RESEARCH PAPER

Lignin-Based Nanoparticles for Controlled Drug Delivery from Forestry Biomass

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ABSTRACT

The valorization of forestry biomass through the conversion of lignin into engineered nanomaterials represents a compelling intersection of renewable resource utilization and pharmaceutical innovation. Lignin, the most abundant aromatic biopolymer on Earth (Oriez, 2019), constitutes approximately 15–35% of lignocellulosic woody biomass (Jiju et al., 2025; Rodríguez, 2016) and is generated in enormous quantities as a byproduct of pulp and paper manufacturing and emerging biorefinery operations (Shrestha et al., 2024). Despite its structural complexity and heterogeneity, lignin possesses a suite of physicochemical attributes including amphiphilicity, intrinsic antioxidant capacity, ultraviolet absorption, and a rich aromatic scaffold amenable to chemical modification (Abdullah et al., 2023; Lv et al., 2023), that render it an attractive candidate for nanoparticulate drug delivery systems. This review provides a comprehensive, critical examination of the pathway from forestry feedstock to functional lignin nanocarriers. It addresses the influence of biomass source species (softwoods, hardwoods, and forestry residue streams) and lignin isolation processes (Kraft, organosolv, soda, sulfite, and enzymatic hydrolysis methods) on the molecular architecture and colloidal behavior of the resulting technical lignins. Nanoparticle fabrication strategies, including solvent shifting, antisolvent precipitation, pH-driven self-assembly, ultrasound-assisted methods, and emulsion-based techniques, are evaluated with respect to control over particle size, morphology, surface charge, and drug loading capacity. Surface functionalization approaches employing polyethylene glycol, chitosan, polysaccharides, and stimuli-responsive linkers are discussed in the context of improving circulation time, mucoadhesion, targeting capability, and controlled release. The review systematically analyzes drug loading and release behavior across multiple cargo classes: anticancer agents, anti-inflammatory compounds, antimicrobials, antioxidants, and wound-healing payloads—and examines the mechanisms governing controlled release, including diffusion, erosion, pH responsiveness, and redox-triggered disassembly. Biological performance, safety considerations, regulatory challenges, and the sustainability dimensions of forestry-derived lignin nanomedicine are critically assessed. The manuscript concludes with a translational roadmap identifying the key scientific, engineering, and regulatory milestones required to advance lignin nanoparticles from laboratory curiosities toward clinically meaningful drug delivery platforms.

Keywords: lignin nanoparticles; forestry biomass; controlled drug delivery; lignocellulosic biorefinery; nanocarrier engineering; biomass valorization; pharmaceutical nanotechnology; green nanomedicine.

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INTRODUCTION

Forests cover approximately 31% of the global land surface and represent one of the most significant repositories of renewable carbon on Earth. The lignocellulosic biomass harvested from forestry operations—comprising timber, thinning residues, bark, sawdust, wood chips, and the side streams of pulping and biorefinery processes—constitutes an immense and perpetually renewed feedstock base. Within the broader framework of the circular bioeconomy, there is growing impetus to extract maximum value from every component of woody biomass, moving beyond the traditional emphasis on cellulose fibers and sugars toward the more recalcitrant, less commercially exploited fractions. Lignin, the second most abundant natural polymer after cellulose, is the principal candidate for such extended valorization (Karunarathna & Smith, 2020).

Lignin is a complex, three-dimensional, amorphous macromolecule composed of phenylpropanoid units—predominantly p-hydroxyphenyl (H), guaiacyl (G), and syringyl (S) monolignols—linked through a variety of ether and carbon–carbon bonds. It provides structural rigidity, hydrophobicity, and pathogen resistance to the plant cell wall. In quantitative terms, lignin accounts for approximately 15–30% of softwood mass and 18–35% of hardwood mass, with exact proportions varying by species,

tissue type, and growth conditions. Despite this abundance, lignin has been historically underutilized: the pulp and paper industry generates roughly 50–70 million tonnes of technical lignin per year, the vast majority of which is combusted as a low-value fuel. Only a small fraction, estimated at less than 5%, is currently directed toward material applications (Wang et al., 2020).

The growing interest in lignin valorization is driven by several converging factors: the imperative to develop sustainable alternatives to petroleum-derived chemicals, the maturation of biorefinery concepts that integrate multiple biomass conversion processes, and the recognition that the unique chemistry of lignin—its aromatic character, polyphenolic functionality, and tunable amphiphilicity—confers properties that are not easily replicated by synthetic polymers. In the pharmaceutical domain, nanoparticulate drug delivery has emerged as a transformative approach to improving the bioavailability, therapeutic index, and targeted action of pharmacologically active compounds. The majority of nanoparticulate carriers reported to date rely on synthetic polymers (e.g., polyethylene glycol, polycaprolactone) or semi-synthetic derivatives. These materials, while effective, present challenges related to petroleum dependence, environmental persistence, and, in some cases, cost. Lignin-based nanoparticles offer an alternative that is renewable, potentially biodegradable, and intrinsically endowed with antioxidant and UV-protective properties (Piccinino et al., 2021).

The concept of lignin nanoparticles (LNPs) as drug delivery vehicles has matured significantly over the past decade. Early work demonstrated that lignin could be processed into stable colloidal particles via straightforward solvent-shifting or pH-adjustment techniques. Subsequent studies expanded the repertoire to include hollow nanoparticles, core–shell architectures, hybrid systems incorporating polysaccharides or metal oxides, and stimuli-responsive formulations capable of triggered release in tumor-mimicking or inflammatory environments. Proof-of-concept studies have shown that LNPs can encapsulate a diverse array of payloads, including hydrophobic anticancer drugs, anti-inflammatory agents, antimicrobial compounds, and diagnostic probes. However, the field remains at an early stage of development, with the vast majority of evidence derived from *in vitro* experimentation and only limited in vivo evaluation (Chapla et al., 2022).

A distinctive feature of lignin as a pharmaceutical material is its direct dependence on the biomass feedstock and the isolation method employed. The molecular weight distribution, monolignol ratio, functional group density, degree of condensation, and residual carbohydrate or sulfur content of a given technical lignin vary substantially depending on whether it originates from a softwood Kraft process, a hardwood organosolv treatment, or an enzymatic hydrolysis residue. These structural differences propagate to the nanoparticle fabrication step, influencing self-assembly behavior, particle morphology, drug–matrix interactions, and ultimately the release kinetics and biological performance of the carrier. This feedstock–structure–function relationship is a central theme of the present review and one that distinguishes lignin nanomedicine from delivery systems based on more chemically homogeneous carrier materials (Nan et al., 2022).

The aim of this review is to provide a comprehensive, critical synthesis of the current state of knowledge on lignin nanoparticles derived from forestry biomass for controlled drug delivery. The scope encompasses: (i) the influence of forest biomass sources and lignin extraction methods on carrier-relevant properties; (ii) the physicochemical attributes of lignin that enable drug loading and controlled release; (iii) nanoparticle fabrication and surface engineering strategies; (iv) drug loading, release mechanisms, and delivery applications across multiple therapeutic areas; (v) biological performance and translational considerations including safety, regulation, and scalability; and (vi) sustainability implications within the context of forest biorefinery development. The review is intended to bridge the disciplinary divide between forestry science, polymer chemistry, and pharmaceutical nanotechnology, offering a resource for researchers seeking to advance lignin-based delivery systems from the laboratory toward clinical relevance.

2. Forestry Biomass Sources and Lignin Heterogeneity

2.1 Woody Biomass Feedstocks

The lignin available for nanoparticle fabrication is not a single, well-defined chemical entity but rather a family of related macromolecules whose composition is determined by both the plant species of origin and the method used to separate lignin from the polysaccharide matrix. Softwood species—particularly *Picea* (spruce), *Pinus* (pine), and *Pseudotsuga* (Douglas fir)—produce lignins that are predominantly composed of guaiacyl (G) units, with minor quantities of p-hydroxyphenyl (H) units. This structural homogeneity results in a relatively high degree of cross-linking and condensation, yielding lignins of higher molecular weight and lower solubility in many organic solvents compared to hardwood lignins. Hardwood species—including *Eucalyptus*, *Betula* (birch), *Populus*

(poplar), and *Fagus* (beech)—produce lignins containing both guaiacyl and syringyl (S) units in roughly comparable proportions, typically with S/G ratios ranging from 1.0 to 3.0. The presence of syringyl units, which bear two methoxy groups on the aromatic ring, reduces the potential for C–C coupling at the C-5 position and consequently yields lignins with a more linear, less branched architecture, lower molecular weight averages, and improved solubility (Martínková et al., 2023).

