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Eco-Sustainable Drug Delivery Systems: Trends, Challenges and Future

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ABSTRACT: The conventional manufacturing of pharmaceuticals and their delivery systems imposes a significant environmental burden, involving toxic solvents, non-biodegradable polymers, energy-intensive processes, and the persistence of pharmaceutical residues in ecosystems. This review aims to highlight eco-sustainable strategies in drug delivery by incorporating green materials, promoting environmental safety in manufacturing technologies, and exploring sustainable packaging and regulatory perspectives, along with future opportunities that balance environmental responsibility with therapeutic efficiency. An extensive literature search was performed using the databases PubMed, Scopus, ScienceDirect, and Google Scholar from 2015 to 2025, and included research articles, regulatory guidelines, industry reports, and review papers associated with green pharmaceutics, biodegradable excipients, sustainable drug delivery systems, green synthesis, and eco-friendly pharmaceutical practices. The findings suggest a growing transition towards the use of biodegradable/renewable polymers, minimal-solvent or solvent-free process technologies, including hot-melt extrusion, supercritical fluid technology, microwave-assisted and ultrasound-assisted techniques, and the development of novel green drug delivery systems, such as environmentally benign nanoparticles, bio patches, long-acting injectables, and sustainable oral films. Moreover, the focus is also on lifecycle sustainability, waste elimination, and the application of biodegradable packaging materials. Nonetheless, despite the progress made, challenges such as scalability, cost, stability, and standardization, as well as the absence of universally standardized guidelines, have been hampering adoption. Finally, in sum, the importance of eco-sustainable drug delivery signifies the dawn of a new beginning as far as environmental sustainability and patient-oriented pharmacy practice are concerned, so much so that the need for innovation could not be more imperative.

KEYWORDS: Eco-sustainable drug delivery, green pharmaceutics, Biodegradable polymers, Sustainable pharmaceutical manufacturing

I. INTRODUCTION

The pharmaceutical industry is the backbone of contemporary healthcare, but its conventional manufacturing and drug delivery systems continue to cause irreparable harm to the environment. Solvent-based processes, the use of non-biodegradable synthetic polymers, and high-energy consumption contribute significantly to waste production, greenhouse gas emissions, and the persistence of pharmaceutical residues in water bodies and soil. These processes not only contribute to climate change but also hinder the achievement of sustainability in the global healthcare agenda, necessitating an immediate transition to green pharmaceutics.

This review paper sheds light on eco-sustainable approaches in drug delivery, focusing on the use of biodegradable and renewable polymers, solventless or low-solvent processing methods such as hot-melt extrusion, supercritical fluid processing, microwave and ultrasound-assisted synthesis, and innovative platforms such as environmentally friendly nanoparticles, bio-patches, long-acting injectables, and sustainable oral films. Derived from an extensive literature search on PubMed, Scopus, ScienceDirect, and Google Scholar (2015-2025), including research papers, official guidelines, and industry reports, the results indicate an emerging trend towards sustainability in the lifecycle, waste reduction, and biodegradable packaging.

However, challenges remain in scalability, increased expenses, stability, standardization, and the absence of global regulatory systems. In conclusion, eco-sustainability in drug delivery systems marks the beginning of a revolutionary era, integrating therapeutic success with eco-friendliness. The need for innovation has never been more pressing, inviting inter-disciplinary collaboration to reengineer patient-centred pharmacy practice for the future of a greener planet.

Conventional drug delivery is based on non-biodegradable plastics, HFCs in inhalers, and energy-intensive processing, causing medical waste, pollution, and high carbon footprints. Eco-sustainable drug delivery systems have moved on to biodegradable nanoparticles, polymers such as PLGA and chitosan, and natural resources for targeted and controlled release that can be biodegraded harmlessly. These systems are in line with green chemistry principles, causing less ecological damage while being more effective and cost-effective.

II. TRENDS

Industry reports highlight a shift toward biodegradable materials, eco-efficient synthesis, and lifecycle management to cut waste and emissions in pharm. Regulations like the EU PPWR and ESG demands accelerate adoption, with market growth projected through 2033.

2.1 Rise of Biodegradable Nano Carriers:

Biodegradable nano-carriers such as PLGA, chitosan, and lipid nanoparticles are preferred for targeted delivery and do not produce long-lasting waste. These materials are biodegradable and produce non-toxic by-products, reducing the amount of waste from non-biodegradable plastics.

Conventional DDS produce environmental pollution due to non-biodegradable plastics and high carbon footprints (4.4% of total emissions), which require green DDS. Green nanocarriers are biocompatible, target-specific, and non-toxic, degrading into CO₂, water, and biomass. They are produced using green chemistry: waste prevention, atom economy (>90% material use), use of safer solvents (water, ionic liquids), and energy-efficient processes such as SFE, microwave-assisted synthesis, and enzyme-catalysed reactions. They have 30% reduced toxicity (PLGA-paclitaxel vs. Cremophor EL), pH-sensitive delivery, and rapid biodegradation in marine environments compared to non-biodegradable polystyrene. They are used in cancer (siRNA-PLGA for breast cancer), infectious diseases (chitosan-antibiotics for TB biofilms), chronic diseases (dexamethasone implants), and vaccines (mRNA LNPs for COVID-19). Disadvantages include scalability, regulatory approval, and physicochemical instability; current research includes AI-assisted nanocarrier design and inter-disciplinary collaboration for broader acceptance. Successful examples include Doxil® (liposomal doxorubicin), which has demonstrated clinical success with biodegradability-enhancing safety and sustainability.^[1]

