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GREEN NANOTECHNOLOGY IN DRUG DELIVERY: FROM SOLVENT-FREE SYSTEMS TO BIODEGRADABLE POLYMERS

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Abstract

Sustainable pharmaceutical manufacturing has brought green nanotechnology into closer focus as a practical route for improving drug delivery while reducing environmental burden. At the interface of green chemistry and nanomedicine, this approach seeks to limit hazardous reagents, reduce waste, and incorporate biodegradable materials without losing the therapeutic advantages associated with nanoscale carriers. This narrative review examines recent developments in green nanotechnology for drug delivery, concentrating on two closely related areas: solvent-free nanocarrier systems and biodegradable polymer-based formulations. Solvent-free methods, including melt emulsification, supercritical fluid processing, and melt electrospinning, provide cleaner alternatives to solvent-dependent fabrication and may simplify downstream processing. Biodegradable polymers, including poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), chitosan, and alginate, offer adaptable platforms for controlled release and degradation into comparatively safe by-products. The review also considers green fabrication strategies, pharmaceutical applications, regulatory expectations, and the barriers that continue to affect translation into industrial practice. Although issues related to scalability, reproducibility, cost, and regulatory harmonization remain unresolved, green nanotechnology offers a realistic framework for developing drug delivery systems that are clinically useful and environmentally responsible. Continued progress will depend on stronger evidence for safety, more scalable manufacturing routes, and clearer regulatory pathways.

Keywords: Green nanotechnology; Sustainable pharmaceutics; Solvent-free nanocarriers; Biodegradable polymers; Nanodrug delivery; Green synthesis; Regulatory harmonization.

1. Introduction

Nanotechnology has reshaped several areas of pharmaceutical development by improving drug targeting, increasing the apparent solubility of poorly water-soluble compounds, and supporting more controlled patterns of drug release. These gains have been particularly relevant in oncology, infectious diseases, and neurological disorders, where conventional formulations often face limitations in delivery efficiency or systemic toxicity (1,2). However, the benefits of nanomedicine have also raised a parallel concern: many established preparation methods still depend on organic solvents, high-energy processing, or materials that may persist in biological and environmental systems (1,2).

The environmental dimension of pharmaceutical nanotechnology is therefore no longer a secondary issue. Solvent residues, manufacturing waste, and exposure risks for production workers have become important considerations, especially as the pharmaceutical sector moves toward cleaner and more sustainable production models (2). At the same time, regulatory authorities and manufacturers are increasingly expected to justify not only product performance but also process safety and environmental responsibility.

Green nanotechnology responds to this need by applying green chemistry principles within nanoscience. Rather than treating sustainability as an additional requirement at the end of formulation development, it encourages safer material selection, reduced solvent use, improved energy efficiency, and the use of renewable or biodegradable components from the early stages of nanocarrier design (3,4). In this sense, the approach attempts to retain the therapeutic value of nanomedicine while reducing avoidable environmental and occupational hazards.

In drug delivery, two strategies have become especially relevant: solvent-free fabrication methods and biodegradable polymer-based delivery platforms. Solvent-free methods reduce or eliminate organic solvents during nanoparticle production, while biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), and poly(lactic-co-glycolic acid) (PLGA) allow carriers to degrade into non-toxic by-products after drug release (6,7). These strategies do not solve all translational barriers, but they provide a more sustainable basis for designing future nanomedicines.

This review provides a structured overview of green nanotechnology in drug delivery, with emphasis on solvent-free nanocarrier systems and biodegradable polymer platforms. It summarizes major principles, fabrication approaches, pharmaceutical applications, regulatory considerations, and current challenges related to scalability and clinical translation.

2. Methodology

This work was designed as a structured narrative review. The aim was to summarize recent evidence on green nanotechnology in drug delivery, with particular attention to solvent-free nanocarrier systems and biodegradable polymer-based delivery platforms. The review was not intended to be a formal systematic review or meta-analysis; instead, it sought to map relevant technologies, applications, and translational issues across the available literature.