Beyond the major timber species, several forestry side streams merit consideration as lignin sources. Bark residues, which are generated in substantial volumes at sawmills and pulp mills, contain lignins that are often more condensed and more heavily associated with suberin, tannins, and extractives than wood lignins, presenting additional purification challenges. Sawdust and wood chips from sawmill operations represent relatively clean feedstocks but are heterogeneous in species composition when sourced from mixed operations. Black liquor, the principal byproduct of Kraft pulping, is the largest single source of technical lignin worldwide and contains Kraft lignin dissolved in an alkaline medium along with degraded carbohydrates, extractives, and inorganic pulping chemicals (Gellerstedt, 2015). Biorefinery residues from cellulosic ethanol production or enzymatic saccharification processes yield enzymatic hydrolysis lignin, which retains a relatively native-like structure but is often contaminated with residual cellulose, protein, and ash.

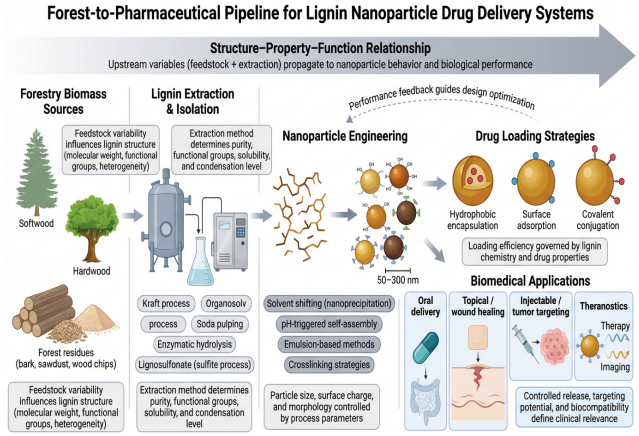

Figure 1. Forest-to-pharmaceutical pipeline for lignin nanoparticle drug delivery systems.

Schematic representation of the conversion of forestry biomass, including softwood, hardwood, and forest residues, into lignin-based nanocarriers for drug delivery. The diagram outlines key stages comprising lignin extraction and isolation through processes such as Kraft, organosolv, soda pulping, and enzymatic methods, followed by nanoparticle engineering via solvent shifting, pH-driven self-assembly, emulsion techniques, and crosslinking. It further depicts multiple drug loading strategies, including hydrophobic encapsulation, surface adsorption, and covalent conjugation, leading to diverse biomedical applications such as oral delivery, wound healing, injectable therapies, and theranostics. The figure highlights the structure–property–function relationship, showing how variations in feedstock and extraction govern nanoparticle characteristics and downstream biological performance.

2.2 Native Versus Technical Lignin

Native lignin, as it exists within the plant cell wall, is a three-dimensional network polymer intimately associated with hemicelluloses through covalent lignin–carbohydrate complexes (LCCs). Its precise in situ structure remains debated, but it is generally accepted that native lignin possesses a higher proportion of β-O-4 ether linkages—the most labile type of inter-unit bond—than any isolated technical lignin. The act of isolation inevitably modifies lignin structure. Kraft pulping, the dominant industrial process, employs sodium hydroxide and sodium sulfide at elevated temperatures (155–175 °C), which cleaves β-O-4 linkages extensively, introduces thiol groups through sulfide addition reactions, and promotes condensation to form new, stable C–C bonds. The resulting Kraft lignin is sulfur-containing, of relatively broad molecular weight distribution (typically 1,000–15,000 Da by gel permeation chromatography), and soluble in alkaline aqueous media (Wang et al., 2019). Organosolv lignin, produced by treating biomass with organic solvents (ethanol, methanol, acetone, or organic acid mixtures) at moderate temperatures, tends to retain a higher proportion of native ether linkages and is generally sulfur-free, lower in molecular weight, narrower in dispersity, and more soluble in common organic solvents. Soda lignin, derived from alkaline pulping without sulfur, is structurally similar to Kraft lignin but free of thiol contamination (Park et al., 2024). Lignosulfonates, produced by sulfite pulping, are water-soluble due to the introduction of sulfonate groups, and while they are commercially available in large volumes, their high charge density and hydrophilicity make them less suitable for encapsulation of hydrophobic drugs unless further modified. Enzymatic hydrolysis lignin, isolated as the solid residue after cellulase treatment of pretreated biomass, retains features closer to native lignin but may contain higher ash, residual carbohydrate, and protein content (Li et al., 2016).

2.3 Impact of Feedstock and Process on Nanoparticle-Relevant Properties

The downstream implications of feedstock and isolation chemistry for nanoparticle fabrication are profound. Molecular weight and dispersity influence self-assembly kinetics during solvent shifting: lower molecular weight lignins with narrower dispersity tend to produce smaller, more uniform nanoparticles (Pylypchuk et al., 2021). Monomer composition affects amphiphilicity—S-rich hardwood lignins, with their higher methoxylation, exhibit different hydrophobic–hydrophilic balances than G-dominant softwood lignins. Hydroxyl content, encompassing both phenolic and aliphatic OH groups, determines the potential for hydrogen bonding with drug molecules and the amenability to chemical modification. Residual sulfur in Kraft lignin may raise safety concerns for biomedical use or interfere with certain drug chemistries. The degree of condensation affects the rigidity and porosity of the nanoparticle matrix, influencing drug diffusion and release kinetics. Solubility in the chosen fabrication solvent is a prerequisite for solution-based particle formation methods, and different lignin types require different solvent systems. Colloidal stability of the resulting nanoparticles in physiological media depends on surface charge, which in turn is governed by the density and type of ionizable functional groups present on the lignin macromolecule (McMichael et al., 2024).

This variability constitutes both an opportunity and a challenge. The opportunity lies in the possibility of tailoring lignin selection to match specific delivery requirements—for example, choosing a low-molecular-weight organosolv lignin for fabrication of small, uniform nanoparticles for intravenous delivery, or selecting a Kraft lignin with high phenolic content for applications where antioxidant co-activity is desired. The challenge lies in the difficulty of achieving batch-to-batch reproducibility when the feedstock itself is variable, and in the absence of widely accepted quality standards for pharmaceutical-grade lignin (Karagöz et al., 2023).

Table 1. Forest Biomass Sources and Associated Lignin Types: Structural Features and Implications for Drug Delivery Nanoparticle Development.

Biomass Feedstock	Lignin Type	Isolation Method	Major Structural Features	Relevance to Drug Delivery	Key Limitations
Softwood (pine, spruce)	Kraft lignin	Kraft pulping (NaOH/Na2S, 155–175 °C)	G-dominant; MW 1–15 kDa; broad dispersity; contains sulfur; high condensation	High phenolic OH enables antioxidant co-activity; good hydrophobic drug loading	Sulfur content; heterogeneity; odor; requires purification for biomedical use
Hardwood (eucalyptus, birch, poplar)	Kraft or organosolv lignin	Kraft or organosolv (ethanol/water, 150–200 °C)	G/S mixed; S/G ratio 1–3; lower MW; less condensed; more linear chains	Improved solubility; smaller, more uniform NPs; tunable amphiphilicity	S/G variability across species; may require solvent optimization
Mixed sawmill residues	Variable (depends on process)	Kraft, soda, or steam explosion	Species mixture; variable composition; moderate MW	Abundant and low cost; suitable for non-injectable routes	Compositional inconsistency; difficult to standardize
Bark residues	Bark lignin (often condensed)	Alkaline extraction or organosolv	High condensation; co-extracted tannins and suberin; complex phenolics	Rich polyphenol content may enhance antioxidant activity	High impurity burden; difficult purification; low yield of clean lignin
Black liquor	Kraft lignin (dissolved)	Acidification or membrane separation from Kraft black liquor	Sulfur-containing; dissolved in alkali with carbohydrate and ash contaminants	Largest volume technical lignin; low cost; established supply chain	Requires extensive purification; sulfur and sodium contamination
Biorefinery residue	Enzymatic hydrolysis lignin	Cellulase treatment of pretreated biomass	Near-native structure; higher residual carbohydrate; protein and ash present	Retains more native ether linkages; potentially lower toxicity	High ash and residual carbohydrate; requires additional purification steps
Sulfite pulp mill	Lignosulfonate	Sulfite pulping with SO2/bisulfite	Water-soluble; sulfonate groups; high charge density; MW 5–50 kDa	Natural water solubility; surfactant properties; established commercial products	Excessive hydrophilicity limits hydrophobic drug encapsulation; sulfur content
Hardwood (poplar, beech)	Soda lignin	Soda pulping (NaOH, no sulfur)	Sulfur-free; moderate MW; phenolic and carboxylic groups	Its sulfur-free nature is advantageous for biomedical use; good reactivity	Lower commercial availability than Kraft lignin; moderate yield

3. Chemistry and Physicochemical Features Relevant to Drug Delivery

The suitability of lignin as a drug delivery matrix rests on several intrinsic physicochemical features that collectively distinguish it from both synthetic polymers and other biopolymers such as cellulose or starch (Creţeanu & Vieriu, 2025).

