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Green Pharmaceutics: Eco-friendly Approaches in Dosage-Form Design — A Review

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Abstract

Pharmaceuticals play an essential role in healthcare but also contribute to environmental burdens throughout their life cycle — from raw material extraction and synthesis to formulation, packaging, distribution, use, and disposal. *Green pharmaceutics* integrates green chemistry, sustainable materials, energy-efficient manufacturing, and life-cycle thinking into dosage-form design to minimize environmental impacts while maintaining safety, efficacy, and regulatory compliance. This review synthesizes recent advances (chemical/process strategies, green excipients and biodegradable carriers, solvent-minimizing and solvent-free techniques, supercritical CO_2, continuous manufacturing, life-cycle assessment (LCA) methodologies), regulatory initiatives, and case studies. We identify current gaps and propose a roadmap for accelerating greener dosage-form development.

Keywords

Green pharmaceutics, sustainable formulation, biodegradable excipients, supercritical CO_2, life-cycle assessment, continuous manufacturing, solventless processing

Introduction

Pharmaceuticals deliver enormous public-health benefits but — like any large, technology-intensive industry — also create measurable environmental impacts across the product life cycle. These impacts arise not only from the active pharmaceutical ingredient (API) itself (manufacturing emissions, solvent use, energy intensity of synthesis), but also from formulation and dosage-form production, packaging, cold chain and distribution, patient use (and excretion), and end-of-life management (waste, persistence in aquatic environments). Growing evidence that many APIs and formulation residues persist in surface waters and that pharmaceutical manufacturing is solvent- and energy-intensive has spurred interest in systematic strategies to reduce environmental burdens while preserving therapeutic performance. The GREENER framework — which maps greener choices across discovery, development and manufacture — is an example of how the sector is beginning to operationalize this shift

"Green pharmaceutics" sits at the intersection of green chemistry, process intensification, sustainable materials science, and life-cycle thinking. At the chemical level it adopts classic green chemistry tenets (prevent waste, maximize atom economy, prefer catalytic routes, minimize hazardous reagents and solvents) and applies them to API synthesis and downstream formulation. At the unit-operation level it emphasizes process changes that reduce solvent consumption and energy demand — for example, solvent-free techniques (hot-melt extrusion, direct compression), use of safer solvents and solvent-recycling, and supercritical CO_2 ($scCO_2$)-assisted particle engineering and impregnation processes. At the systems level it embraces continuous manufacturing, in-line process analytical technology (PAT), and supply-chain measures (light-weight/mono-material packaging, decentralized manufacturing) that collectively shrink material use, waste, and greenhouse gas (GHG) intensity per effective therapeutic dose. Recent comparative life-cycle assessment (LCA) studies show that choices made during formulation and packaging can materially change a product's overall environmental footprint, and that LCA is therefore an essential decision-support tool for green pharmaceutics.

Material substitution is a central strategy for greener dosage forms. Replacing traditional synthetic, non-biodegradable excipients or multi-component packaging with responsibly sourced, bio-based or biodegradable polymers (e.g., PLA, PCL, PHAs, chitosan, cellulose derivatives) can reduce reliance on fossil feedstocks and reduce persistent microplastic burden — but such substitutions require careful evaluation. Bio-based does not automatically mean lower overall impact: feedstock cultivation, land use, processing energy and end-

of-life behavior must be included in a full LCA to avoid burden shifting. Moreover, biopolymers frequently have different thermal/mechanical properties and moisture sensitivities that affect manufacturability and stability; thus formulation redesign, process optimization, and sometimes new regulatory data are required.

Process technologies that concretely reduce solvent inventories and emissions are high-impact levers. Supercritical CO_2 techniques have matured for extraction, particle formation (e.g., RESS, GAS, SAS variants) and polymer impregnation; they can dramatically reduce or eliminate organic solvent use, often producing particles with favorable size and morphology for improved bioavailability. Nevertheless, $scCO_2$ systems demand high-pressure equipment and careful energy accounting — the net environmental benefit depends on specifics of solvent substitution, equipment life, and energy source. Similarly, solventless and low-solvent formulation approaches (hot-melt extrusion, spray-drying with low solvent load, melt granulation) reduce volatile organic compound emissions and often simplify solvent-recovery logistics.