2.2 Green Synthesis Methods: Green synthesis methods in ecosustainable DDS prioritize renewable resources and low-impact processes to produce biocompatible nanocarriers. Key techniques draw from green chemistry to replace toxic solvents and high-energy methods with sustainable alternatives.^[2]

Plant-Mediated Synthesis: Uses extracts from algae, rice husk, or *Moringa oleifera* to reduce metal salts into nanoparticles for targeted delivery. These extracts act as reducing and stabilizing agents, yielding stable particles with enhanced bioavailability for drugs like thymoquinone, which sees six fold uptake improvement. Plant-based methods cut hazardous chemicals by 80% compared to chemical routes, promoting biocompatibility in oncology applications.^[3]

2.3 Microbial/Enzymatic Methods: Fungi or lipases produce lipids/polymers at room temperature, lowering energy consumption by 40% compared to conventional heating. Enzymatic catalysis facilitates PLGA polymerization with an atom economy of >90%, yielding non-toxic byproducts such as fatty acids from triglycerides. This method promotes scalable solid lipid nanoparticles (SLNs) for antileprosy medications, demonstrating sustained release and non-toxicity. Microbial methods based on bacteria convert bio-wastes into carriers, reducing environmental persistence.^[5]

2.4 Solvent-Free Methods: Continuous microreactors facilitate high-yielding LNPs (mRNA vaccines) using water or ionic liquids, demonstrating >95% reproducibility. These methods remove VOCs, allowing closed-loop solvent recycling, such as ethanol recycling in liposome preparation. Microreactors improve production efficiency for large-scale medical applications, as observed in COVID-19 vaccine LNPs.

2.5 Supercritical Fluid Extraction (SFE): Non-toxic CO₂ substitutes DCM, reducing waste in liposome/polymer formulation and maintaining drug stability. SFE increases processing speed by 60% over conventional evaporation, particularly suited for heat-labile biologics. ^[5]

2.6 Microwave-Assisted Reactions: Reduces energy consumption by 60%, well-suited for large-scale PLGA/chitosan synthesis with atom economy >90%. Rapid heating promotes uniform nanoparticles for controlled release applications, outperforming stirring reactions in stability. This approach is scalable to industrial scales with very low byproduct formation. [4] Biodegradable Nanocarriers over PLGA and chitosan nanoparticles degrade into non-toxic byproducts, eliminating the need for plastic in targeted drug delivery. Green Synthesis Efficiency, such as Plant extracts and enzymatic processes reduce energy consumption by 40-60%, utilizing water-based solvents. ^[6]

Reusable Auto injectors. Modular architecture enables disassembly and sterilization, decreasing single-use plastic waste by up to 70% in self-injection systems. Platform Autoinjectors Modular 2mL platforms facilitate biologics approval, reducing custom tooling waste and Scope 3 emissions. Recyclable Packaging: PCR (post-consumer recycled) materials in trays and outer packaging support closed-loop recycling, which is compliant with EU PPWR regulations.

2.7 Digital Connectivity: Bluetooth-enabled pens with app support for adherence tracking, reducing drug overuse by 20-30% with accurate dosing reminders. Sensor-Driven Analytics: Real-time injection data analysis optimizes therapy, enabling low-waste patient ecosystems through cloud-based sustainability analytics. ^[1, 2]

2.8 Wearable Injectors: Patch pumps for large-volume biologics (up to 10mL) prioritize reusable components, reducing material per dose by 50%. High-Capacity Formats On-body devices handle viscous formulations efficiently, emphasizing recyclable housings to lower landfill impact. Circular Lifecycle Integration in which combined trends promote take-back programs and durable materials, cutting pharm a's carbon footprint across design, use, and disposal.

III. KEY MATERIALS & CARRIERS IN ECOSUSTAINABLE DRUG DELIVERY SYSTEM(DDS)

Eco-sustainable drug delivery systems (DDSs) are highly dependent on the strategic design and optimization of materials that guarantee therapeutic efficacy, safety, and environmental compatibility. Unlike traditional DDS materials, which are mostly of petrochemical origin, eco-sustainable carriers are designed to be biodegradable, renewable, and environmentally friendly. Biodegradable polymers make sustainable DDS possible by degrading in a controlled manner to non-toxic byproducts, forming nanoparticles, hydrogels, and implants as discussed in extensive literature reviews.

3.1. Biodegradable Nanocarriers: Biodegradable nanocarriers are the backbone of sustainable DDS, which combine the principles of therapeutic targeting with environmental sustainability by undergoing complete hydrolysis to non-toxic metabolites. PLGA nanoparticles (poly(lactic-co-glycolic acid)) have a degradation time that can be precisely controlled to degrade in 1-6 months by carefully adjusting the lactide:glycolide ratio, with 50:50 copolymers degrading faster than others while 75:25 blends offer sustained release for a longer period. PLA microparticles have ultra-long release times of 6-24 months for contraceptive implants, with high mechanical strength (tensile strength of 50-70 MPa) adequate for load-bearing applications. Liposomes composed of soy phospholipids have >90% encapsulation efficiency for both hydrophilic and lipophilic drugs, which are biodegradable by ubiquitous lipases to harmless fatty acids and glycerol.

