RESEARCH PAPER

Bio-Based Nanomaterials for Drug Delivery: Recent Advances, Applications and Translational Challenges

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Abstract

Bio-based nanomaterials have emerged as a transformative platform for drug delivery, offering biocompatibility, biodegradability and lower toxicity than many conventional synthetic nanocarriers. This review summarizes recent progress in the synthesis, functionalization and application of bio-based nanocarriers, including protein-based nanoparticles, biodegradable polymers, polysaccharide-based nanomaterials, dendrimers, lipid-based nanostructures and green-synthesized metallic nanoparticles. Advances in surface modification and stimuli-responsive design have improved site-specific drug release, while combination therapies delivered through bio-based nanocarriers help to overcome multidrug resistance. Pulmonary delivery and personalized medicine illustrate how these systems can achieve localized delivery and tailor treatment to individual patient profiles. Despite this progress, large-scale manufacturing, long-term stability, safety assessment and regulatory approval remain major barriers to clinical translation. Continued advances in green synthesis, multifunctional design and nanocarrier optimization are expected to address these barriers and support precision medicine. By highlighting the eco-friendly, biocompatible and biodegradable character of bio-based nanomaterials, this review underscores their potential to meet the growing demand for safer and more sustainable drug delivery platforms.

Keywords: Bio-based nanomaterials; Drug delivery systems; Biopolymers; Dendrimers; Lipid nanoparticles; Green synthesis; Targeted delivery; Biocompatibility.

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1. Introduction

Oral and parenteral administration remain the mainstays of conventional drug delivery. Oral dosing (tablets, capsules and solutions) is convenient and favors patient adherence, but it is limited by degradation in the gastrointestinal tract, hepatic first-pass metabolism and gastrointestinal irritation, all of which reduce the amount of active drug that reaches the systemic circulation [1 –3]. Oral formulations may also suffer from low drug-loading capacity and stability problems. Parenteral routes bypass the gastrointestinal tract and act rapidly, but they are invasive, painful and prone to infection, and they usually require trained personnel [4].

Conventional dosage forms also offer limited control over drug release. The resulting fluctuations in plasma concentration can reduce efficacy and increase the risk of side effects [5]. Their non-specific biodistribution exposes healthy tissues to the drug and can lead to systemic toxicity. Further obstacles include poor drug solubility and permeability, instability under changing environmental conditions, and the difficulty of directing drugs to specific tissues or cells, particularly across biological barriers such as the blood–brain barrier [6]. These limitations have driven the development of novel delivery systems that improve bioavailability, target specificity, controlled release and patient compliance [2].

Nanomaterial-based drug delivery systems (NDDS) are among the most promising of these approaches. They use nanoparticles, engineered materials typically 1–100 nm in size, to improve the transport and efficacy of therapeutic agents [7]. Their large surface-area-to-volume ratio and tunable geometric and chemical properties enable higher drug loading, better stability and controlled release (Figure 1) [8]. NDDS can improve bioavailability by protecting drugs from degradation and facilitating their uptake across cellular membranes [9]. Nanoparticles can also be functionalized with antibodies or ligands that bind to receptors on diseased cells. This targeting concentrates the drug at the site of action and spares healthy tissue, thereby reducing adverse effects while enhancing efficacy [10,11]. In addition, NDDS prolong circulation time and permit sustained, controlled release, overcoming key drawbacks of conventional systems [1]. By addressing non-specific distribution, rapid elimination and poor solubility, nanomaterial-based systems offer improved safety and therapeutic outcomes across a range of diseases [12,13].

Bio-based nanomaterials are nanoscale materials derived from living organisms, such as lipids, proteins (e.g., albumin and silk fibroin), polysaccharides (e.g., cellulose and chitosan) and other biomolecules [14,15]. Because their structure resembles that of biological components, they are

generally biocompatible and biodegradable, which lowers the risk of toxicity and adverse immune responses [14]. They can be tuned to control release kinetics, improve drug stability and enable targeted delivery to specific tissues or cells, thereby increasing efficacy and reducing systemic side effects [8]. Their biodegradability also ensures breakdown into non-toxic by-products, limiting long-termaccumulation andtoxicity [16]. Together, these features make bio-based nanomaterials a safer and more effective platformfor drugadministration, improving patient outcomes through precise targeting and release [17–19]. This review provides an overview of bio-based nanomaterials for drug delivery, with emphasis on their biocompatibility, biodegradability and capacity for site-specific delivery.