2.1. Search Strategy

A literature search was conducted using PubMed, Scopus, and Web of Science. The search focused mainly on studies published between 2019 and 2025 in order to capture recent developments in sustainable drug delivery and green nanocarrier fabrication. Older references were included when they provided foundational concepts, such as established biodegradable polymers or green chemistry principles.

Search terms included combinations of the following keywords: “green nanotechnology”, “drug delivery”, “biodegradable polymers”, “solvent-free synthesis”, “nanocarriers”, and “sustainable pharmaceutical systems”. Boolean operators (AND, OR) were used to combine terms and refine the search results.

2.2. Inclusion and Exclusion Criteria

Articles were considered eligible when they were peer-reviewed, published in English, and directly related to green nanotechnology, pharmaceutical applications, solvent-free nanocarrier systems, or biodegradable polymers in drug delivery. Both original research articles and review papers were used when they contributed relevant mechanistic, formulation, regulatory, or translational information.

Studies were excluded when they were unrelated to pharmaceutical applications, lacked sufficient scientific detail, were not available in English, or were published only as conference abstracts, editorials, or opinion pieces.

2.3. Study Selection and Data Extraction

Titles and abstracts were first screened for relevance, followed by full-text evaluation of articles that matched the scope of the review. Information was extracted on the type of nanocarrier system, fabrication method, materials used, drug delivery application, reported advantages, and key limitations.

2.4. Data Synthesis

The extracted information was synthesized qualitatively and organized into two main themes: solvent-free nanocarrier systems and biodegradable polymer-based drug delivery systems. A narrative synthesis was used to compare technologies, identify recurring advantages and limitations, and highlight sustainability-related considerations such as environmental impact, process safety, and regulatory relevance (2,4).

3. Green Nanotechnology and Its Applications in Drug Delivery: Principles

3.1. Definition and Scope

Green nanotechnology is an interdisciplinary field that combines green chemistry with nanoscience to develop drug delivery systems with lower environmental and toxicological burden. In pharmaceutical applications, it focuses on nanocarriers that use safer materials, generate less waste, and maintain adequate product stability and therapeutic performance (4). The central idea is not simply to make nanoparticles smaller or more efficient, but to make their design and manufacture more responsible.

3.2. Renewable Feedstocks and Biogenic Synthesis

A key principle of green nanotechnology is the use of renewable and biologically derived materials during nanocarrier synthesis. Plant extracts, microorganisms, and naturally occurring biopolymers can replace some synthetic reagents and reduce dependence on hazardous chemical inputs. Chitosan, alginate, and cellulose derivatives are frequently used because they combine biodegradability, biocompatibility, and relatively sustainable sourcing (5).

Biogenic synthesis methods can reduce the use of toxic reagents and support more eco-compatible production. Their value, however, depends on reproducible material quality and process control, both of which remain important considerations for pharmaceutical manufacturing.

3.3. Solvent-Free and Energy-Efficient Techniques

Another core objective is to reduce or eliminate organic solvents during nanoparticle fabrication. Techniques such as supercritical fluid processing, microwave-assisted synthesis, and melt-based fabrication have attracted attention because they can reduce chemical waste and improve operator safety (6).

These methods may also improve control over particle size, morphology, and drug loading. Nevertheless, their practical value depends on balancing environmental benefits with energy requirements, equipment cost, and scalability.

3.4. Design for Degradation and Biodegradable Polymers

Design for degradation is essential in green nanocarrier development. Ideally, a carrier should perform its delivery function and then break down into products that are non-toxic and readily cleared from the body or environment. Biodegradable polymers are therefore central to many green drug delivery platforms.

Polylactic acid (PLA), polyglycolic acid (PGA), and poly(lactic-co-glycolic acid) (PLGA) are among the most established biodegradable polymers in pharmaceutical research and have well-documented safety profiles (7). Their degradation behavior can be tuned to support controlled drug release while reducing the risk of long-term accumulation.

3.5. Waste Prevention and Catalytic Efficiency

Waste prevention is closely linked to green chemistry concepts such as atom economy, catalytic efficiency, and improved material utilization. In nanocarrier synthesis, these principles encourage processes that produce fewer by-products and require fewer purification steps.