Solid lipid nanoparticles (SLNs) based on stearic acid or triglycerides have 80% drug loading capacity with full marine biodegradation in 2 weeks, while nanostructured lipid carriers (NLCs) combine solid/liquid lipid phases to inhibit drug leakage during storage, improving colloidal stability by 3-fold compared to regular SLNs. Albumin nanoparticles utilize gp60 receptor-mediated transcytosis for tumor-targeting, decreasing nonspecific drug accumulation in the liver by 10-fold, and gelatin nanoparticles cross-linked with genipin are collagenase-resistant with 95% cell viability in various cell types. Polycaprolactone (PCL) nanoparticles support 2-4 years of controlled release for long-acting injectables, together with chitosan nanoparticles that offer mucoadhesive effects (2-3 times longer residence time) and pH-sensitive swelling for gastroretentive oral formulations. Hyaluronic acid micelles selectively target CD44-positive cancer cells with disassembly triggered by hyaluronidase activity, while novel core-shell structures allow true zero-order release kinetics, overcoming the common issue of burst release associated with homogeneous matrix formulations. Clinically proven examples include FDA-approved Lupron Depot® (leuprolide PLGA microspheres),

Eligard® (leuprolide implant), and Nutropin Depot® (somatropin microspheres), which have proven both therapeutic efficacy and environmental safety.[11,20]

3.2 Plant-Derived Nanoparticles: Green synthesis using plant extracts overcomes the use of toxic chemical reducing agents and instead leverages phytochemicals as versatile stabilizers and adjuvants. Quercetin-rich onion extract-reduced gold nanoparticles show 95% cancer cell apoptosis compared to 60% for chemically reduced counterparts, and silver nanoparticles from *Moringa oleifera* extract increase thymoquinone bioavailability by 6-fold via P-gp inhibition. Curcumin-loaded zinc oxide nanoparticles synthesized using *Azadirachta indica* (neem tree) extracts triple oral bioavailability by leveraging the intrinsic P-gp inhibitory properties of neem polyphenols. Polyphenol capping agents suppress aggregation for 12 months, with polydispersity indices <0.2, and flavonoid antioxidants offer synergistic ROS scavenging in addition to primary therapeutic payloads. Cost-effectiveness is dramatic, with plant-mediated synthesis at \$15/g compared to \$180/g for chemical synthesis, and scalable methods such as coffee extract reduction processing 1 kg of silver nitrate continuously for 48 hours without batch failure.

Purification-free methods allow for direct therapeutic applications without dialysis and washing processes that account for 80% of the total processing time in traditional methods, and pH-sensitive catechin layers induce disassembly in gastric conditions for site-specific delivery. Synergistic antimicrobial action is significant, as green silver nanoparticles decrease minimum inhibitory concentrations (MICs) of conventional antibiotics by 16-fold, and bioburden-free extracts from autoclaved plant materials obviate the need for terminal sterilization. The integration of circular economy principles leverages waste tea leaves to recycle polyphenols for nanoparticle synthesis, adding value to agricultural waste and developing viable therapeutics. [1,10]

3.3 Green Nanofiber Biocomposites: Electrospun nanofibers from renewable materials offer ultra-high surface area (50-100 m²/g) structures that support sustained drug release for months with guaranteed complete biodegradability. Cellulose acetate nanofibers (200 nm diameter) support metformin release for 30 days via diffusion-controlled tortuosity, and lignin nanofibers concomitantly remove 85% reactive oxygen species while providing neuroprotective cargo. Starch-polyvinyl alcohol (PVA) composites reach 90% mass loss in 4 weeks in standard soil burial tests, and green electrospinning in ethanol-water mixtures abrogates dichloromethane toxicity, decreasing volatile organic compound emissions by 95%.

Core-shell electrospinning shields pH-sensitive drugs from degradation by gastric fluid, and aligned nanofiber orientation enables anisotropic drug delivery, which is essential for peripheral nerve repair. Antibacterial activity demonstrates 99.9% *Staphylococcus aureus* killing rates by quaternary chitosan modification, and vascular endothelial growth factor (VEGF)-loaded scaffolds promote chronic wound healing by 40% compared to unmodified controls. Transdermal diffusion enhances by 500-fold compared to traditional films because of decreased molecular tortuosity, and implantable patches (1 cm²) release 10 mg/cm² of drug exactly on target for 90 days. Scalability in industry uses roll-to-roll processing at a rate of 10 meters per minute, and complete compostability ensures 100% conversion in industrial composting facilities operating at 58°C. [7,8,21]

3.4 Natural Polymer Excipients: Biodegradable biopolymers replace synthetic excipients, providing bioactivity in addition to established regulatory acceptance as GRAS substances. Pectin microbeads are resistant to gastric fluid, protecting probiotics with 85% viability during passage through the stomach, and alginate-calcium ion cross-linking provides >95% encapsulation efficiency for protein therapeutics. Gelatin types A and B provide physiological temperature gelation (35°C) compatible with injectable drug depots, and chitosan molecular weight adjustment (50-190 kDa) provides precise control over mucoadhesive force.