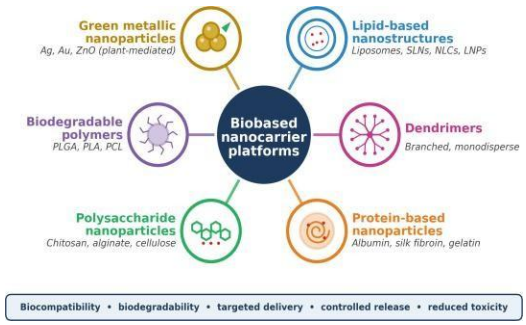

Figure 1. Major classes of bio-based nanocarriers for drug delivery: lipid-based nanostructures, dendrimers, protein-based nanoparticles, polysaccharide nanoparticles, biodegradable polymers and green-synthesized metallic nanoparticles.

2. Types of Bio-Based Nanomaterials

Bio-based nanomaterials are attractive for drug delivery because they are biocompatible, biodegradable and derived from natural sources, which minimizes toxicity andenvironmental impact [8]. The main classes (proteins, biodegradable polymers, polysaccharides, dendrimers, lipid-based structures and green-synthesized metallic nanoparticles) havebeen studied extensively andare nowappliedto controlled andtargeted drugdelivery [15,20]. These classes are summarized in Figure 1, and Table 1 compares the principal methods used to prepare biodegradable nanoparticles.

Table 1. Synthesis approaches for biodegradable nanoparticles: principles, advantages, disadvantages and applications.

Synthesis approach	Principle	Advantages	Disadvantages	Applications
Emulsification	Mixing of two immiscible phases with a stabilizer	Simple and scalable	High energy input	Drug delivery, cosmetics, food industry
Nanoprecipitation	Rapid mixing of organic and aqueous phases	High encapsulation efficiency	Use of organic solvents	Gene therapy, drug delivery, tissue engineering
Solvent evaporation	Dissolution of polymer and drug in a solvent, followed by solvent removal	Controllable particle size	Residual solvent traces	Imaging, encapsulation, agriculture
Self-assembly	Spontaneous organization of molecules into ordered structures	Use of biocompatible materials	Limited control over morphology	Tissue engineering, drug delivery, diagnostics

Synthesis approach	Principle	Advantages	Disadvantages	Applications
Electrospray	Application of high voltage to a polymer solution to generate fine droplets	Narrow size distribution	Requires specialized equipment	Controlled release, drug delivery, inhalation therapy

2.1 Protein-based nanomaterials

Protein-based nanoparticles are generally prepared by chemical, physical or self-assembly approaches [21]. Chemical methods, such as emulsification and complex coacervation, offer control over particle size and shape and achieve high encapsulation efficiency [22], but they may yield relatively large particles and require surfactants and stabilizers. Physical methods include nano spray drying and electrospray. Nano spraydryingis cost-effective and producesstablenanoparticlesundermild conditions, but it is suitable only for small-scale production and is less appropriate for hydrophobic drugs, whereas electrospray can degrade macromolecules because of operational stresses [23]. In self-assembly approaches such as desolvation, proteins that tolerate the process conditions spontaneously form nanoparticles in response to changes in solvent composition, and the resulting particles are then stabilized.

Protein nanoparticles are biocompatible and biodegradable. They protect encapsulated drugs from enzymatic degradation and premature renal clearance, therebyprolongingdrughalf-life, activity and stability [24]. Their size, surface properties and shape can be tuned through the synthesisparameters to achievecontrolledandsustained release, and they show high stability and drug-loading capacity [21]. Surface modification enables targeted delivery, which improves efficacy and reduces unwanted side effects. Protein-based nanoparticles have been used successfully to deliver nucleic acids, proteins, peptides and anticancer drugs [25], and they have been applied in vaccines, targetedtherapyfor cancer and lung diseases, and cellular uptake via endocytosis. By improving bioavailability and targetingwhilereducingtoxicity, they provide a safe and adaptable platform that overcomes many shortcomings of conventional approaches [26].