3.1 Aromatic Scaffold and Functional Group Landscape

The phenylpropanoid backbone of lignin provides a dense aromatic scaffold capable of participating in π–π stacking interactions with aromatic drug molecules, a feature that is particularly relevant for the encapsulation of many anticancer agents, anti-inflammatory drugs, and antimicrobials that contain aromatic ring systems. Phenolic hydroxyl groups (typically 2–6 mmol/g in technical lignins) are available for hydrogen bonding, ester or ether coupling reactions, and pH-dependent ionization (Esakkimuthu, 2020; Li et al., 2023). Aliphatic hydroxyl groups provide additional sites for chemical conjugation (Liu et al., 2024). Methoxy groups contribute to hydrophobicity, while carboxyl groups introduced or exposed during pulping confer surface charge at physiological pH and contribute to colloidal stability in aqueous media (Sheridan et al., 2024). This diversity of functional groups within a single macromolecule is unusual among biopolymers and enables

lignin to interact with a broad spectrum of drug chemistries through multiple simultaneous non-covalent mechanisms: hydrophobic partitioning, hydrogen bonding, π–π stacking, and electrostatic interactions (Gao et al., 2019; Szabó et al., 2016).

3.2 Amphiphilicity and Self-Assembly

Lignin is inherently amphiphilic. Its aromatic and methoxylated domains are hydrophobic, while its hydroxyl, carboxyl, and (in some lignin types) sulfonate groups are hydrophilic. This dual character enables lignin to self-assemble at solvent interfaces and to form stable nanoparticles through controlled changes in solvent quality; for example, by adding water to a lignin solution in a water-miscible organic solvent, the increasingly polar environment drives the hydrophobic segments inward, forming a compact core stabilized by a more hydrophilic outer surface. This process, often termed solvent shifting or nanoprecipitation, is the most widely used method for LNP fabrication and is energetically favorable because it exploits the thermodynamic drive to minimize unfavorable hydrophobic-water contact (Markwalter et al., 2019).

3.3 Intrinsic Bioactivity: Antioxidant and UV-Protective Properties

A feature that sets lignin apart from most synthetic carrier materials is its intrinsic antioxidant activity, which derives from the ability of phenolic hydroxyl groups to scavenge free radicals through hydrogen atom transfer and single-electron transfer mechanisms. This antioxidant capacity has been documented across multiple lignin types and is generally enhanced in lignins with higher phenolic OH content and lower molecular weight. In a drug delivery context, this property is potentially advantageous because oxidative stress is a component of the pathophysiology of cancer, inflammation, wound healing, and neurodegenerative disease. A carrier that simultaneously delivers a therapeutic payload and provides antioxidant protection could, in principle, offer synergistic therapeutic benefits. Similarly, the strong ultraviolet absorption of lignin, arising from the conjugated aromatic system, is relevant for topical and dermal formulations where UV protection of photolabile drugs or the skin itself is desirable. These intrinsic bioactivities, however, require careful assessment: the antioxidant capacity may be attenuated by chemical modification, and the extent to which it contributes to therapeutic outcomes in vivo remains to be established rigorously (Bucci et al., 2017; Dunaway et al., 2018).

3.4 Hydrophobic Drug Encapsulation

A large proportion of newly developed pharmaceutical compounds are classified as poorly water-soluble, presenting formidable formulation challenges. The hydrophobic core of lignin nanoparticles provides a compatible environment for the encapsulation of such compounds via hydrophobic partitioning, π–π interactions, and van der Waals forces. The loading capacity and efficiency depend on the affinity between the specific drug and the lignin matrix, which is in turn governed by the lignin's aromatic density, methoxylation, molecular weight, and the fabrication conditions. Reported encapsulation efficiencies for hydrophobic model drugs such as curcumin, resveratrol, and doxorubicin in LNPs range widely from approximately 20% to over 90%, reflecting the diversity of lignin types, fabrication methods, and drug–lignin combinations explored. The ability of lignin to interact with both aromatic and non-aromatic hydrophobic molecules through multiple mechanisms suggests broad applicability, though it also means that predicting loading behavior a priori is difficult without empirical optimization (Anghel et al., 2022).

In summary, the physicochemical profile of lignin—aromatic scaffold, amphiphilicity, hydrogen-bonding capacity, intrinsic antioxidant activity, and structural tunability—provides a robust rationale for its use as a nanoparticulate drug delivery material. However, this profile is not uniform across all lignin types, and the match between a specific lignin and a specific drug–delivery application must be assessed on a case-by-case basis.

4. Lignin Nanoparticle Fabrication and Engineering

The translation of dissolved or suspended lignin into well-defined nanoparticles requires careful control of the self-assembly or precipitation process (Österberg et al., 2020). Multiple fabrication strategies have been developed, each offering distinct advantages and limitations with respect to particle size control, scalability, solvent use, and compatibility with drug loading (Lourenço & Gominho, 2023).

4.1 Solvent Shifting (Nanoprecipitation)

Solvent shifting, also known as nanoprecipitation or the anti-solvent method, is the most widely reported technique for LNP preparation. Lignin is first dissolved in a water-miscible organic solvent—commonly tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), acetone, or ethanol—and the resulting solution is added dropwise to a large excess of water (or vice versa) under stirring. As the organic solvent mixes with water, the increasing polarity of the medium reduces lignin solubility, driving nucleation and growth of

nanoparticles stabilized by the amphiphilic character of the lignin itself. Particle size can be modulated by adjusting the initial lignin concentration, solvent-to-water ratio, addition rate, stirring speed, and temperature. Typical particle diameters achieved by this method range from 50 to 500 nm, with polydispersity indices (PDI) that can be as low as 0.05–0.15 under optimized conditions. The organic solvent is subsequently removed by evaporation or dialysis. Drug molecules can be co-dissolved with lignin in the organic phase and co-precipitated, resulting in physical encapsulation within the nanoparticle matrix (Lourenço & Gominho, 2023).

4.2 pH-Triggered Self-Assembly

Lignin's phenolic groups are ionized at high pH, rendering the polymer soluble in alkaline solutions. Controlled acidification of such solutions causes progressive protonation of phenolate groups, increasing hydrophobicity and driving self-assembly into nanoparticles. This approach avoids the use of organic solvents entirely, which is advantageous from a green chemistry perspective. However, pH-shifted particles may exhibit broader size distributions than solvent-shifted counterparts, and the process is sensitive to the rate of acid addition, the buffering capacity of the medium, and the specific lignin type. Lignins with higher carboxyl content may remain partially soluble at mildly acidic pH, requiring optimization of the final pH to achieve complete precipitation without particle aggregation (Hubbe et al., 2019a, 2019b).

4.3 Ultrasound-Assisted Methods

The application of high-intensity ultrasound during nanoprecipitation or pH shifting can improve particle uniformity and reduce mean particle size by providing intense local mixing and cavitation energy that promotes rapid nucleation and limits particle growth. Ultrasonication has been reported to produce LNPs with diameters below 100 nm and narrow size distributions. The technique is compatible with both solvent-shifting and solvent-free approaches and can be combined with simultaneous drug loading. However, excessive sonication energy may degrade the lignin polymer or generate localized heating that affects drug stability (Sadeghifar et al., 2019).

4.4 Emulsion-Based Approaches

Oil-in-water or water-in-oil emulsification followed by solvent evaporation or crosslinking represents an alternative route to LNPs, particularly for the encapsulation of highly hydrophobic drugs that partition preferentially into an organic phase. In these systems, lignin may serve as a stabilizer at the emulsion interface, forming a polymeric shell around the dispersed phase. Emulsion methods can produce particles in the 100 nm to several micrometers range and offer high loading capacities for lipophilic compounds. They are, however, more complex than nanoprecipitation, often require surfactants, and may leave residual organic solvents or oils that complicate purification and raise safety concerns (Huguet-Casquero et al., 2020; Lammari et al., 2020).

4.5 Hollow Lignin Nanoparticles

Hollow LNPs, possessing an internal cavity surrounded by a lignin shell, have been fabricated by templating lignin onto sacrificial cores (such as silica or calcium carbonate nanoparticles) followed by core removal via dissolution or etching. Hollow particles offer higher drug loading capacity per unit mass than solid particles due to the availability of the internal void for cargo storage (Yang & Ciftci, 2016). They also exhibit distinct release kinetics, with the shell acting as a diffusion barrier. The additional fabrication steps, however, increase process complexity and cost, and the use of inorganic templates raises questions about residual template contamination (Nirala et al., 2016).

4.6 Crosslinking Strategies

To improve the colloidal stability and reduce premature disassembly of LNPs in complex biological media, chemical or physical crosslinking can be applied. Glutaraldehyde, genipin, and epichlorohydrin have been employed as chemical crosslinkers, reacting with lignin's hydroxyl groups to form covalent bridges between chains. Enzymatic crosslinking using laccases, which catalyze the oxidative coupling of phenolic units, offers a more biocompatible alternative. Crosslinking generally improves particle stability and slows drug release but may reduce the biodegradability of the carrier and, in the case of chemical crosslinkers, introduce cytotoxic residues (Österberg et al., 2020).

