 | Multifunctional Nanoparticles

Emerging PNPs are being developed as theranostic systems that integrate imaging and therapy [7], [13]. They can co-deliver anticancer drugs with MRI or PET contrast agents for visualization, or incorporate CRISPR/Cas9 and RNAi tools for combined gene and drug therapy [17], [18].

8.4 | Green and Scalable Synthesis

Future fabrication emphasizes eco-friendly and scalable methods. Water-based, microfluidic, and biodegradable polymer systems (e.g., chitosan, alginate, cellulose) reduce toxicity and improve reproducibility [5], [22–27]. Such sustainable approaches enhance industrial feasibility while minimizing environmental impact [15].

8.5 | Regulatory Developments

Advancing PNP technologies requires updated regulatory frameworks. Agencies such as the FDA and EMA are developing standardized protocols for characterization, toxicity testing, and clinical validation [14], [19]. Harmonized international guidelines will be essential for safe and efficient clinical translation [18], [28].

9 | Conclusion

PNPs have emerged as a versatile and efficient platform for targeted and controlled drug delivery, offering significant advantages over conventional systems. Their nanoscale size, tunable surface properties, and biocompatibility enhance drug stability, solubility, and bioavailability while minimizing systemic toxicity. By enabling both passive and active targeting, PNPs are particularly effective in treating complex diseases such as cancer, infections, and inflammatory disorders.

Beyond conventional drug delivery, PNPs show promise in gene therapy and theranostics, where they can carry genetic materials or combine therapeutic and diagnostic functions in a single system. These capabilities highlight the broad potential of polymeric nanocarriers across diverse biomedical applications.

However, several challenges hinder their clinical translation. Toxicity, biodegradability, large-scale synthesis, and regulatory approval remain significant obstacles. Variations in formulation can affect both performance and safety, emphasizing the need for standardized manufacturing methods and rigorous quality control. Techniques such as microfluidic synthesis are being explored to enable consistent, scalable production, while global regulatory harmonization is essential to advancing PNP-based therapeutics toward clinical use. Looking forward, the future of PNPs lies in the development of stimuli-responsive, multifunctional, and patient-specific systems. These innovations will enable precise drug release, integration of diagnostic imaging, and alignment with personalized medicine approaches. Moreover, adopting green and sustainable synthesis methods will reduce environmental impact and enhance scalability.

In summary, PNPs represent a cornerstone of modern nanomedicine, with the potential to revolutionize disease treatment through safer, more targeted, and efficient therapeutic delivery. Continued research into their design, safety, and clinical translation will pave the way for personalized and sustainable healthcare solutions in the future.

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