2.2 Biodegradable polymers

Biodegradable polymers can be tailored through a variety of synthesis routes to achieve controlled, targeted and long-lasting drug delivery [27]. Common fabrication techniques, including single and double emulsion methods, polymerization, solvent evaporation and nanoprecipitation, yield nanoparticles, microparticles, hydrogels and implantable devices customized to individual therapeutic needs [28]. Both synthetic polymers (polylacticacid[PLA] and polyglycolicacid[PGA]) and natural polymers (chitosan, alginate and collagen) are used. They degrade into harmless by-products such as carbon dioxide and water, which makes surgical removal unnecessary [29]. The degradation rate, and therefore the release profile, can be tuned by altering the chemical composition, crystallinity and hydrophilicity of the polymer [30] (Table 2).

Table 2. Biodegradable polymers used for nanoparticle applications.

Polymer	Biocompatibility	Tunable properties	Degradation kinetics
PLGA (poly(lactic-co-glycolic acid))	Well established; generally non-toxic	Lactide-to-glycolide ratio controls degradation rate, hydrophobicity and mechanical strength	Faster degradation with higher glycolic acid content
PLA (polylactic acid)	Good	Molecular weight, crystallinity and processing method influence mechanical properties, drug release and degradation rate	Slower degradation than PLGA

Polymer	Biocompatibility	Tunable properties	Degradation kinetics
PCL (polycaprolactone)	Excellent; low inflammatory response	Crystallinity and molecular weight affect hydrophobicity, mechanical properties and degradation rate	Slowest degradation among these polymers
Chitosan (natural polysaccharide)	Biocompatible, biodegradable, mucoadhesive	Molecular weight, degree of deacetylation and processing method influence encapsulation efficiency, drug release and gelation	Depends on factors such as pH and enzymatic activity

Biodegradable polymers are biocompatible, mechanically robust and able to prevent the premature degradationof encapsulated drugs, which improves stability and bioavailability [31]. Extended release and targeted administration reduce systemic adverse effects and lower dosing frequency, which improves patient adherence [32]. Their surfaces can also be modifiedto enhance mucoadhesion or tissue targeting. Applications include ocular delivery (overcoming anatomical barriers and providing sustained release for conditions such as glaucoma and retinal disorders), colon-specific delivery, cancer therapy and vaccine delivery [33]. This versatility, demonstrated in implantable devices, microspheres, hydrogels and nanoparticles, makes biodegradable polymers an essential component of safe and effective drug delivery systems [34].

2.3 Polysaccharide-based nanomaterials

Polysaccharide-basednanomaterials areabundant in nature, biodegradable and biocompatible, which makes them well suited to drug delivery [35]. Emulsification, nanoprecipitation, complex coacervation and advanced techniques such as microfluidics allow fine control over particle size, shape and drug-loading capacity. These methods exploit the chemical reactivity of polysaccharides, particularly their free carboxyl andhydroxylgroups, to form stable nanoparticles that can encapsulate a range of drugs [36]. Polysaccharide nanoparticles combine low toxicity under physiological conditions, good targeting ability, rapid but regulated release and high drug-loading efficiency. Their surfaces can be chemically modified to improve stability, targeting specificity and interaction with biological systems [37].

Potential applications include anticancer therapy and targeted delivery to the intestine and oral cavity [38]. Functionalized polysaccharide nanoparticles have delivered poorly water-soluble drugs successfully, and polysaccharide–gold nanocomplexes have been designed for regulated drug release. Overall, polysaccharide-based nanoparticles provide a durable and adaptable platform that improves bioavailability, reduces side effects and enables precise delivery to target tissues [39].

2.4 Dendrimers

Dendrimers are radially symmetrical, highly branched and monodisperse nanoscale polymers. They are synthesized by two basic approaches, the divergent and convergent methods [40]. In the divergent method, established by Tomalia in the 1980s, synthesis starts from a multifunctional core and expands outward through the successive addition of monomer units, yielding generations of increasing size and surface functionality. This approach allows rapid growth and large payload capacity, which suits imaging and drug delivery applications, but it requiresan excess of monomer to limit by-products and may introduce structural defects through side reactions [41,42]. The convergent method, introduced by Hawker and Fréchet in 1990, first builds dendritic branches (dendrons) and then attaches themto a core. It offers better structural control, fewer impurities and accurate surface functionalization; however, it is less suited to large-scale production, is more labor-intensive and limits dendrimer sizebecause of steric hindrance.

Dendrimers have a highly ordered structure, a high degree of branching, tunable surface chemistry, drug-encapsulating internal cavities and excellent water solubility [43]. These properties enable improved bioavailability, controlled and targeted release, enhanced cellular penetration and high drug loading through covalent or non-covalent interactions [40]. In drugdelivery, dendrimers serve as carriers for anticancer drugs, imaging agents and gene vectors, supporting targeted distribution and reducing systemic toxicity. Because drugs can be either encapsulated or conjugated, release can be made stimulus-responsive and the drug half-life extended[44]. Despite drawbacks, notably potential toxicityandcomplex production, dendrimersremain a versatile platform for safe and effective drug delivery [45].