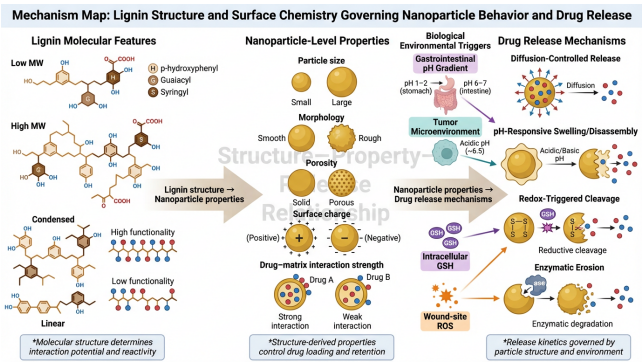

Figure 2. Mechanism map: lignin structure and surface chemistry governing nanoparticle behavior and drug release.

Conceptual schematic illustrating the hierarchical relationship between molecular-level lignin features, nanoparticle properties, and drug release mechanisms. Variations in lignin structure, including monolignol composition, functional group density, molecular weight, and degree of condensation, influence key nanoparticle characteristics such as size, morphology, surface charge, porosity, and drug–matrix interaction strength. These physicochemical properties determine drug loading efficiency and retention, which in turn regulate release pathways including diffusion-controlled release, pH-responsive swelling or disassembly, redox-triggered bond cleavage, and enzymatic erosion. The figure further highlights the role of biological environmental triggers, including gastrointestinal pH gradients, acidic tumor microenvironments, intracellular glutathione, and wound-site reactive oxygen species, in modulating nanoparticle behavior and controlling release kinetics.

4.7 Scalability and Reproducibility Considerations

While laboratory-scale fabrication of LNPs is well established, translation to manufacturing scale presents significant hurdles. Solvent-shifting methods require handling and recovery of large volumes of organic solvents, which has both economic and environmental implications. Batch-to-batch reproducibility is limited by the inherent variability of the lignin feedstock, as discussed in Section 2, and by the sensitivity of the self-assembly process to minor variations in conditions. Microfluidic mixing devices have been explored as a means of achieving more precise control over nucleation kinetics and producing highly uniform particles, yet throughput remains limited. The development of scalable, continuous-flow processes with in-line monitoring of particle attributes is an important engineering priority for the field (Lorber et al., 2010).

Table 2. *Summary of lignin nanoparticle fabrication methods, characteristics, and translational considerations.*

Preparation Method	Principle	Typical Particle Characteristics	Advantages	Drawbacks	Scalability	Suitable Drug Classes
Solvent shifting / nanoprecipitation	Dissolution in organic solvent followed by anti-solvent (water) addition	approx. 28 nm; negatively charged (e.g., -52 mV)	Simple; tunable size; high reproducibility at lab scale; drug co-precipitation	Requires organic solvent removal; solvent residue risk	Moderate; continuous flow promising	Hydrophobic small molecules; aromatic drugs
pH-triggered self-assembly	Alkaline dissolution followed by controlled acidification	100–600 nm; broader PDI; charge-dependent stability	Solvent-free; green chemistry compatible; low cost	Broader size distribution; process sensitive to acid addition rate	Good; simple scale-up	Phenolic drugs; pH-stable compounds
Ultrasound-assisted precipitation	Nanoprecipitation with high-intensity ultrasonication	30–200 nm; narrow PDI achievable	Small particles; rapid process; narrow size distributions	Risk of lignin degradation; equipment cost; local heating	Limited; batch-dependent	Drugs requiring small carrier size
Emulsion-based methods	O/W or W/O emulsification with solvent evaporation or crosslinking	100 nm–1 µm; variable PDI; high loading possible	High hydrophobic drug loading; shell-core architecture	Complex process; surfactant residues; solvent use	Moderate	Highly lipophilic drugs; essential oils
Hollow nanoparticle templating	Lignin deposition on sacrificial template followed by core removal	100–500 nm shell thickness 10–50 nm; hollow interior	Very high loading capacity; controlled shell thickness	Multi-step; template residue risk; higher cost	Low	High-payload applications; large molecules
Crosslinked nanoparticles	Chemical or enzymatic crosslinking after nanoparticle formation	Depends on base method; improved stability	Enhanced stability in biological media; slower release	Crosslinker toxicity risk; reduced biodegradability	Moderate	Drugs requiring sustained release

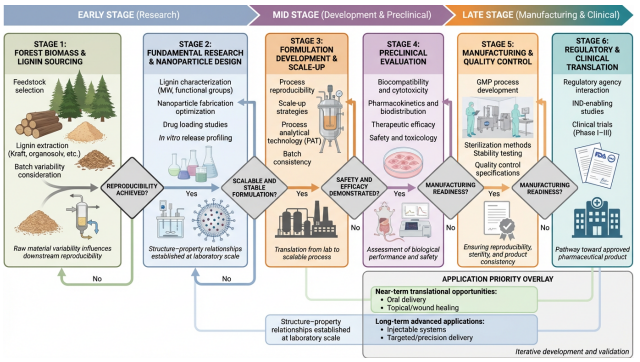

Figure 3. Translational roadmap for lignin nanoparticle drug delivery from forest biomass to pharmaceutical product. *Schematic representation of the staged progression from forestry-derived lignin sourcing to clinical translation of nanoparticle-based drug delivery systems. The roadmap outlines sequential phases including fundamental research and nanoparticle design, formulation development and scale-up, preclinical evaluation of safety and efficacy, manufacturing and quality control under GMP conditions, and regulatory, and clinical advancement. Key decision gates highlight critical requirements such as reproducibility, scalability, safety, and manufacturing readiness, with iterative feedback loops enabling optimization at each stage. The figure also distinguishes near-term translational opportunities, including oral and topical applications, from longer-term goals such as injectable and targeted delivery systems.*

5. Surface Functionalization and Hybrid Systems

Unmodified LNPs, while possessing inherent colloidal stability in many aqueous conditions (Pylypchuk &

Sipponen, 2022), often require surface engineering to meet the demands of specific biomedical applications (Zhao et al., 2025). The rich functional group landscape of lignin provides ample sites for covalent conjugation or physical adsorption of modifying agents (Zhao et al., 2025).

5.1 PEGylation

The covalent grafting of polyethylene glycol (PEG) chains onto lignin nanoparticles is one of the most explored modification strategies. PEGylation is expected to reduce opsonization, extend systemic circulation time, and improve stability in high-ionic-strength biological fluids by creating a hydrophilic steric barrier around the particle (Bennie et al., 2018). PEG can be conjugated to lignin's hydroxyl groups via ester (Sougrati, 2024) or ether (Yamada et al., 2023) linkages. The effectiveness of PEGylation depends on the grafting density and chain length of the PEG, with longer chains and higher surface coverage generally providing superior stealth properties (Bennie et al., 2018; Friedl et al., 2021). However, the "PEG dilemma," in which PEGylation improves circulation but may hinder cellular uptake at the target site, applies equally to lignin-based systems as to other PEGylated nanoparticles (Bennie et al., 2018; Friedl et al., 2021).

5.2 Chitosan Coating and Polysaccharide Hybridization

Chitosan, a cationic polysaccharide derived from chitin, can be adsorbed onto or conjugated with negatively charged LNPs to reverse surface charge and confer mucoadhesive properties. This is particularly relevant for oral drug delivery, where mucoadhesion can prolong gastrointestinal residence time and enhance epithelial contact. Similarly, hybridization with other polysaccharides such as dextran, hyaluronic acid, or alginate can modulate surface chemistry, improve biocompatibility, or introduce receptor-targeting functionality (e.g., hyaluronic acid targeting CD44 receptors on tumor cells). These approaches often involve electrostatic layer-by-layer assembly or covalent grafting via carbodiimide chemistry (Abesekara & Chau, 2022).

5.3 Stimuli-Responsive Linkers and Targeting Ligands

The introduction of stimuli-responsive elements such as disulfide bonds that cleave under the reducing conditions of the tumor intracellular environment, or acid-labile hydrazone linkages that dissociate at the mildly acidic pH of endosomes or the tumor microenvironment enables the design of LNPs capable of triggered drug release at the site of action. Targeting ligands, including folic acid, transferrin, peptides, and antibodies, can be conjugated to the LNP surface to promote receptor-mediated endocytosis by specific cell types. These strategies add complexity and cost but are essential for achieving the selectivity and spatial control demanded by advanced therapeutic applications such as tumor-targeted chemotherapy. The feasibility of decorating lignin nanoparticles with such sophisticated functional elements has been demonstrated in proof-of-concept studies, though systematic optimization is still in its early stages (Richter et al., 2016).