Closed-loop manufacturing, solvent recycling, and the use of recyclable or recoverable materials may further reduce environmental burden. These strategies are particularly relevant when green nanotechnology is translated from laboratory experiments to industrial-scale pharmaceutical production (8).

4. Solvent-Free Nanocarrier Systems

4.1. Overview

Solvent-free nanocarrier systems represent one of the most direct ways to reduce the environmental and safety concerns associated with conventional nanoparticle preparation. Many traditional methods require organic solvents that must later be removed, monitored, and controlled. Avoiding these solvents can reduce residual toxicity, simplify downstream processing, and improve the environmental profile of manufacturing (9).

From an industrial perspective, solvent-free technologies are attractive not only because they are cleaner, but also because they may reduce solvent-removal steps and associated validation requirements. However, each method still has its own technical constraints, especially with respect to equipment, energy input, and formulation compatibility.

4.2. Melt Emulsification and Solid Lipid Nanoparticles (SLNs)

Melt emulsification is a widely used solvent-free approach for preparing solid lipid nanoparticles (SLNs). In this method, the lipid phase is melted, the drug is incorporated into the molten lipid, and the mixture is dispersed into an aqueous surfactant phase using high shear or sonication. As the system cools, the lipid solidifies and forms nanoparticles that entrap the drug.

The method avoids organic solvents and therefore reduces risks linked to residual solvent contamination. SLNs also offer formulation advantages, including improved physical stability, controlled release, and enhanced bioavailability of poorly soluble drugs. The lipid matrix can protect sensitive compounds and can be modified at the surface to support targeted delivery.

Because the processing steps are relatively simple, melt emulsification is suitable for scale-up compared with several other nanoscale techniques. SLNs have been investigated for anticancer agents, antibiotics, peptides, and genetic materials, with potential use through oral, parenteral, and topical routes (10).

4.3. Supercritical Fluid-Based Techniques

Supercritical fluid technologies, particularly those using carbon dioxide (CO2), offer solvent-minimizing or solvent-free routes for nanoparticle production. Supercritical antisolvent (SAS) precipitation and rapid expansion of supercritical solutions (RESS) are two commonly discussed methods.

In SAS, a drug solution is introduced into a chamber containing supercritical CO2, which acts as an antisolvent and induces rapid precipitation. In RESS, the drug is dissolved in supercritical CO2 and then rapidly expanded through a nozzle, leading to particle formation. These techniques can provide control over particle size, morphology, and crystallinity while avoiding many conventional solvent-related problems.

Their relatively mild processing conditions make them useful for some heat-sensitive compounds, and the high purity of the resulting particles is attractive for pharmaceutical use. However, the need for specialized equipment and careful pressure control remains an important limitation for routine industrial adoption (11).

4.4. Solvent-Free Electrospinning

Solvent-free electrospinning, especially melt electrospinning, is used to produce nanofibrous drug delivery systems without residual organic solvents. A polymer is melted and extruded through a spinneret under an electric field, producing fine fibers as the jet cools and solidifies.

The absence of solvent residues is a major advantage for safety and regulatory acceptability. The resulting fibers have high surface area and porosity, which can support drug loading and controlled release. Melt electrospun systems have been explored in wound healing, transdermal delivery, and tissue engineering.

The main drawback is the need for elevated temperatures, which restricts the method to thermally stable polymers and drugs. For heat-labile active ingredients, additional formulation strategies or alternative solvent-free technologies may be required (12).

4.5. Solvent-Free Nanogels

Solvent-free nanogels are commonly prepared using aqueous crosslinking methods. These systems are often based on biocompatible polymers such as chitosan, alginate, gelatin, or polyethylene glycol derivatives, and they avoid the use of organic solvents during preparation.

Nanogels are attractive because of their high water content, soft structure, and responsiveness to physiological triggers such as pH, temperature, and enzymatic activity. These properties allow more localized or controlled release at the intended site of action.

Their mild preparation conditions make them suitable for sensitive biomolecules, including proteins, peptides, and nucleic acids. Reported applications include transdermal, ophthalmic, injectable, and tissue engineering-related delivery systems (13).