2.5 Lipid-based nanostructures

Lipid-based nanostructures, including solid lipid nanoparticles (SLNs) and nanostructured lipid

carriers (NLCs), enable efficient drugencapsulation and controlled release [46]. The most common preparation methods are microemulsion, ultrasonic homogenization, thin-film hydration, nanoprecipitation and high-pressure homogenization (HPH) [12]. HPH is a top-down technique in which an emulsion of molten lipid and surfactant is forced through narrow gaps at high pressure. It produces particles of controlled size and good stability on a large scale. The microemulsion method disperses a warmlipid phase into an aqueous surfactant solution, followed by rapid cooling; it is laborious and requires high surfactant concentrations and dilution steps [47]. Ultrasonic homogenization breaksdown lipid particlesthrough cavitation, but it may degrade lipids and give low encapsulation efficiency [48]. In thin-film hydration, lipids dissolved in organic solvents are dried into a thin film that self-assembles into nanoparticles on hydration (a bottom-up process); size control and batch-to-batch variability are common problems with this approach [49,50]. Nanoprecipitation is a solvent-based self-assembly technique in which an organic phase containing lipids is mixed with an aqueous phase, triggering nanoparticle formation through rapid solvent diffusion [51]. Related solvent-injection and microfluidic mixing approaches offer excellent size control and high encapsulation efficiency and are preferred for advanced formulations such as mRNA vaccines.

Lipid-based nanostructures can encapsulate both hydrophilic and hydrophobic molecules, are biodegradable andbiocompatible, have a high drug-loadingcapacity and protect labile drugs [52]. Their amphiphilic character allows selective drug release, higher bioavailability and lower systemic toxicity [48]. By crossing biological barriers and enhancing cellular uptake, they are used in cancertherapy, gene therapy, vaccine delivery and the treatment of neurological disorders [53]. With scalable manufacturing methods and favorable physicochemical and biological properties, they provide a versatile platform for modern drug delivery [54].

2.6 Green-synthesized metallic nanoparticles

Metallic nanoparticles (MNPs) can be produced by sustainable, low-cost and environmentally friendly approaches that use natural sources, including plants, bacteria, fungi and algae, as reducing and stabilizing agents [55]. Conventional physical and chemical routes often involve hazardous chemicals and high energy consumption. Green synthesis instead uses natural biomolecules, such as plant phytochemicals, to reduce metal ions to their zero-valent nanoparticleformunder mildconditions [56]. Extracts fromleaves, bark, fruits and roots typically containpolyphenols, flavonoidsand proteinsthatact as both reducing and capping agents, allowing control over particle size and shape [57]. Mixing the extract witha metal salt solution leads to nucleation, growth and stabilization phases and yields stable nanoparticles with tunable physicochemical properties [58]. Particle formation and morphology are confirmedby characterizationtechniquessuchas X-ray diffraction (XRD), transmission electron microscopy (TEM) and UV-Vis spectroscopy [59]. Compared with their chemically synthesized counterparts, green MNPs show better biocompatibility, stronger antibacterial and anticancer activity and fewer adverse effects [60]. Their distinctive optical, electrical and surface properties make them effective drug carriers that support targeted therapy, controlled release and improved bioavailability [57]. Green MNPs hold significant promise in nanomedicine, including cancer therapy, antimicrobial treatment and diagnostic imaging, while addressing sustainability concerns in nanotechnology [61].