5.4 Metal Oxide and Magnetic Hybrid Systems

The incorporation of inorganic components such as iron oxide nanoparticles for magnetic targeting and MRI contrast, zinc oxide for antimicrobial enhancement, or silver nanoparticles for wound-healing applications into lignin nanoparticle architectures creates multifunctional hybrid carriers. Lignin serves as both the organic matrix and a reducing and stabilizing agent during the synthesis of metal nanoparticles, exploiting the polyphenolic chemistry inherent to the polymer (Lizundia et al., 2021). These hybrids can combine drug delivery with imaging or theranostic capabilities, although the addition of inorganic components raises safety and regulatory considerations (Kim et al., 2017).

Table 3. *Surface modification and hybridization strategies for lignin nanoparticles.*

Modification Strategy	Chemical Rationale	Functional Effect	Typical Use Case	Translational Benefit	Main Caveat
PEGylation	Ester/ether/urethane grafting of PEG to lignin OH groups	Steric stabilization; reduced opsonization; extended circulation	Injectable systemic delivery	Improved pharmacokinetics; stealth behavior	PEG dilemma: may hinder cellular uptake
Chitosan coating	Electrostatic adsorption of cationic chitosan onto anionic LNP surface	Charge reversal; mucoadhesion; enhanced epithelial interaction	Oral drug delivery	Prolonged GI residence; improved permeation	pH-dependent stability; requires charge optimization
Hyaluronic acid conjugation	Carbodiimide coupling or layer-by-layer assembly	CD44 receptor targeting; improved biocompatibility	Tumor-targeted delivery	Active targeting to CD44-overexpressing tumors	HA molecular weight affects targeting efficiency
Disulfide crosslinking	Introduction of S–S bonds via thiol-disulfide chemistry	Redox-responsive disassembly in intracellular GSH-rich environment	Intracellular drug release in tumor cells	Triggered release in reducing microenvironments	Stability in blood vs. rapid release in cells requires fine-tuning
Folic acid conjugation	Covalent coupling via amide or ester bond to LNP surface	Targeting folate receptor-overexpressing cells	Cancer therapeutics (ovarian, breast)	Enhanced tumor selectivity	Folate receptor expression is variable across tumors
Iron oxide incorporation	In situ co-precipitation or physical embedding in lignin matrix	Magnetic responsiveness; MRI contrast	Magnetically guided delivery; theranostics	Dual imaging and therapy	Inorganic component raises regulatory complexity
Cyclodextrin inclusion	Physical or covalent inclusion of cyclodextrin cavities	Enhanced loading of poorly soluble drugs via host–guest interaction	Oral bioavailability enhancement	Improved drug solubilization	Added cost; potential competitive displacement
Alginate/polysaccharide shell	Electrostatic or covalent layer formation	pH-responsive gastric protection; controlled GI release	Oral delivery of acid-labile drugs	Stomach acid protection; colon targeting	Swelling behavior needs optimization

6. Drug Loading and Delivery Applications

The versatility of lignin nanoparticles as drug carriers is illustrated by the breadth of cargo classes that have been investigated. The following subsections organize the evidence by therapeutic category, discussing the rationale for lignin as a carrier, representative formulation approaches, and observed delivery performance.

6.1 Hydrophobic Small Molecules

The hydrophobic core of LNPs is inherently suited for the encapsulation of poorly water-soluble drugs, which constitute a significant and growing proportion of the pharmaceutical development pipeline. Curcumin, a well-known polyphenolic compound (Alqahtani et al., 2019; Nguyen et al., 2020) with anti-inflammatory and anticancer properties (Liu et al., 2016; Nguyen et al., 2020) but notoriously poor aqueous solubility and oral bioavailability (Ma et al., 2019; Nguyen et al., 2020), has served as a widely used model compound for LNP encapsulation studies (Alqahtani et al., 2019; Pilkington et al., 2023). The aromatic character of curcumin enables π–π stacking with the lignin matrix (Zhou et al., 2019), and reported encapsulation efficiencies are generally high (Çelikten et al., 2022; Dinari et al., 2021). Resveratrol, another polyphenolic nutraceutical (Machado et al., 2019), has similarly been encapsulated with favorable loading characteristics (Feijén et al., 2013; Ke et al., 2023). The general principle is that drugs sharing structural complementarity with the lignin aromatic scaffold—particularly those bearing aromatic rings, phenolic groups, or extended conjugated systems—tend to exhibit stronger interactions and higher loading (Dinari et al., 2021).

6.2 Anticancer Agents

The delivery of anticancer drugs is the most extensively investigated therapeutic application of LNPs. Doxorubicin, an anthracycline antibiotic used widely in oncology, has been loaded into various LNP formulations with reported encapsulation efficiencies typically in the range of 40–80%. The π–π interaction between doxorubicin's planar aromatic system and the lignin matrix, combined with hydrogen bonding through its hydroxyl and amino groups, provides a strong physical basis for retention within the nanoparticle. Paclitaxel, another major chemotherapeutic agent with extreme hydrophobicity, has been incorporated into LNPs using solvent-shifting approaches, with the lignin matrix serving as a solubilization environment that obviates the need for toxic co-solvents such as Cremophor EL. The pH-responsive behavior of lignin nanoparticles, with accelerated release under the mildly acidic conditions (pH 5.0–6.5) characteristic of the tumor microenvironment and intracellular endosomes, is frequently exploited to achieve preferential release at the tumor site. Cisplatin and its analogues, which interact with lignin through coordination with hydroxyl and carboxyl groups, have also been explored, although the evidence is more limited (Duan et al., 2016; Zhao et al., 2025).

6.3 Anti-Inflammatory Agents

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen are candidates for LNP encapsulation, primarily to reduce gastrointestinal side effects associated with oral administration and to achieve sustained release that reduces dosing frequency. The hydrophobic partitioning of these drugs into the lignin matrix provides a basis for encapsulation, and the intrinsic antioxidant activity of the lignin carrier may complement the anti-inflammatory action of the drug (Anghel et al., 2022; Li et al., 2017). Corticosteroids, including dexamethasone, have been formulated with LNPs for potential application in treating inflammatory conditions of the skin, joints, or gastrointestinal tract (Libánská et al., 2020).

6.4 Antimicrobials and Antibiotics

Lignin nanoparticles have been investigated as carriers for antimicrobial agents including silver nanoparticle lignin composites, ciprofloxacin, tetracycline, and antimicrobial essential oils. The combination of drug-loaded LNPs and the inherent antimicrobial activity reported for some lignin fractions may provide synergistic antimicrobial effects. For wound-healing applications, antimicrobial LNPs can be incorporated into hydrogels, films, or wound dressings to provide both sustained antimicrobial release and

antioxidant protection at the wound site (Freitas et al., 2020).

6.5 Antioxidants and Nutraceuticals

Beyond their role as carriers, LNPs can function as antioxidant delivery systems in which the carrier itself is part of the therapeutic strategy. Encapsulation of antioxidant compounds such as quercetin, vitamin E, and β-carotene within LNPs can protect these labile molecules from degradation during storage and transit through the gastrointestinal tract, enhancing their bioavailability while simultaneously delivering lignin-derived phenolic antioxidant activity. This dual-function concept is attractive for oral nutraceutical formulations and topical anti-aging products, though rigorous clinical evidence for synergistic antioxidant benefits is not yet available (Zubair et al., 2024).

6.6 Wound-Healing and Topical Payloads

The application of LNPs in wound healing is supported by the convergence of several favorable properties: antioxidant activity to modulate reactive oxygen species at the wound site, UV protection for photosensitive wounds, and the ability to deliver growth factors, antibiotics, or anti-inflammatory drugs in a controlled manner. LNP-loaded hydrogels and electrospun nanofiber mats have been reported to promote wound closure in vitro scratch assays and preliminary animal models. The topical route avoids many of the systemic delivery challenges (opsonization, hepatic clearance) that complicate injectable applications and represents one of the more translationally accessible avenues for LNP deployment (Bolsoni et al., 2023).