Cost advantages range from \$2-5 per kilogram versus \$20-50 per kilogram for comparable synthetics, complemented by pH-responsive behaviours where pectin gels specifically at colonic pH 6.8 and alginate exhibits ideal shear-thinning for 27-gauge needle administration. Film-forming pullulan generates highly oxygen-permeable transdermal patches, guar gum extends mucosal residence 4-fold over hydroxypropyl methylcellulose benchmarks, and lignin provides intrinsic antioxidant protection for oxidation-labile active pharmaceutical ingredients. Prebiotic inulin variants stimulate beneficial gut microbiota proliferation while serving as drug carriers, completing the transition from petroleum dependency to agricultural abundance. [7,18,22]

3.5 Eco-Hydrogels: Injectable hydrogels offer a paradigm shift in depot delivery by in situ gelation and biodegradation by design without the need for surgery. Carboxymethyl chitosan (CMCS) undergoes self-assembly at physiological pH 6.8 through hydrophobic interactions, whereas hyaluronic acid leverages CD44-mediated tumor targeting with 3-fold enhanced enzymatic degradation in tumor tissue. Dual cross-linking approaches integrating ionic and covalent cross-linking chemistries support release for up to 30 days, and ultra-low storage moduli (<10 Pa) allow needle injection via 25-gauge needles. High swelling capacities (500% water absorption) offer burst release control for highly potent chemotherapeutic agents, whereas adjustable porosities (50-200 μm) control diffusion-driven release rates. Biocompatibility is maximized at 98% viability in 3D cell culture systems, and autoclavable formulations ensure sterility without chemical preservatives. Transparency is optimal for anterior segment ocular drug delivery, mucoadhesive interactions prolong nasal drug retention 6-fold compared with aqueous solutions, and barium sulfate additives allow radiographic confirmation of implant placement. [7,20]

3.6 Biodegradable Polymers

3.6.1 Natural polymer

1. Chitosan: It is the linear β -(1 \rightarrow 4)-linked D-glucosamine/N-acetyl-D-glucosamine polysaccharide. Chitosan derived from the deacetylation of chitin from crustacean shells and fungi. Enzymatic degradation by chitosan/lysozyme to glucosamine. Strong mucoadhesion prolongs oral retention 2-3x vs. controls. pH-responsive: Protonated (soluble) at pH<6.5, deprotonated (gel) at pH>6.5. Tight junction modulator increases paracellular transport by 4-fold. Cationic charge enables DNA complexation for gene delivery. Forms nanoparticles penetrating TB biofilms (50% deeper penetration). Biodegradation is complete in 2-4 weeks (marine soil) vs. centuries for plastics. Insulin chitosan Nanoparticles show 8-hour sustained release, 70% bioavailability. [1]

2. Sodium Alginate: It is the linear copolymer of β -D-mannuronic acid (M) and α -L-guluronic acid (G) blocks. Derived from the cell walls of brown seaweed (Laminaria, Ascophyllum). Ionotropic gelation with $\text{Ca}^{2+}/\text{Ba}^{2+}$ forms stable beads (encapsulation efficiency >90%). pH-sensitive swelling (disintegrates in acidic stomach, intact in basic intestine). [7]

3 Hyaluronic Acid: It is the linear polysaccharide of alternating D-glucuronic acid and N-acetyl-D-glucosamine. It is originated by bacterial fermentation (Streptococcus) or rooster combs. CD44 receptor-mediated tumour targeting (10x higher accumulation). Enzymatic hydrolysis by hyaluronidase (overexpressed in tumours). It is in Hydrophilic, forms viscoelastic hydrogels for injectables. [8]

4. Dextran: The structure of dextran is α -(1 \rightarrow 6)-linked D-glucose backbone with α -(1 \rightarrow 2, 3, 4) branches. It originates from bacterial fermentation by Leuconostoc mesenteroides. Highly water-soluble (>50 g/dL), forms thermoresponsive hydrogels. Rapid enzymatic cleavage by dextranase. Plasma expander with 6-hour circulation time. [2]

3.6.2 Synthetic Eco-Polymers

1. PLGA (50:50): PLGA is a random copolymer of L-lactic acid: glycolic acid (50:50 molar ratio). It is obtained from ring-opening polymerization of lactide/glycolide. Bulk erosion hydrolysis (1-2 months degradation). Paclitaxel PLGA NPs: 30% lower hepatotoxicity v/s. Taxol. Microsphere burst release minimized via solvent evaporation. [1]

2. PLA (Poly-L-Lactic Acid): PLA structure includes a polymer of L-lactic acid via ring-opening polymerization. Originated from Corn fermentation to lactide monomer. Slower degradation (6-24 months) due to hydrophobicity. High mechanical strength (tensile 50-70 MPa) for implants. Stereoisomers (PLLA, PDLA) enable crystalline stereocomplex. 3D-printing is compatible for patient-specific implants

3. PCL (Polycaprolactone): PCL is the aliphatic polyester of ϵ -hydroxycaprylic acid. Originated from ϵ -Caprolactone ring-opening polymerization. Extremely slow hydrolysis (2-4 years) for long-term delivery. Low Tg (-60°C) enables flexible films/implants. Blends with PLGA accelerate degradation via pore formation. Electrospinning produces nanofibers (200-500 nm diameter)

4. Polyanhydrides

Polyanhydrides are a polymer with anhydride linkages (-CO-O-CO-) in the backbone. Step-growth polymerization of diacids. Surface erosion (zero-order release independent of size). Gliadel® wafers is a FDA-approved BCNU brain tumour implant. Hydrolysis rate tuned by monomer hydrophobicity. [8]