3. Current Trends in Bio-Based Nanomaterials for Drug Delivery

To overcome the limitations of conventional drug delivery, recent work on bio-based nanomaterials has focused on combining sustainability, biocompatibility and improved targeting [62]. Current efforts aim to build multifunctional nanocarriers from biomolecules and natural polymers that offer higher bioavailability, regulated release and lower systemic toxicity [63]. Surface modification and ligand attachment are being applied to proteins, polysaccharides and biodegradable polymers to improve targeted delivery and cellular uptake [57]. Lipid nanoparticles (LNPs), most notably in mRNA COVID-19 vaccines, show how bio-based carriers can protect biologics and deliver them to cells, driving the growth of RNA-based therapies and vaccines [64]. Metallic nanoparticles produced with plant extracts and microbial processes are also attracting interest for smart, localized therapy, particularly in oncology andchronicdisease [65,66]. Advances in nanobiotechnology, materials engineering and micro-robotics, built on biocompatiblebio-basedplatforms, are openingnew possibilities for individualized and highly regulated drug administration [67]. Improvements in scalable and reproducible synthesis are moving bio-based nanomaterials fromthe laboratory toward the clinic, and the field is trending toward patient-centric, ecologically sustainable delivery systems that pair state-of-the-art nanotechnology with the inherent advantages of bio-based materials [68]. These systems also offer improved safety profiles and environmentally friendly manufacturing [1]. One example is a nanocarrier that senses changes in environmental factors such as pH and temperature and releases its drug accordingly.

3.1 Targeted and stimuli-responsive delivery

Bio-based nanomaterials are widely used for targeted delivery, typically by attaching targeting ligands such as antibodies, peptides and aptamers to the nanoparticle surface to enable tumor recognition

[69,70]. These ligands bind preferentially to receptors that are overexpressed on cancer cells, improvingcellular uptakeandminimizingoff-target effects. In addition, stimuli-responsive nanoparticles are engineered to release their cargo in response to triggers characteristic of diseased tissue, such as acidic pH, elevatedenzymelevels, redox stateor the temperature changes typical of tumor microenvironments [62]. For example, pH-responsive nanoparticles exploit the slightly acidic tumor milieu to initiate drugrelease, whereas redox-responsive systems exploit the high intracellular glutathione concentration in cancer cells to cleave disulfide bonds and release drugs intracellularly. Multi-stimuli-responsive systems that combine pH, redox and enzyme triggers allow precise, on-demand release, which improves therapeutic efficacy and reduces systemic toxicity [65,71].

Examples of targeted bio-based systems include ligand-functionalized polysaccharide nanoparticles for cancer therapy, protein-based nanocarriers designed for receptor-mediated uptake, and liposomes modified with targeting moieties for infectious and cardiovascular diseases [72,73]. Stimuli-sensitive bio-based nanocarriers have provedeffective forregulateddrugreleasein cancer, infections and cardiovascular disorders, leading to better treatment outcomes [74]. For instance, keratin nanoparticles that respond to three stimuli (pH, glutathione and enzymes) have been designed to deliver anticancer drugs and showed superior targeting and release profiles [71]. Combining surface-ligand modification with stimuli-responsive mechanisms therefore offers an effective, safe and precise strategy for targeted drug delivery across a wide range of disorders [75].

3.2 Combination therapy

Combination therapy based on nanodrug delivery systems has emerged as a key strategy to combat drug resistance and increase therapeutic effectiveness, particularly in the management of complex diseases such as cancer [76,77]. Bio-based nanocarriers can co-deliver several drugs with different physicochemical properties withina single nanoparticle, maintaining optimal synergistic drug ratios and enabling simultaneous intracellular uptake by target cells [58]. This approach addresses the problems of monotherapy, including systemic toxicity, narrowtherapeuticwindows and multidrug resistance (MDR) [78,79]. When combined with immunotherapy, chemotherapy and targeted therapy, bio-based nanomaterials, including polymeric nanoparticles, liposomes, dendrimers and hybrid nanocarriers, have improved pharmacokinetics, reduced side effects and enhanced tumor targeting [80].

Several examples illustrate this potential. A polymeric nanoparticle combining paclitaxel with the P-glycoprotein modulatortariquidar andsurface-functionalized with biotin for tumor targeting overcame multidrug resistance and showed much higher cytotoxicityand tumorgrowth inhibition than single-drug formulations [49]. Chitosan nanoparticles loaded with curcumin increased cellular uptake and cytotoxicity in cervical cancer cells, whereas free curcumin had no effect. A biodegradable triblock nanocarrier with a polycaprolactone (PCL) block and a carboxyl-functionalized core co-delivered doxorubicin and cisplatin synergistically in breast cancer cells, even though the free drugs acted antagonistically [81]. In preclinical studies, micellar nanoparticles functionalized with phage proteins selectively deliveredpaclitaxel to breast cancer cells, producing marked tumor shrinkage and necrosis [77]. Amphiphilic diblock copolymers in dual-drug systems have likewise improved therapeutic effects by enabling the simultaneous delivery of doxorubicin and platinum-based drugs to cells [82]. Overall, combination therapy mediated by bio-based nanomaterials provides a promisingplatformfor the synergistic, controlled delivery of multiple drugs, with improved efficacy, reduced drugresistanceand fewer side effects in cancer and other diseases [83].