Continuous manufacturing (CM) — integrated, steady-state production for solid oral dosage and increasingly for other modalities — provides multiple sustainability advantages: reduced material transfer losses, smaller facility footprints, fewer batch changeovers, lower rework rates through PAT-enabled control, and potential energy savings per unit product. Implemented carefully, CM has been shown to reduce waste and GHG emissions versus conventional batch routes in several techno-economic and LCA studies, and major industry/regulatory bodies are actively supporting CM deployment. Still, realization of environmental benefits depends on facility design, energy source decarbonization, and process intensification choices.

Finally, greener formulation design must be evidence-based. Life-cycle assessment provides the quantitative backbone to compare alternatives (e.g., polymer A vs B; solvent route vs $scCO_2$; batch vs continuous) on multiple environmental indicators (global warming potential, water use, human toxicity, eutrophication). However, limitations remain: data gaps for many excipients and unit operations, inconsistent system boundaries across studies, and limited inclusion of downstream fate and ecotoxicology for novel excipients and nanocarriers. Overcoming these gaps — via shared LCA inventories, standardized biodegradability testing under realistic environmental conditions, and cross-stakeholder collaboration — is essential if green pharmaceutics is to move from concept to routine practice.

2. Principles and framework of green pharmaceutics

Green pharmaceutics draws on Green Chemistry's 12 principles (atom economy, safer solvents, waste prevention, energy efficiency, renewable feedstocks, design for degradation, etc.) and extends them across product life cycles using tools such as QbD (Quality by Design) and LCA to identify environmental hotspots and optimize trade-offs between performance and sustainability. Key components of the framework:

- **Design for degradation:** choose APIs/excipients and formulation strategies that reduce environmental persistence where clinically feasible.
- **Safer solvent and material selection:** prefer low-toxicity, low-VOC, and recyclable solvents or solvent-free methods.
- **Process intensification and energy efficiency:** continuous processing, microwave/ultrasound assistance, and reduced temperature/pressure steps.
- **Life-cycle thinking:** apply LCA early to guide material and process choices and quantify trade-offs.

3. Green excipients and biodegradable carriers

Replacing petrochemical/non-biodegradable excipients with **bio-based and biodegradable polymers** (e.g., polylactic acid [PLA], polycaprolactone [PCL], cellulose derivatives from renewable sources, alginates, chitosan) has been widely studied. These materials can reduce packaging and microplastic burden and support controlled-release designs, but their sourcing, processing footprint, and end-of-life behavior must be assessed. Recent reviews document advances and commercialization barriers for biodegradable excipients and green nanocarriers.

Practical notes:

- Biopolymers often require different processing conditions (temperature, shear) and compatibilizers.
- Biodegradability in lab conditions does not always translate to rapid environmental degradation—LCA and ecotoxicology data are necessary.

4. Solvent minimization and alternative solvents

Solvents are major contributors to pharmaceutical environmental burden. Strategies include:

- **Solvent substitution:** replace hazardous solvents (chlorinated solvents, high-boiling ethers) with greener alternatives based on solvent selection guides and metrics (toxicity, GWP, VOC, recyclability).

- **Solvent minimization/solvent-free processes:** hot-melt extrusion, melt granulation, direct compression, and spray-drying with reduced solvent loads. These eliminate or greatly reduce organic solvent emissions in formulation steps.

- **Supercritical CO_2 ($scCO_2$):** $scCO_2$ is a powerful green solvent for extraction, particle engineering (e.g., rapid expansion of supercritical solutions, RESS), and solvent-free impregnation/degassing techniques; it reduces organic solvent use and enables cleaner processes, though high capital and compression energy must be considered.

5. Process innovations: continuous manufacturing & process intensification

Continuous manufacturing (CM) replaces batch processes to reduce material losses, energy use, and variability. CM enables smaller footprints, fewer changeovers, and in-line monitoring (PAT), which reduces rework and resource waste. Combined with QbD and PAT, CM supports greener production by improving yields and minimizing rejects. Several LCAs show CM can lower environmental impacts versus traditional batches, though benefits depend on energy sources and scale.

6. Particle engineering and energy-efficient technologies

Advanced particle engineering (nanosuspensions, supercritical assisted processes, spray freeze drying) can improve API bioavailability and reduce dose strength — potentially lowering material use and environmental burden per therapeutic effect. Energy-efficient drying (vacuum drying, optimized spray-drying) and adoption of alternative energy sources also contribute to sustainability. When assessing these technologies, compare energy inputs and secondary impacts (e.g., solvent recycling needs).

7. Packaging, distribution and end-of-life

Packaging is a significant contributor to lifecycle impacts. Approaches include lightweighting, mono-materials for recycling, biodegradable packaging materials for appropriate applications, and reduction of over-packaging. Cold-chain optimization and decentralized manufacturing (point-of-care or localized fills/3D printing) can reduce transport emissions. Importantly, packaging decisions must also preserve product integrity and shelf life.