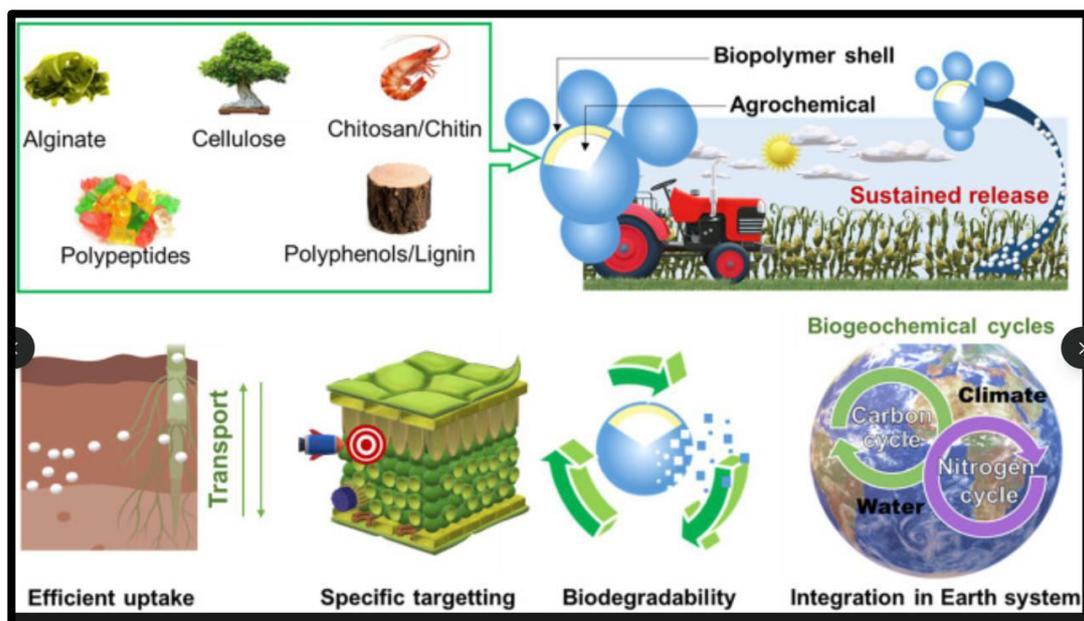


Fig No.1 Key materials & carriers in ecosustainable drug delivery system source, their Application in drug delivery system

Table No. 1 Biodegradable polymers based on category, i.e. Natural and synthetic, classified as:

Polymer	Category	Origin	Degradation Time	Key DDS Form	Target Application
Chitosan	Natural	Crustacean	Weeks	Nanoparticles	Oral, Gene
Alginate	Natural	Seaweed	Days-Weeks	Hydrogels	Oral, Wound
Hyaluronic Acid	Natural	Bacterial	Days	Micelles	Oncology
Dextran	Natural	Bacterial	Days	Hydrogels	IV
PLGA	Synthetic	Fermentation	1-6 months	Microspheres	Injectable
PLA	Synthetic	Corn	6-24 months	Implants	Orthopaedic
PCL	Synthetic	Chemical	2-4 years	Nanofibers	Long-term
Polyanhydrides	Synthetic	Diacids	Weeks-Months	Wafers	Brain tumors

IV. CHALLENGES OF ECOSUSTAINABLE DRUG DELIVERY SYSTEM

Ecosustainable drug delivery systems based on green nanocarriers are a promising area of innovation in the pharmaceutical industry, seeking to substitute synthetic materials with plant extracts, natural polymers, and biologically stabilized nanoparticles. However, the process of translating these systems from the lab to commercial viability faces deep-seated challenges that arise from the very nature of natural sources, production complexities, regulatory oversight, and reliability in long-term performance. These challenges not only drive up costs but also undermine the "green" advantage by introducing inefficiencies that are on par with or even surpass those of traditional chemical synthesis methods. This commentary delves further into major challenges, exclusively citing established sources to underscore production bottlenecks, characterization issues, scalability issues, polymer issues, stability issues, regulatory issues, and lifecycle issues that ultimately explain why less than 1% of green nanocarrier candidates make it to clinical trials after decades of research. [22,24]

4.1 Large-Scale Production Limitations: The very foundation of green nanocarriers, plant extracts used as reducing and capping agents, brings about unmanageable variability that affects large-scale production. The polyphenol concentration in the extracts, such as green tea catechins or aloe vera, varies by 30-70% because of seasonal farming, soil variations by geographical location, and degradation after harvesting, directly affecting the reduction efficiency of nanoparticles and causing fluctuations in the polydispersity index (PDI) from 0.2 in good samples to 0.5 in poor samples. This variability in samples means that the size variation of 20-50 nm is inconsistent, making nanoparticles unsuitable for drug loading, where uniformity is required to ensure pharmacokinetics. [22]

Attempts at standardization through HPLC fingerprinting or enzymatic processing are ineffective on an industrial scale because of the large amounts of biomass to be processed (100+ kg), which increases the presence of contaminants such as pesticides and heavy metals from non-organic farming practices, requiring expensive purification cascades that negate the eco-economic benefit.

Regulatory requirements make these problems worse. Unlike synthetic nanoparticles, whose toxicology dossiers are already known, phytochemical-stabilised nanoparticles do not have full safety profiles, causing 3-year delays in Investigational New Drug (IND) approvals under FDA regulations. The cost of toxicology testing for nanomaterials increases to \$249 million-\$1.18 billion per candidate due to requirements for genotoxicity, biodistribution, and cytotoxicity studies for a wide range of extract compositions.