3.3 Pulmonary drug delivery

Inhalable nanodrugdelivery systems arean exciting approach for deliveringtherapeutics directly to lung tumors and couldmarkedly reducethe systemic side effects of conventional chemotherapy [84,85]. Biodegradable polymeric nanoparticles, lipid-based carriers and ligand-functionalized nanocomplexes are used to improve localized delivery. These nanomaterials must overcome physiological barriers, notably the mucus layer and mucociliary clearance, to increase drug retention and permeability in lung tissue [86]. Strategies to improve retention include designing mucoadhesive particles that cling to mucosal surfaces, using stimuli-responsive materials that release drug in response to the acidity or alkalinity of the lung microenvironment, and optimizing particle size and surface charge to maximize mucus penetration [87,88]. In metastatic lung cancer models, nanoparticles conjugated with epidermal growth factor ligands improved therapeutic efficacy and local drug concentration, and inhalable doxorubicin nanoparticles decorated with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) showed synergistic tumor targeting and apoptosis induction [85,89].

Despite these advances, obstacles remain. They include patient-specific variation in lung function that affects drug deposition, difficulty in accurately measuring drug release at tumor sites and the possibility of local toxicity at high drug concentrations [44]. Further refinement of aerosolization technology could improve dose control, reproducibility and patient compliance[90]. Future efforts aim to create multifunctional bio-based nanocarriers that target tumors precisely, release their contents in a controlled and sustained manner and modulate the immune system to

enhance antitumor immunity; nano-based vaccines administered by the pulmonary route are one example [91]. By enhancinglocalefficacy, reducing systemic toxicity and improving patient quality of life, bio-based nanomaterials have the potential to transform the treatment of lung cancer [92].

3.4 Advances in nanocarrier design and surface engineering

The development of more biocompatible nanocarriers has centered on optimizing shape, size and surface characteristics to improve targeting efficiency and prolong circulation [93]. These properties can be fine-tuned by adjusting synthesis conditions and applying surface modification strategies [94]. For example, NLCs, which combine solid and liquid lipids, show higher drug-loading capacity, better physical stability and improved biocompatibility than earlier lipid systems such as SLNs [95,96]. Their occlusive properties and small size make them suitable for drug delivery through difficult routes with minimal adverse effects [97]. Hybrid lipid–polymer nanoparticles combine the advantages of both components and improve encapsulation efficiency and stability [73,98], whereas polymer-based nanoparticles improve drug solubility and controlled release but may provoke immune responses.

Surface modification techniques such as PEGylation, ligand conjugation and charge modulation can improve nanoparticle stability, immune evasion, cellular uptake and targeting specificity [62,99,100]. PEGylation prolongs circulation time by providing a hydrophilic stealth coating, whereas ligand conjugation enables receptor-mediatedendocytosis for selective delivery [101,102]. Depending on the therapeutic setting, charge modulation can enhance interactionwith cell membranes or mucus barriers. Advances in nanocarrier design and surface engineering are enabling the creation of tailored, safe and effective drug delivery systems with wide-ranging implications for the treatment of cancer, infections, neurological diseases and other conditions [103 – 105].

3.5 Personalized medicine

Bio-based nanoparticles are vital to personalized medicine because they allow treatments to be customized to the disease characteristics of each patient [106–108]. Engineering of NDDS can improve the bioavailability and absorption of drugs, enhance the solubility of poorlywater-solubledrugs and give more precise control over the timing of drug release [109]. This level of personalization allows therapeutic agents to be administered at optimal concentrations, improving treatment outcomes while reducing adverse effects [110,111]. By modifying the composition, size and surface properties of nanoparticles, NDDS can be matched to patient-specific parameters such as genetic variants, disease stage and tissue environment, supporting more effective individualized treatment regimens [112,113]. Targeted distribution and regulated release are essential for optimizing therapeutic efficacy while avoiding systemic toxicity, which is especially important in complex disorders such as infections and cancer [72,106,114].