4.6. Benefits and Challenges

Overall, solvent-free nanocarrier systems reduce residual solvent toxicity, improve process safety, and support cleaner pharmaceutical production. They may also improve regulatory acceptability by reducing the need to control solvent residues. At the same time, they are not free from limitations. Supercritical fluid systems, melt processing, and advanced electrospinning methods can require expensive equipment, high technical expertise, or substantial energy input. These barriers need to be addressed before solvent-free approaches can become widely adopted in routine manufacturing.

5. Biodegradable Polymers for Nanodrug Delivery

5.1. Introduction to Biodegradable Polymers

Biodegradable polymers are important in green nanotechnology because they can degrade into by-products that are generally less persistent and more biologically acceptable than many non-degradable materials. This property reduces the likelihood of long-term accumulation and supports safer, more sustainable drug delivery design.

Common examples include PLA, PGA, PLGA, chitosan, and alginate. These polymers have been widely studied because of their favorable biocompatibility, tunable degradation rates, and compatibility with several drug delivery approaches (14).

5.2. Advantages in Drug Delivery

Biodegradable polymers offer several formulation advantages. Their biocompatibility can reduce the risk of severe immune responses, while their degradation behavior can be adjusted to provide sustained, delayed, or targeted release. This can help maintain drug concentrations within the therapeutic range and may reduce dosing frequency.

The surface of polymeric nanocarriers can also be modified with ligands or functional groups to improve tissue or cell selectivity. PLGA nanoparticles, for example, are frequently studied in tumor-targeted delivery because they can support controlled release and may benefit from the enhanced permeability and retention effect. Chitosan-based systems, by contrast, are often used for mucosal delivery because of their mucoadhesive behavior and ability to enhance drug absorption (15,16).

5.3. Green Synthesis Approaches

Biodegradable polymeric nanocarriers can be produced by conventional techniques such as emulsion-solvent evaporation, nanoprecipitation, and spray drying. Although these methods are effective, many depend on organic solvents and therefore raise safety and sustainability concerns.

Greener alternatives include aqueous nanoprecipitation, supercritical fluid-assisted processes, and solvent-free or solvent-minimized methods. Ionic gelation is another useful approach, particularly for natural polymers such as chitosan and alginate, where nanoparticles can be formed through crosslinking with multivalent ions in aqueous media.

These techniques can reduce hazardous waste while maintaining relevant formulation properties such as encapsulation efficiency, colloidal stability, and controlled release. Future improvements are likely to involve continuous processing and better integration of green chemistry principles into industrial nanomedicine (17).

5.4. Applications and Case Studies

Biodegradable polymer-based nanocarriers have been explored in oncology, vaccine delivery, gene therapy, and anti-inflammatory treatment. PLGA nanoparticles are commonly studied for the controlled delivery of chemotherapeutic agents, where improved localization and reduced systemic toxicity are desired.

Chitosan nanoparticles have shown value in nasal and mucosal vaccine delivery by improving mucosal uptake and immune response. Alginate-based systems have also been investigated for gastrointestinal delivery, including colon-targeted formulations.

Beyond conventional drug delivery, biodegradable carriers are being evaluated for nucleic acid delivery, where they can protect siRNA, plasmids, or other genetic materials from enzymatic degradation. In tissue engineering, similar platforms can provide controlled release of growth factors and other bioactive molecules (18-20).

5.5. Regulatory and Environmental Considerations

Biodegradable polymers are generally viewed favorably from regulatory and environmental perspectives, particularly when their degradation pathways and safety profiles are well understood. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved several polymer-based drug delivery systems, especially those involving PLGA and polyethylene glycol (PEG)-modified materials (21).

Nevertheless, regulatory acceptance requires careful characterization of polymer composition, degradation kinetics, impurities, drug-carrier interactions, and potential toxicity of degradation products. From an environmental standpoint, biodegradable polymers can reduce long-term persistence compared with non-degradable materials, but their overall sustainability still depends on production route, energy use, and end-of-life behavior.

For this reason, life cycle assessment (LCA) and green analytical methods are becoming increasingly important in evaluating the true environmental value of biodegradable nanocarriers (22).