6.7 Diagnostic and Theranostic Systems

The incorporation of imaging agents—fluorescent dyes, near-infrared probes, or gadolinium chelates—into LNPs has been explored for potential diagnostic applications. When combined with therapeutic payloads in a single nanoparticle, these systems become theranostic platforms capable of simultaneous imaging and treatment. The feasibility of such systems has been demonstrated in laboratory settings, but the additional regulatory burden of combination imaging-therapeutic products represents a significant translational hurdle (Gupta et al., 2024).**Table 4.** *Representative drug delivery applications of lignin nanoparticles across therapeutic categories.*

Cargo / Drug Class	Delivery Route	Formulation Type	Release Behavior	Biomedical Advantage	Development Stage
Curcumin (anti-inflammatory polyphenol)	Oral, topical	Solid LNP; LNP-in-hydrogel	Sustained release over 24–72 h; pH-responsive	Improved oral bioavailability; antioxidant synergy with carrier	In vitro; limited in vivo
Doxorubicin (anthracycline anticancer)	Injectable (IV)	Core–shell LNP; PEGylated LNP	pH-triggered acceleration at pH 5.0–5.5; sustained at pH 7.4	Reduced cardiotoxicity; tumor-selective release	In vitro cell studies; some animal data
Paclitaxel (taxane anticancer)	Injectable	Solid LNP; lignin–PEG conjugate NP	Slow, diffusion-controlled release; pH-responsive component	Avoids Cremophor EL; improved tolerability	Proof-of-concept in vitro
Ibuprofen (NSAID)	Oral	LNP; lignin–polysaccharide composite	Sustained release; reduced gastric burst	GI protection; reduced dosing frequency	In vitro dissolution studies
Silver nanoparticle–lignin composite	Topical (wound dressing)	LNP hybrid in hydrogel or film	Sustained Ag^+ ion release	Synergistic antimicrobial; antioxidant wound environment	In vitro; preliminary wound models
Quercetin (flavonoid antioxidant)	Oral	Solid LNP	Diffusion-controlled; protected from GI degradation	Enhanced oral bioavailability of labile antioxidant	In vitro release and stability studies
Dexamethasone (corticosteroid)	Topical, ocular (potential)	LNP dispersion	Sustained release; potential burst reduction with crosslinking	Localized anti-inflammatory action	Early proof-of-concept
Essential oils (thymol, carvacrol)	Topical, agricultural	LNP encapsulation; emulsion-based LNP	Volatility-controlled slow release	Sustained antimicrobial activity; reduced volatilization	In vitro; some field trials (agricultural)

7. Controlled Release Mechanisms

Understanding the mechanisms by which drug molecules are released from lignin nanoparticles is essential for rational formulation design. In most LNP systems, release is governed by a combination of overlapping mechanisms rather than a single dominant process (Lucero-Acuña et al., 2019).

7.1 Diffusion-Controlled Release

For drugs physically entrapped within the lignin matrix, release occurs primarily through diffusion of drug molecules from the interior of the nanoparticle to the surrounding medium. The rate of diffusion depends on the drug's molecular size, its partition coefficient between the lignin matrix and the aqueous phase, the tortuosity and porosity of the lignin network, and the particle size. Smaller particles, with shorter diffusion path lengths, generally exhibit faster release. The initial burst release, commonly observed in LNP formulations where a substantial fraction of the loaded drug is released within the first few hours, is typically attributed to the rapid desorption of drug molecules adsorbed on or near the particle surface, before the slower

diffusion of more deeply embedded cargo begins to dominate (Islan et al., 2016).

7.2 pH-Responsive Release

Lignin's phenolic groups undergo protonation–deprotonation transitions in the physiologically relevant pH range. At acidic pH (below approximately pH 5.5), phenolic groups are fully protonated, and the lignin matrix becomes more hydrophobic and compact, potentially slowing the release of encapsulated drugs or, conversely, if the drug–lignin interaction is pH-sensitive (as with doxorubicin, whose protonation state changes near pH 5–6), the weakening of electrostatic or hydrogen-bonding interactions at lower pH can accelerate release. The net effect depends on the specific drug–lignin pairing. In many reported systems, accelerated release at acidic pH has been observed, which is desirable for tumor-targeted delivery because tumor extracellular pH is typically 6.5–6.8, and endosomal/lysosomal pH is 4.5–5.5. This intrinsic pH sensitivity of lignin is a distinguishing advantage over carriers that require the addition of synthetic pH-responsive elements (Fattahi et al., 2024).

7.3 Redox-Responsive Release

In systems where disulfide crosslinks have been introduced, exposure to reducing agents such as glutathione (GSH), which is present at millimolar concentrations inside cells but at much lower concentrations in the extracellular space, triggers reductive cleavage of the crosslinks and destabilization of the nanoparticle structure, resulting in accelerated drug release. This mechanism is particularly relevant for intracellular delivery of anticancer agents, where the elevated GSH levels in tumor cells can serve as an endogenous trigger (Kharkar et al., 2014; Zhang et al., 2015). The design challenge is to achieve crosslink densities that provide adequate stability during circulation while permitting efficient disassembly upon cellular internalization (Kharkar et al., 2014; Zhang et al., 2015).

7.4 Erosion and Degradation-Controlled Release

Although lignin is generally regarded as slowly biodegradable under physiological conditions, enzymatic or hydrolytic degradation of the lignin matrix can contribute to drug release over extended time periods. Enzymes such as laccases, peroxidases, and certain esterases may cleave inter-unit bonds in the lignin structure, gradually eroding the nanoparticle and releasing entrapped cargo. The rate of enzymatic degradation is highly dependent on the lignin type, the degree of condensation, and the availability of susceptible linkages. This mechanism is most relevant for applications requiring sustained release over days to weeks, such as implantable depots or wound dressings, rather than for rapid systemic delivery (Nan et al., 2022; Yiamsawas et al., 2014).

7.5 Formulation Variables Affecting Release

Beyond the inherent mechanism, several formulation parameters exert strong influence on the release profile. Particle size dictates the surface-area-to-volume ratio and diffusion path length (Dawes et al., 2009; Singh & Lillard, 2009). Surface charge affects interaction with biological interfaces and can modulate drug desorption from the surface (Cheung et al., 2023; Nairi et al., 2017). Drug loading level influences the concentration gradient driving diffusion and may affect matrix structure if loading is very high (Cerea et al., 2018; Hua et al., 2021). Crosslink density controls matrix rigidity and permeability (Martinez et al., 2013; Vigata et al., 2020). The degree of lignin modification (e.g., PEGylation, acetylation) alters hydrophilicity and swelling behavior (Li et al., 2024a, 2024b). Rational optimization of these variables, guided by mechanistic understanding, is necessary to achieve the desired release kinetics for a given therapeutic application.

8. Biological Performance and Biomedical Translation

8.1 Biocompatibility and Cytotoxicity

The biocompatibility of LNPs has been evaluated in numerous in vitro studies using a variety of cell lines, including fibroblasts, epithelial cells, macrophages, and cancer cells. The consensus emerging from this body of work is that unmodified LNPs are generally well tolerated at concentrations up to several hundred micrograms per milliliter, with cell viability typically exceeding 80–90% in standard MTT or WST-1 assays. Hemocompatibility studies have similarly indicated low hemolytic activity for most LNP formulations. However, these findings must be interpreted with caution: in vitro cytotoxicity assays represent a limited surrogate for in vivo safety, and the specific lignin type, degree of purification, residual solvent content, and surface chemistry all influence the observed biocompatibility. Lignins with high residual sulfur, sodium, or organic solvent content may exhibit greater cytotoxicity than purified, sulfur-free lignins (Österberg et al., 2020).

8.2 Cellular Uptake and Intracellular Trafficking

The uptake of LNPs by mammalian cells has been demonstrated using fluorescently labeled particles and confocal microscopy, as well as flow cytometry. Uptake primarily occurs through endocytic pathways, with evidence for both clathrin-mediated and macropinocytic routes

depending on particle size and surface chemistry. Following internalization, LNPs are typically trafficked to endo-lysosomal compartments, where the acidic pH may trigger drug release. The extent and rate of uptake can be modulated by surface modification: for example, cationic chitosan coatings enhance uptake by increasing electrostatic attraction to the negatively charged cell membrane, while PEGylation may reduce non-specific uptake. Targeting ligands such as folic acid or hyaluronic acid can redirect uptake to receptor-expressing cells, improving selectivity (Sanità et al., 2020).

8.3 In Vivo Evidence and Delivery Routes

In vivo data on LNP drug delivery remain limited relative to the volume of in vitro work. Oral administration has been the most explored route in animal studies, with several reports indicating improved oral bioavailability of poorly soluble drugs when formulated in LNPs compared to free drug suspensions. Topical application of LNP-loaded hydrogels in wound models has shown promising acceleration of wound closure in rodent studies. Injectable (intravenous) administration has been explored primarily in murine tumor models, with evidence of tumor accumulation attributed to the enhanced permeability and retention (EPR) effect, though the translational relevance of EPR in human tumors remains debated. Data on other routes—pulmonary, ocular, transdermal—are sparse and largely at the proof-of-concept stage. The absence of systematic pharmacokinetic, biodistribution, and long-term toxicity studies represents a critical gap that must be addressed before any clinical translation can be contemplated (Shen & Minko, 2020).

8.4 Biodegradation and Elimination

The biodegradation of lignin in mammalian systems is not fully characterized. Unlike cellulose, which is resistant to mammalian enzymatic digestion, lignin may be partially degraded by reactive oxygen species and peroxidase enzymes present in inflammatory environments. However, the rate and completeness of degradation under physiological conditions are uncertain, particularly for chemically modified or crosslinked LNPs. The elimination pathways for LNPs following systemic administration—whether through renal clearance of degradation products, hepatobiliary excretion, or macrophage-mediated sequestration in the reticuloendothelial system—have not been rigorously mapped. This is a fundamental knowledge gap that has implications for both safety assessment and regulatory evaluation (Wong et al., 2013).

9. Safety, Toxicology, and Regulatory Considerations

The transition from laboratory exploration to clinical application requires that lignin nanoparticles satisfy stringent safety and quality standards. Several categories of concern merit attention.