8. Life-Cycle Assessment (LCA) for dosage forms

LCA provides a quantitative method to compare environmental impacts across a product's entire life cycle and identify hotspots (solvents, energy, packaging). Recent reviews and case studies emphasize the need for standardized LCA methodologies specific to pharmaceuticals and for including downstream impacts (use phase, excretion, environmental fate). Limitations include data availability, allocation rules for multi-product facilities, and regional energy grid differences. Nevertheless, LCA is essential for evidence-based decisions in green formulation design.

9. Regulatory landscape, incentives, and standards

Regulatory agencies and policy bodies are increasingly encouraging sustainable practices: guidelines on emissions, solvent residues, and waste management exist, and environmental risk assessments (ERAs) are part of approval in some jurisdictions. Some recent policy analyses outline incentives and barriers for deploying greener pharmaceuticals, while pushing for stronger LCA-based labels or procurement criteria in healthcare systems. Industry initiatives and public procurement (healthcare systems prioritizing low-carbon pharmaceuticals) can accelerate uptake.

10. Case studies & examples (selected)

- **Supercritical CO_2 in particle engineering & extraction:** demonstrated reductions in organic solvent use for natural-product extraction and certain particle formation processes, with commercial deployment in specific niches.

- **Continuous manufacturing for solid oral dose forms:** pilot and commercial examples show decreased waste, faster scale up, and improved yields — LCAs frequently report GHG reductions per unit product in well-implemented CM setups.

- **Biodegradable polymer carriers:** successful research prototypes for controlled-release implants and microparticulate systems using PLA/PCL and chitosan; commercial translation is active but constrained by regulatory and cost factors.

11. Metrics and decision tools for greener formulation choices

To operationalize green pharmaceutics, combine metrics: mass intensity (kg input per kg API), solvent-use intensity, energy per batch, LCA endpoint metrics (GWP, eutrophication, human toxicity), and regulatory compliance indicators. Decision frameworks should integrate clinical benefit (therapeutic efficiency) so that sustainability improvements are assessed on a per-effective-dose basis. Tools and solvent selection guides developed for green chemistry can be adapted for formulation teams.

12. Challenges and knowledge gaps

- **Data scarcity for LCAs** at the formulation and excipient level, especially for emerging bio-based materials.
- **Economic and regulatory barriers**: higher up-front capital costs (e.g., $scCO_2$ or CM equipment) and limited regulatory clarity for novel excipients or biodegradable packaging.
- **End-of-life uncertainty**: biodegradability claims lack standardization across environments (compost vs. marine vs. soil).
- **Potential trade-offs:** e.g., a bio-based excipient might have lower fossil carbon but higher land-use impacts; hence multidimensional assessment is needed.

13. Roadmap & recommendations for stakeholders

For formulators and industry R&D

- Apply LCA and green metrics early in candidate selection.
- Prioritize solventless or low-solvent processes where feasible (hot-melt, direct compression, supercritical processes).
- Pilot continuous manufacturing and PAT to reduce rework and improve material efficiency.

For regulators & policymakers

- Provide clearer pathways for approval of novel green excipients and standardized biodegradability test methods.
- Encourage transparency of environmental performance via procurement incentives and guidance documents.

For researchers & academia

- Develop open LCA inventories for excipients and unit processes.
- Study environmental fate and ecotoxicology of novel excipients and nano-carriers.

14. Future perspectives

Advances in green chemistry, computational design (predicting environmental fate and process impacts), AI-driven optimization of formulations, and modular localized manufacturing (e.g., 3D printing for personalized doses) will further enable lower-impact dosage forms. Cross-sector collaboration (academia, industry, regulators, healthcare purchasers) and harmonized metrics are crucial to mainstream green pharmaceutics. Continued investment in LCA databases and eco-toxicological testing will reduce uncertainty and facilitate evidence-based choices.

15. Conclusions

Green pharmaceutics is an actionable, multidisciplinary field that integrates green chemistry, process engineering, materials science, and life-cycle thinking into dosage form design. While technical and regulatory challenges remain, the combined use of greener excipients, solvent-minimizing technologies (including $scCO_2$), continuous manufacturing, and LCA-guided decision making can

substantially reduce the environmental footprint of pharmaceuticals without compromising patient care. Strategic policy incentives and open data sharing will accelerate adoption.

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