4. Challenges and Future Perspectives

Bio-based nanomaterials show great potential for drug delivery because of their biodegradability, biocompatibility and other favorable properties, which could enable controlled and targeted drug release [14,115]. Several obstacles nevertheless limit their widespread clinical translation. First, some nanomaterials may trigger unwanted immune responses or accumulate in organs, causing harmful effects [116–119]. Ensuring consistent biocompatibility and limiting toxicity are therefore key challenges, and a range of in vitro, in vivo and computational methods is used to evaluate nanoparticle safety (Table 3). Second, the stability of bio-based nanoparticles under physiological conditions and during storage is a concern, because degradation or aggregationcan reducethe efficiency of drug delivery [1,120,121]. Third, high targeting efficiency remains difficult to achieve because biological barriers, including the blood–brain barrier, heterogeneity of the tumor microenvironment and mucus layers, limit nanoparticle penetration and accumulation at disease sites [122–124]. Fourth, mass-producing bio-based nanomaterials in a cost-effective and reproducible manner, with precise control over size, shape and surface properties, remains challenging [125]. Finally, regulatory constraints and the need for thorough safety-assessment methods slow clinical adoption [125,126].

Table 3. Methods for assessing the toxicity and compatibility of biodegradable nanoparticles.

Method / approach	Focus	Advantages	Disadvantages
In vitro studies	Cellular and molecular effects	Controlled environment; high-throughput screening; fewer ethical concerns than in vivo studies	Limited representation of complex biological systems; possible artifacts from isolated cell cultures

Method / approach	Focus	Advantages	Disadvantages
Cell viability assays	Measurement of cell death or proliferation	Simple and reliable; informative on cytotoxicity	May not reflect in vivo effects
Reactive oxygen species (ROS) assays	Detection of oxidative stress caused by nanoparticles	Indicate potential for cellular damage	Not specific to nanoparticle exposure
Gene expression analysis	Identification of changes in gene expression after nanoparticle exposure	Provides insight into cellular response mechanisms	Requires specialized techniques and interpretation
In vivo studies	Whole-organism response to nanoparticles	More realistic toxicity assessment; allows study of biodistribution and excretion	Ethical considerations; higher cost and longer duration than in vitro studies
Histopathology	Examination of tissue structure for signs of damage	Detailed information on organ and tissue effects	Requires sacrificing animals
Blood tests	Analysis of blood cell counts and inflammatory markers	Indicate potential systemic effects	May not be specific to nanoparticle exposure
Physicochemical characterization	Analysis of nanoparticle size, shape, surface charge and degradation rate	Crucial for understanding nanoparticle behavior and interactions with biological systems	Requires specialized equipment and expertise
Computational modeling	Simulation of nanoparticle–cell interactions	Can predict potential risks and guide further testing	Depends on accurate input data; may not capture full biological complexity

Future work is focused on novel nanoparticle designs with stimuli-responsive and multifunctional properties to improve site-specific drug release and reduce adverse effects [127,128]. Surface-engineering strategies such as ligand conjugation, charge modulation and PEGylation arebeingrefined to improve targetingspecificity and circulation time [126]. Environmental and economic concerns have also spurred advances in green synthesis and scalable manufacturing. Integrating bio-based nanomaterials into personalized medicine holds promise for safer, more effective and individually tailored treatments [126,129]. Another emerging direction is theranostics, which combines drug delivery with diagnostic capability. Sustained interdisciplinary collaboration among materials scientists, biologists and clinicians will be needed to overcome the remaining limitations of bio-based nanomaterials in next-generation drug delivery systems.

5. Conclusion

Bio-based nanomaterials have transformed drug delivery relative to conventional methods by improving bioavailability, enabling targeted administration and controlled release, and reducing toxicity. Their natural origin ensures biodegradability and compatibility with living systems, and surface functionalization with ligands enhances targeting specificity and therapeutic effectiveness. By delivering drugs selectively to diseased sites, these nanomaterials reduce systemic adverse effects and improve patient outcomes. Emerging designs such as polymer–lipid hybrid nanoparticles combine the advantages of different materials to give stable, efficiently loaded,

sustained-release formulations. Bio-based nanocarriers also allow combination therapies to be integrated with personalized medicine, so that treatment canbe adaptedto each patient's profileand disease characteristics. Their adaptability positions bio-based nanomaterials as transformative tools that can improve therapeutic outcomes across a diverse range of diseases and usher in a new era of personalized therapy. Realizing their full potential will require interdisciplinary collaboration to achieve scalable manufacturing, demonstrate long-term biosafety and meet regulatory standards for clinical adoption, pavingthe way for safer and more effective therapeutic interventions.

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