Batch-to-batch variability, stemming from feedstock heterogeneity and process sensitivity, is perhaps the most pervasive challenge. Pharmaceutical manufacturing demands reproducible product quality, and current lignin sourcing and processing methods may not provide the level of consistency expected by regulatory agencies such as the U.S. Food and Drug Administration or the European Medicines Agency. The development of pharmaceutical-grade lignin specifications encompassing molecular weight range, functional group content, elemental composition, impurity profiles, and endotoxin levels is a prerequisite for serious translational effort. Residual solvents from the fabrication process, particularly THF, DMSO, and chlorinated solvents, must be reduced to levels below the limits specified by pharmacopoeial guidelines (e.g., ICH Q3C). Endotoxin contamination, a common concern with natural-product-derived materials, must be assessed and controlled. Sterilization of nanoparticulate dispersions presents its own challenges: filtration may be impractical for larger particles, autoclaving may alter particle structure, and gamma irradiation may modify lignin chemistry. Storage stability—the capacity of the formulation to maintain its physicochemical attributes and drug content over months to years under defined conditions—is rarely addressed in the current literature (Balguri et al., 2016; Chávez, 2022; Deruyver et al., 2021; Sohail et al., 2018).

From a regulatory standpoint, LNPs occupy an ambiguous position. They are not yet classified under any established regulatory category, and the pathway to approval for a nanoparticulate drug product based on a novel biomass-derived excipient is inherently longer and more uncertain than for formulations using established pharmaceutical materials. The need for comprehensive preclinical safety data—including acute and chronic toxicity, genotoxicity, reproductive toxicity, and immunotoxicity—is clear but represents a substantial resource commitment (Jesus et al., 2019; Mohammadpour et al., 2019).

Table 5. *Key barriers to translation of lignin nanoparticles and practical mitigation strategies.*

Barrier	Why It Matters	Practical Mitigation Strategy	Expected Outcome
Feedstock variability	Inconsistent lignin structure leads to irreproducible nanoparticle properties	Define feedstock specifications; use single-species, single-process lignin; establish QC checkpoints	Improved batch-to-batch reproducibility
Residual solvents	Organic solvents used in fabrication may exceed pharmacopoeial limits	Optimize dialysis/evaporation; transition to solvent-free pH-shift methods; validate residual levels by GC-MS	Compliance with ICH Q3C solvent limits
Endotoxin contamination	Natural biomass-derived materials may carry endotoxin	Source certified low-endotoxin raw materials; implement depyrogenation steps; validate with LAL assay	Endotoxin levels below 0.5 EU/mL
Sterilization	Terminal sterilization may alter NP structure or drug content	Develop aseptic processing; evaluate gamma irradiation effects; validate filtration for sub-200 nm particles	Sterile product with preserved attributes
Biodegradation uncertainty	Unclear whether LNPs fully degrade in vivo and through what pathways	Conduct systematic degradation studies using radiolabeled lignin; assess metabolite fate	Clear degradation and elimination profile
Regulatory pathway ambiguity	No established category for biomass-derived nanocarrier excipients	Engage with regulatory agencies early; compile comprehensive safety dossier; align with nanomedicine guidelines	Defined regulatory strategy and timeline
Limited in vivo data	Most evidence is in vitro; clinical relevance unestablished	Prioritize well-designed animal pharmacokinetic and efficacy studies; select clinically relevant endpoints	Preclinical data package supporting IND filing
Storage stability	Long-term stability of LNP dispersions under pharmaceutical storage conditions is unknown	Conduct ICH-aligned stability studies; explore lyophilization with cryoprotectants	Defined shelf-life and storage conditions

10. Characterization and Evaluation Methods

The rigorous characterization of LNPs requires a multi-technique approach encompassing physical, chemical, and biological assays. The complexity of lignin—a polydisperse, amorphous, and chemically heterogeneous polymer—demands that characterization goes beyond the standard particle sizing and zeta potential measurements common to simpler nanoparticle systems (Obrzut et al., 2024).

Table 6. *Characterization and evaluation toolkit for lignin nanoparticle drug delivery systems.*

Technique	What It Measures	Why It Matters for LNPs	Typical Output / Interpretation
Dynamic light scattering (DLS)	Hydrodynamic diameter and polydispersity index	Primary method for size and uniformity assessment; sensitive to aggregation	Mean diameter (nm); PDI; size distribution curve
Zeta potential (electrophoretic mobility)	Surface charge	Predicts colloidal stability; informs surface modification success	Zeta potential (mV); values < −30 mV or > +30 mV suggest good stability
Scanning/transmission electron microscopy (SEM/TEM)	Morphology, shape, internal structure	Confirms spherical vs. irregular morphology; reveals hollow vs. solid architecture	Micrographs showing size, shape, and surface texture
FTIR spectroscopy	Functional group identification	Confirms lignin identity; detects chemical modifications; identifies drug-lignin interactions	Absorption bands for OH, C=O, aromatic C=C, methoxy, etc.
31P NMR spectroscopy	Quantification of hydroxyl groups (phenolic, aliphatic, carboxylic)	Provides precise functional group profiling; critical for understanding reactivity and drug interaction sites	mmol/g of each OH type
Gel permeation chromatography (GPC)	Molecular weight distribution (Mn, Mw, PDI)	Links feedstock/process to lignin MW; MW affects self-assembly and NP size	Mw, Mn, dispersity; comparison across lignin types
UV-Vis spectrophotometry	Drug loading and encapsulation efficiency; antioxidant capacity	Quantifies drug content; assesses intrinsic UV absorption and radical scavenging	Drug EE (%); loading capacity (wt%); DPPH/ABTS scavenging
In vitro drug release (dialysis method)	Cumulative drug release over time at specified pH and temperature	Characterizes release kinetics; evaluates pH responsiveness	Release profile curve; kinetic model fitting (Higuchi, Korsmeyer-Peppas)
Cell viability assays (MTT, WST-1, Live/Dead)	Cytotoxicity and biocompatibility	Essential safety screening; evaluates dose-response relationships	IC50 values; cell viability (%) at defined concentrations
Confocal laser scanning microscopy (CLSM)	Cellular uptake and intracellular localization	Visualizes NP internalization; co-localization with lysosomes or other organelles	Fluorescence images showing uptake and trafficking
Thermogravimetric analysis (TGA)	Thermal stability; residual solvent/moisture	Assesses processing stability; detects organic solvent residues	Decomposition temperatures; mass loss events
X-ray photoelectron spectroscopy (XPS)	Surface elemental composition and chemical state	Confirms surface functionalization; detects sulfur or metal contamination	Atomic % of C, O, N, S on particle surface

11. Comparison with Other Biomass-Derived Delivery Materials

Lignin nanoparticles exist within a broader landscape of biomass-derived nanocarriers, and a balanced assessment requires comparison with alternative materials. Cellulose nanocrystals (CNCs) and cellulose nanofibers (CNFs) are among the most studied cellulose-based carriers; they offer high mechanical strength, tunable surface chemistry, and well-characterized safety profiles. However, CNCs are highly hydrophilic and crystalline, making them less amenable to the encapsulation of hydrophobic drugs without substantial surface modification. Hemicellulose-based carriers, including xylan and mannan nanoparticles, share some of the biodegradability advantages of polysaccharides but are generally less structurally robust and offer fewer sites for chemical diversification than lignin. Starch nanoparticles are inexpensive and biocompatible but lack the aromatic scaffold and antioxidant properties of lignin. Chitosan nanoparticles, derived from crustacean shells, offer cationic surface charge and mucoadhesive properties that are advantageous for mucosal delivery but are not aromatic and do not provide the UV-protective or radical-scavenging functionality of lignin (Coltelli et al., 2022; Kolibaba et al., 2020).

When compared to synthetic polymer carriers such as PLGA or polycaprolactone nanoparticles, LNPs offer advantages in renewability, cost, and intrinsic bioactivity but are currently disadvantaged by less well-defined structure–property relationships, lower regulatory familiarity, and limited clinical data. A fair assessment is that lignin nanoparticles occupy a distinctive niche offering a unique combination of amphiphilicity, aromaticity, antioxidant activity, and renewable origin but do not yet match the maturity or clinical validation of established carrier platforms (Verdini et al., 2022).