6. Challenges and Future Perspectives

6.1. Regulatory, Toxicity, and Scale-Up Challenges

Despite the promise of green nanotechnology, several barriers continue to limit its wider implementation in drug delivery. A major issue is the lack of harmonized regulatory frameworks for nanotechnology-enabled pharmaceutical products. FDA and EMA guidance continues to evolve, particularly regarding classification, characterization, and safety evaluation of nanomedicines (23).

Differences in terminology, testing standards, and documentation requirements across regions complicate regulatory assessment and may delay market access. Nanomaterials also show properties that are not always captured by conventional toxicology models, including changes in surface charge, aggregation behavior, and biodistribution.

Toxicity remains another important concern. Although biodegradable nanocarriers are generally expected to be safer than persistent materials, their long-term biological effects are not fully established. Potential risks include tissue accumulation, immune activation, and unexpected interactions with biological systems. Comprehensive short- and long-term in vitro and in vivo studies are therefore needed (24).

Scalability and manufacturing cost represent additional barriers. Supercritical fluid processing, advanced electrospinning, and other green nanotechnology approaches often require specialized equipment and technical expertise. Maintaining particle size, drug loading, sterility, and batch-to-batch consistency during scale-up remains difficult and can increase production costs (25).

6.2. Clinical Translation and Commercialization

Clinical translation of green nanocarriers remains limited. Although preclinical studies often report promising results, relatively few systems have progressed to advanced clinical evaluation. This gap reflects the combined effect of limited clinical evidence, high development costs, and regulatory uncertainty.

Another difficulty is the translation of laboratory performance into predictable clinical outcomes. Patient variability, disease heterogeneity, and differences in biological barriers can substantially affect delivery efficiency. In addition, the lack of standardized evaluation methods reduces reproducibility and makes comparison across studies more difficult (26).

Economic considerations are equally important. Some green systems still require energy-intensive processing, complex purification, or expensive raw materials. For commercialization, sustainability must therefore be achieved together with cost-effectiveness, scalability, and regulatory compliance (27).

6.3. Future Directions in Research

Future research should move beyond proving that green nanocarriers can be prepared and should focus more strongly on reproducibility, safety, and scalable manufacturing. LCA can help identify environmental hotspots across the full production chain, from raw material sourcing to disposal (28).

Stimuli-responsive nanocarriers also remain a promising direction. Systems responsive to pH, temperature, enzymes, or redox conditions may improve site-specific release and reduce dosing frequency, provided that their safety and manufacturing reproducibility are adequately established (29).

Continuous manufacturing, flow chemistry, and 3D printing may further support greener scale-up by improving process control and reducing waste. These approaches could help bridge the gap between laboratory-scale innovation and industrial pharmaceutical production (30).

6.4. Policy Harmonization and Innovation

Wider adoption of green nanotechnology will require better alignment among regulatory frameworks. Harmonized guidance would improve consistency in safety assessment, product characterization, and international approval pathways.

Collaboration between academia, industry, and regulatory agencies is also essential. Multi-stakeholder platforms and international research networks can help address knowledge gaps and support regulatory science for nanotechnology-enabled products (31).

Ethical governance and public engagement should not be overlooked. Transparent communication about benefits, risks, and uncertainties can strengthen public trust and support the responsible integration of green nanotechnology into healthcare systems (32).

7. Conclusion

Green nanotechnology offers a useful framework for developing drug delivery systems that combine therapeutic performance with environmental responsibility. Solvent-free fabrication methods and biodegradable polymers provide practical routes for reducing solvent exposure, limiting persistent waste, and improving the sustainability profile of nanomedicine.

At the same time, the field still faces important barriers. Regulatory uncertainty, scale-up complexity, manufacturing cost, and incomplete long-term safety data continue to restrict clinical and industrial translation. Addressing these issues will require coordinated work among researchers, manufacturers, and regulatory authorities.

Future progress will depend on cost-effective manufacturing, stronger characterization methods, improved LCA integration, and the development of delivery systems that are both clinically meaningful and environmentally justified. With continued research and clearer regulatory pathways, green nanotechnology may contribute substantially to the next generation of safer and more sustainable pharmaceutical products.

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