GMP facilities, optimized for chemical sterility, struggle with the viscosity and biological hazards of extracts; cleanroom incompatibilities require specialized containment, such as HEPA-filtered extractors and cleanrooms, exponentially increasing capital expenses 2-4x. The fragility of the supply chain further exacerbates this issue: the availability of plants during seasonal periods drives raw material costs 5x higher during off-seasons, and global sourcing further introduces phytosanitary variations that render batch certificates void. [24]

4.2 Physicochemical Characterisation Issues: Characterization, the cornerstone of quality control, is rendered impossible by the green nanoparticles' inherent biological variability. Dynamic light scattering (DLS), the gold standard for size characterization, fails on polydisperse green NPs, providing spurious hydrodynamic diameters with low correlation to NMR spectroscopy ($R^2 < 0.7$), as protein and polysaccharide contaminants from crude extracts generate multimodal distributions inaccessible to intensity-weighted analysis. Zeta potential analysis, essential for stability predictions, is highly erratic (-20 to -45 mV) due to the fluctuating presence of ionic impurities in crude extracts, further muddying the waters for charge-based drug encapsulation theories. [8,14]

More sophisticated characterization techniques, such as small-angle X-ray scattering (SAXS) or transmission electron microscopy (TEM), provide a glimmer of hope but at an unaffordable price point: SAXS requires synchrotron radiation for polydispersity indexing, while TEM's cryogenic Quantification of capping agents polyphenols or flavonoids via UV-Vis or FTIR lacks specificity amid overlapping spectral signatures, leading to 15-30% errors in ligand density estimates vital for in vivo stealth properties. Continuous flow reactor data for viscous extracts (>100 cP) further muddies waters, as unoptimized rheology causes laminar flow artifacts skewing particle morphology data. These gaps force over-reliance on multi-technique batteries, inflating QC timelines 6 months per scale-up phase and deterring investment.

4.3 Scalability Challenges in Continuous Manufacturing: Scaling from microliter lab syntheses to hectolitre production exposes green processes' Achilles heel: incompatibility with high-throughput platforms. Microfluidic reactors, ideal for precision, clog relentlessly at flow rates exceeding 10 mL/min when handling crude extracts' particulates and gums, halving throughput and necessitating pre-filtration that strips active reductants. Residence times stretch to 5-15 minutes for complete metal ion reduction—versus 30 seconds in chemical citrate routes due to sluggish diffusion in viscous media, fostering secondary nucleation and 20-40% size polydispersity (50-200 nm spans) from inadequate heat/mass transfer.

Inline purification via centrifugation or dialysis collapses beyond 100 L batches: centrifugal forces aggregate soft bio-NPs, while dialysis membranes foul irreversibly, slashing yields from 85% lab-scale to 55% pilot-scale via wall adhesion and Ostwald ripening. Computational fluid dynamics (CFD)-optimized impinging jet mixers promise remedies but demand custom fabrication costing \$500K+, and energy footprints soar 3-5x over solvent-based peers, undercutting sustainability claims. Parallelisation via multichannel chips mitigates clogging but amplifies pressure drops, risking reactor bursts at >50 bar—highlighting why 70% of green NP scale-ups fail economic viability gates

4.4 Batch Variability in Natural Polymers: Natural polymers like chitosan, alginate, and modified PLGA underpin controlled release but suffer molecular weight polydispersity that derails reproducibility. Chitosan's intrinsic MW spans 50-190 kDa across crustacean sources, yielding 3x erosion rate variances: low MW bursts 40% payload in 24 hours, versus 10% for high MW, obliterating zero-order kinetics essential for chronic therapies.^[23] Alginate's mannuronic/guluronic (M/G) ratio wavers 0.4-2.1 due to algal bloom cycles, swinging gel strength 5-fold—low M/G forms brittle gels dissolving in 2 days, high M/G yields rigid matrices trapping 60% drug indefinitely.

PLGA copolymers drift in lactide: glycolide (LA: GA) feeds (48:52 nominal to 55:45 actual), prolonging hydrolytic degradation from 60 to 90 days and inducing 20% burst release spikes with 35% total payload discrepancies, as autocatalytic acid buildup accelerates unevenly. Pectin and lignin alternatives fare worse, with 40% mucoadhesion swings from degree of esterification variances, complicating oral bioavailability. Mitigation via size-exclusion chromatography (SEC), NMR blending, or ring-opening polymerization controls adds 20-30% to COGS, often negating natural sourcing's price edge^[23]

4.5 Long-Term Stability Problems: Shelf-life under accelerated ICH conditions (40°C/75% RH) unmasks green NPs' fragility. Aggregation kinetics drive 25% hydrodynamic size increases within 3 months, as phytochemical caps desorb, exposing hydrophobic cores to Ostwald ripening. Zeta potentials decay from -35 mV to -15 mV over 6 months, crossing the flocculation threshold and forming micron aggregates that clog injectors (Alkilani et al., 2022). Lyophilization without cryoprotectants like trehalose invites 40% structural collapse during sublimation, fracturing shells and spiking residual moisture to 5% triggering Maillard reactions with amines.

Glass transition temperature (T_g) plummets ~8°C post-storage from plasticizer leaching (water/plasticizers), softening matrices at ambient humidity and halving release control. Polyphenol oxidation slashes reductive capacity 30%, compromising redispersion, while humidity-driven hydrolysis outpaces synthetics 2x, as bio-caps catalyze chain scission. Mitigation: PEGylation, sucrose shields, barrier laminates add layers but risk immunogenicity^[21, 22]