Table 7. *Comparative assessment of lignin nanoparticles versus other biomass-derived and synthetic nanocarrier materials.*

Carrier Material	Source	Key Strengths	Key Weaknesses	Best-Suited Applications	Development Maturity
Lignin nanoparticles	Forestry biomass; pulp/paper byproduct	Amphiphilic; antioxidant; UV-absorbing; tunable; low cost	Heterogeneous; limited *in vivo* data; regulatory uncertainty	Hydrophobic drug delivery; oral; topical; wound care	Early preclinical
Cellulose nanocrystals	Wood pulp; cotton; bacteria	High crystallinity; well-characterized; high strength	Hydrophilic; limited hydrophobic drug loading without modification	Hydrophilic drug carriers; tissue scaffolds; reinforcing fillers	Advanced preclinical
Starch nanoparticles	Corn, potato, cassava	Inexpensive; biocompatible; biodegradable	No aromatic scaffold; no antioxidant activity; limited drug interaction	Oral delivery of hydrophilic drugs; food-grade nutraceuticals	Moderate preclinical
Chitosan nanoparticles	Crustacean chitin	Cationic; mucoadhesive; promotes permeation	Not aromatic; no UV protection; allergenicity in shellfish-sensitive individuals	Mucosal delivery; gene delivery; oral vaccines	Late preclinical; some clinical trials
PLGA nanoparticles	Synthetic (petroleum-derived)	FDA-approved; well-characterized; tunable degradation	Non-renewable; no intrinsic bioactivity; cost	Injectable sustained release; implants; FDA-approved formulations	Clinical / commercial
Hemicellulose-based carriers	Wood; agricultural residues	Biodegradable; low toxicity; renewable	Mechanically weak; limited drug interaction sites; less studied	Oral delivery; colon targeting	Early research

12. Sustainability and Forestry Valorization Perspective

The development of LNP drug delivery systems is inseparable from the broader sustainability narrative of the forest biorefinery. In a fully integrated biorefinery, cellulose is directed to fiber products or fermentable sugars, hemicelluloses to platform chemicals or hydrocolloids, and lignin, traditionally the least valorized fraction, to high-value material applications. The conversion of lignin into nanoparticulate pharmaceutical carriers represents an extreme case of value addition: transforming a byproduct currently worth approximately USD 50–200 per tonne (as fuel) into a functional material potentially worth orders of magnitude more per unit mass. This economic proposition is one of the most powerful arguments for pursuing lignin nanomedicine, provided that the technical and regulatory challenges can be solved (Lizundia et al., 2021).

However, the sustainability credentials of LNP fabrication must be scrutinized critically. Many reported fabrication methods rely on organic solvents such as THF, DMSO, or acetone, and the environmental and health implications of solvent use at manufacturing scale must be considered. Solvent recovery and recycling can mitigate these concerns but add process complexity and cost. The solvent-free pH-shift method is more attractive from a green chemistry perspective but may produce particles with less favorable size distributions. Crosslinking agents such as glutaraldehyde are petrochemical-derived and toxic, partially undermining the bio-based narrative. A life-cycle assessment (LCA) perspective encompassing raw material sourcing, energy inputs, solvent use, purification, sterilization, and end-of-life fate is needed to substantiate green claims quantitatively. To date, such assessments are largely absent from the LNP drug delivery literature (Galant et al., 2023).

From a forestry management perspective, the creation of high-value outlets for lignin can improve the economic viability of sustainable forest management practices, incentivize the utilization of low-grade wood and harvest residues, and reduce the environmental burden of lignin disposal by combustion. This alignment with circular economy principles is genuine but should not be overstated: the pharmaceutical market for lignin nanoparticles, even in an optimistic scenario, would consume only a tiny fraction of the total lignin produced globally. The broader impact would be indirect, demonstrating that lignin is a platform chemical capable of supporting diverse high-value applications and thereby encouraging investment in lignin upgrading infrastructure (Lan & Luterbacher, 2019).

13. Future Directions and Research Agenda

The translation of lignin nanoparticles from laboratory curiosity to clinically relevant drug-delivery platform requires coordinated progress along several fronts.

Standardization of lignin feedstocks. The establishment of pharmaceutical-grade lignin standards specifying molecular-weight range, functional-group content, elemental purity, endotoxin limits, and process traceability is a foundational requirement (Hua et al., 2018; Nilza & Salam, 2025). Collaboration between lignin producers, biorefinery operators, and pharmaceutical scientists is needed to define these standards and to develop quality-control protocols that are practical at an industrial scale.

Structure–function relationships. Systematic studies correlating specific lignin structural features (monomer ratio, molecular weight, degree of condensation, functional-group density) with nanoparticle properties (size, stability, loading, release) and biological performance (uptake, toxicity, efficacy) are essential (Pylypchuk et al., 2021, 2023). Such studies require well-characterized lignin libraries prepared from defined feedstocks under controlled conditions.

Reproducible and scalable manufacturing. The development of continuous-flow fabrication processes with in-line process analytical technology (PAT) for real-time monitoring of particle attributes represents a critical engineering challenge. Microfluidic and impinging-jet mixing approaches show promise but require scale-up validation (Chai et al., 2021; Ju et al., 2019).

Clinically relevant payloads and combination therapies. Moving beyond model compounds and commonly studied

drugs (curcumin, doxorubicin) toward clinically prioritized payloads—including newer small-molecule oncology drugs, biologics, nucleic acid therapeutics, and combination regimens—would substantially increase the field's translational relevance (Alqahtani et al., 2019; Zhou et al., 2019).

Targeted and stimuli-responsive systems. While proof-of-concept studies have demonstrated pH- and redox-responsive LNPs, the efficiency, selectivity, and *in vivo* performance of these systems remain to be validated in clinically relevant animal models. The development of dual- or multi-responsive systems that respond to the specific biochemical environment of the target tissue could enhance therapeutic precision.

Oral and wound delivery as near-term opportunities. Given the lower regulatory burden and the inherent compatibility of lignin with oral and topical applications, these routes represent the most realistic near-term translational targets (Alqahtani et al., 2019; Morena & Tzanov, 2022). Oral delivery of poorly soluble nutraceuticals and topical delivery of wound-healing agents are applications where the risk–benefit calculus and the existing evidence base are most favorable.

Rigorous in vivo and preclinical evaluation. The field must transition from predominantly in vitro work to well-designed animal studies that assess pharmacokinetics, biodistribution, target tissue accumulation, therapeutic efficacy, and long-term safety (Bragato et al., 2024; Okoro et al., 2021). Standardized experimental protocols and reporting guidelines would facilitate cross-study comparison.

Translational pathways. Early engagement with regulatory agencies, investment in good manufacturing practice (GMP) process development, and the assembly of comprehensive preclinical safety dossiers are necessary to bridge the gap between academic proof-of-concept and clinical reality. The timeline for this transition is likely measured in decades rather than years, and the field would benefit from realistic articulation of milestones and resource requirements.

14. Conclusion

Lignin nanoparticles derived from forestry biomass represent a scientifically compelling and practically attractive platform for controlled drug delivery. The case for lignin rests on a convergence of favorable attributes: renewable and abundant feedstock supply from the forest biorefinery; an aromatic, amphiphilic molecular architecture uniquely suited for interaction with hydrophobic drug molecules; intrinsic antioxidant and UV-protective bioactivities that complement therapeutic function; and a rich functional group landscape that enables chemical modification and surface engineering. The diversity of fabrication methods available from simple solvent shifting to sophisticated hollow-particle templating and stimuli-responsive crosslinking provides a versatile toolbox for tailoring nanoparticle properties to the requirements of specific drugs and delivery routes (Mitchell et al., 2020).

The field has progressed substantially from early demonstrations of lignin nanoparticle formation to a state in which systematic studies of drug loading, controlled release, surface functionalization, and in vitro biological performance are routine. Proof-of-concept has been established for a wide range of cargo types, including anticancer agents, anti-inflammatory drugs, antimicrobials, antioxidants, and wound-healing payloads. The intrinsic pH responsiveness of many LNP formulations, enabling accelerated release under the acidic conditions of tumors and inflamed tissues, is a valuable feature that does not require additional synthetic modification.

However, an honest appraisal must acknowledge the substantial hurdles that remain. The heterogeneity of lignin, a consequence of feedstock variability and the inherent complexity of the macromolecule, poses a persistent challenge to reproducibility and standardization. In vivo evidence for therapeutic efficacy, pharmacokinetics, and safety is scarce. The biodegradation and elimination pathways of LNPs in mammalian systems are poorly understood. No regulatory pathway has been established for pharmaceutical products based on lignin nanocarriers, and the comprehensive preclinical safety data required for regulatory submission have not been generated. Sustainability claims, while directionally valid, require life-cycle assessment validation (Jiju et al., 2025).

Looking forward, the most promising near-term applications appear to be in oral delivery of poorly soluble nutraceuticals and topical or wound-healing formulations, where the regulatory requirements are less stringent and the intrinsic properties of lignin antioxidant activity, UV protection, and sustained release align closely with clinical needs. The longer-term aspiration of injectable, tumor-targeted lignin nanocarriers will require more rigorous preclinical development, scalable manufacturing, and regulatory engagement. The realization of this potential depends not only on scientific advances but also on interdisciplinary collaboration among forestry scientists, polymer chemists, pharmaceutical formulators, toxicologists, and regulatory strategists. If these challenges can be met, lignin nanoparticles may ultimately fulfill their promise as a

sustainable, multifunctional drug delivery platform rooted in the responsible utilization of the world's forest resources.

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