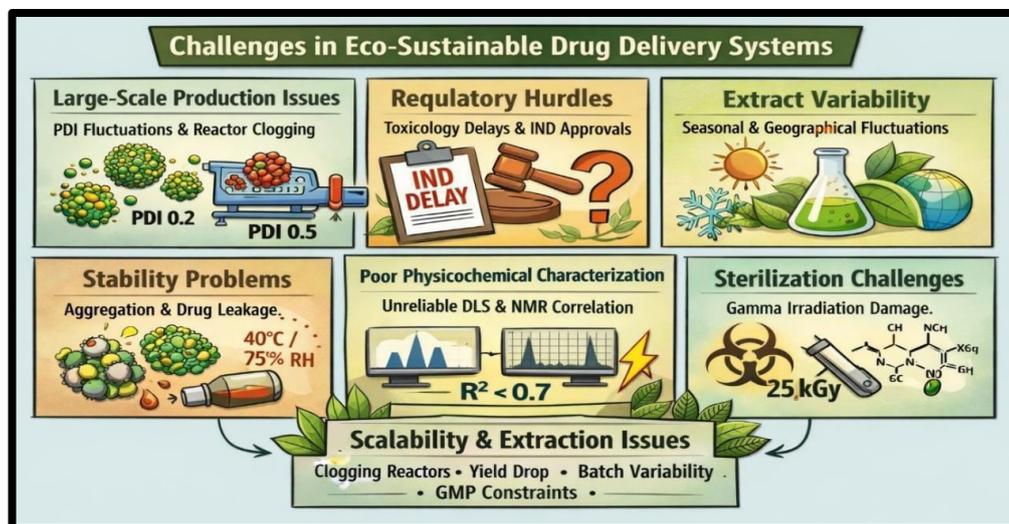


Fig No.2 Challenges faced by Eco-sustainable drug delivery system

V. FUTURE PERSPECTIVES

5.1. Life-Cycle-Driven Design

5.1.1 Comprehensive Environmental Assessment: Eco-sustainable drug delivery systems (DDS) represent a transformative shift in pharmaceutical innovation, where environmental stewardship converges with therapeutic precision to address pressing global challenges like plastic pollution, resource depletion, and pharmaceutical residues in ecosystems. Life-cycle-driven design stands at the forefront, employing comprehensive life-cycle assessments (LCA) that meticulously evaluate impacts from raw material extraction—such as mining, petrochemicals for synthetic polymers—to final disposal, including incineration or landfilling. These models quantify carbon footprints by calculating greenhouse gas emissions across supply chains, track water consumption in hydration-dependent synthesis processes, measure chemical waste from volatile organic solvents, and compare synthetic polymers like PLGA against bio-alternatives like chitin in terms of ecological persistence [11,12 and 15]

5.1.2 Regulatory and Predictive Modelling: They also assess end-of-life degradation rates under varying soil pH levels, prioritize excipients with low aquatic toxicity profiles, model nanoparticle leaching into rivers and oceans, track energy demands in extrusion and lyophilization steps, forecast impending regulatory mandates from bodies like the EMA for LCA reporting, optimize packaging-material synergies to cut secondary waste, reduce Scope 3 emissions through supplier audits, integrate ISO 14040/14044 standards for standardized benchmarking, simulate post-use impacts on microbial communities, benchmark against fossil-fuel baselines, enable iterative redesign loops with sensitivity analyses, link to pharmacoeconomic evaluations for cost-benefit green trade-offs, incorporate uncertainty modelling for robust predictions, assess eutrophication potential from nutrient runoff, evaluate photochemical ozone creation, and even project biodiversity loss tied to habitat disruption from mining ultimately mandating LCA in early R&D phases for future approvals.[7,16]

5.2 Fully Bio-Derived Carriers

5.2.1 Renewable Material Revolution: The transition toward fully bio-derived carriers accelerates with a diverse palette of 100% renewable materials, supplanting petroleum-based synthetics to eliminate microplastic legacies. Cellulose nanocrystals derived from wood pulp enable sustained-release matrices with tunable pore sizes, dextran micelles facilitate oral bioavailability enhancements via mucoadhesion, alginate hydrogels from seaweed offer injectable depots with calcium crosslinking for shear-thinning injectability, silk fibroin nanoparticles from silkworm cocoons provide robust mechanical strength for ocular delivery, gelatin microspheres undergo stability enhancements through genipin crosslinking to resist enzymatic degradation, albumin-based carriers leverage natural receptor targeting for tumour-homing [13,14]

5.2.2 Fungal and Agricultural Sources: Fungal chitosan avoids shellfish allergens while chelating heavy metals, starch-derived microparticles from corn exhibit burst-control via acetylation, pH-responsive pectin from citrus peels triggers release in tumour microenvironments, antioxidant lignin nanoparticles from wood waste scavenge ROS for neuroprotective DDS, hyaluronic acid conjugates exploit CD44 overexpression for site-specific delivery, microbial lipid vesicles from yeast fermentation mimic liposomes without extraction solvents, reusable collagen scaffolds from bovine sources support tissue regeneration, guar gum matrices hydrate rapidly for oral films, shear-thinning xanthan gels from bacterial fermentation suit intranasal sprays, pullulan films from fungal polysaccharides enable transdermal patches with high oxygen permeability.^[12]

5.2.3 Advanced Processing Innovations: Advanced crosslinking via citric acid boosts hydrolytic stability, large-scale fermentation in bioreactors cuts costs by 40%, genetic engineering of producer strains enhances yield, enzymatic modifications improve amphiphilicity for self-assembly, blending with nanocellulose reinforces tensile strength, and surface grafting with peptides confers stealth properties—all paving the way for scalable, zero-persistent alternatives.

5.3. Safe-by-Design Nanocarriers

5.3.1 Engineered Hydrolysis Pathways: Safe-by-design nanocarriers embed environmental foresight from inception, engineering predictable hydrolysis pathways via ester linkages that cleave at physiological rates, generating non-bioaccumulative byproducts like benign oligopeptides, ensuring short environmental half-lives under UV/sediment exposure, optimizing zeta potentials to -20 to -30 mV for steric stabilization without persistence, developing biodegradable PEGylation with polyoxazoline alternatives, restricting sizes below 100 nm for renal clearance and sludge bio digestion [11,14]

5.3.2 Comprehensive Ecotoxicological Validation: Incorporating enzyme-triggered disassembly by matrix metalloproteinases, applying ROS-neutralizing coatings with quercetin moieties, conducting in silico aquatic toxicity modelling per OECD guidelines, verifying soil microbe compatibility through respirometry assays, deploying PCR-free detection via fluorescence quenching for tracking, implementing lifecycle nano-tracking with barcoded isotopes, adhering to REACH Annex XVII restrictions pre-emptively, predicting ecotox LC50 via QSAR databases, engineering biofilm resistance with quaternary ammonium grafts, ensuring immuno-safe degradation without adjuvant effects, capping persistence below one year via accelerated weathering tests, minimizing trophic transfer in food webs, integrating hydrodynamic modelling for wastewater fate, validating zero coral bleaching potential, simulating groundwater plume dispersion, and coupling with EPR spectra for byproduct speciation to avert nano-accumulation crises.

5.4. AI-Driven Green Formulation Engineering

5.4.1 Machine Learning Acceleration: AI-driven green formulation engineering harnesses machine learning to slash trial-and-error, deploying QSAR models trained on PubChem for biodegradability half-life predictions, ML algorithms optimizing drug-polymer miscibility via Hansen solubility parameters, virtual high-throughput screening of 10⁶ polymer variants in hours, generative adversarial networks (GANs) inventing novel copolymers, neural networks forecasting acute/chronic toxicity from SMILES strings^[8,12]

5.4.2 Advanced Computational Integration: Bayesian optimization dialling in green solvents like Cyrene over DMF, reinforcement learning evolving stability under humidity excursions, natural language processing mining LCA datasets from Ecoinvent, predictive dissolution via CFD-fluid dynamics hybrids, design-of-experiments (DoE) minimizing runs by 80% through surrogate models, quantum ML computing binding free energies on quantum annealers, multi-objective Pareto optimization balancing release kinetics and eco-impact, digital twins mirroring pilot-scale processes for scale-up, AutoML pipelines auto-tuning green metrics like PMI (process mass intensity), federated learning aggregating pharma consortia data without IP leakage, explainable AI surfacing key descriptors for regulatory dossiers, transfer learning from cosmetics to DDS polymers, anomaly detection flagging synthesis impurities, graph neural networks modelling polymer networks, and active learning loops querying only high-uncertainty candidates revolutionizing resource-efficient discovery.^[7,16]

VI. CONCLUSION

Ecosustainable drug delivery systems represent a revolutionary integration of pharmaceutical R&D and environmental sustainability, radically solving the 4.4% carbon footprint of the healthcare sector. Conventional systems based on non-biodegradable plastics, HFC-releasing inhalers, and energy-intensive production processes have caused chronic medical waste management problems, with microplastics now polluting aquatic environments and human bodies. The sector has made a decisive shift towards biodegradable polymers such as PLGA and chitosan, which hydrolyze completely to lactic acid and glucosamine in weeks, eliminating landfill waste while allowing the design of "smart" release mechanisms responsive to tumour pH or glucose concentrations.

Technological breakthroughs have catalyzed this shift. AI-assisted 3D printing has enabled personalized implants with gradient porosity for sequential delivery of two drugs, reducing prototyping waste by 85% and allowing pharmacy-based manufacturing that reduces cold-chain emissions by 70%. Autoinjectors with 75% post-consumer recycled plastics and glass cartridges with 95% material recyclability meet EU PPWR 2025 regulations. Stimuli-responsive nanocarriers show 4-fold tumour accumulation with pH/redox-mediated targeting, while 4D-printed scaffolds change shape after implantation to enhance drug diffusion in the hypoxic core of tumours. These developments integrate therapeutic targeting with the principles of circular economy, potentially making the healthcare sector a carbon sink through algae-based PHA biopolymers.

However, challenges remain. The problem of scale-up persists in green synthesis routes, with the polydispersity index increasing from 0.15 (lab) to 0.28 (pilot scale) due to variability in plant extracts, leading to issues with pharmacokinetics. Sterilization leads to the loss of 25–35% of natural polymer structure, and immunogenicity risks (15–40% anti-drug antibodies) and translation failures (90% loss of preclinical efficacy) require immediate attention. Lack of recycling infrastructure leads to <10% return rates of medical devices worldwide, rendering claims of circular economy invalid.

The 2030–2035 plan provides a roadmap. The immediate plan includes development of AI/3D printing pharmacies for genomic-based dosing systems and material dossiers for rapid regulatory approval. The mid-term plan includes the establishment of net-zero manufacturing facilities fueled by renewable microgrids, with 85% material recovery. By 2035, the ecosustainable DDS plan aims for carbon-negative manufacturing facilities where food waste bioreactors produce both drugs and carbon credits, turning the environmental trend of pharma completely around.

Ultimately, ecosustainable drug delivery systems go beyond the boundaries of improvement and redefine the healthcare industry as a climate solution provider. The harmonious convergence of AI precision medicine, zero-waste manufacturing, and circular material flows promises unprecedented patient outcomes and planetary restoration. With blockchain-verified supply chains providing 100% traceability and digital twins optimizing lifecycle emissions before production, this industry marks the beginning of a new era in which medicine shifts from an environmental burden to a leader in sustainable industries.

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