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Development of stable nanosuspensions: A strategy to improve the aqueous solubility of drugs

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Abstract

Poor aqueous and lipophilic solubility remains a significant bottleneck in pharmaceutical development. Nanosuspensions address this challenge by stabilizing submicron drug particles within a liquid phase using biocompatible surfactants or polymeric matrices. Lowering particle size into the nanometre range dramatically expands total surface area, driving higher dissolution kinetics and boosting systemic bioavailability. Formulation approaches generally fall into top-down mechanical attrition (such as high-pressure homogenization and media milling) or bottom-up molecular precipitation. Hybrid approaches like Nanoedge technology merge precipitation with homogenization to yield sub-micron systems with high physical stability and minimal crystal growth. Beyond oral administration, nanosuspensions facilitate non-invasive and targeted delivery across parenteral, pulmonary, ocular, and transdermal routes, including targeted delivery across the blood–brain barrier. Key quality attributes—such as particle size distribution, active content, encapsulation efficiency, and saturation solubility—are systematically evaluated to ensure performance. Overall, nanosuspensions represent a scalable, robust platform for delivering poorly soluble active pharmaceutical ingredients (APIs).

Keywords: Nanosuspensions; Homogenization; Precipitation; Dissocubes; Co-grinding; Stability

1. Introduction

Nanosuspensions are biphasic colloidal dispersions containing sub-micron drug particles suspended in an aqueous or non-aqueous continuous phase, stabilized by amphiphilic surfactants or polymers (1). These systems can incorporate inert polymeric matrix carriers to optimize physical stability (1). By overcoming dissolution rate-limited absorption, nanosuspensions substantially raise the rate and extent of systemic drug exposure.

A variety of fabrication methodologies exist, classified into:

- **Top-down processes:** Media milling, high-pressure homogenization (e.g., DissoCubes, Nanopure), and combined hybrid strategies (e.g., Nanoedge) (2).
- **Bottom-up processes:** Antisolvent precipitation techniques (2).

Formulating hydrophobic and lipophobic drugs into nano-sized suspensions improves their intrinsic dissolution rates, enabling rapid peak plasma concentrations following oral or parenteral administration.

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2. Ingredients used in formulation of nanosuspensions

- **Stabilizers:** Prevent particle growth via Ostwald ripening and steric/electrostatic aggregation (e.g., lecithin, povidone derivatives) (2).
- **Cosurfactants:** Modify interfacial tension and phase behavior in microemulsion-templated processes (e.g., bile salts, short-chain alcohols) (2).
- **Organic Solvents:** Facilitate initial drug solubilization in precipitation methods (e.g., ethyl acetate, benzyl alcohol) (2).
- **Functional Excipients:** Regulate tonicity, pH, and physical integrity based on the target route of delivery (e.g., osmotic agents, buffers, polyols) (2).

2.1. Advantages of nanosuspensions

- **Economical Processing:** Cost-effective formulation compared to complex lipid nanocarriers (2).
- **Biocompatibility:** Reduced local tissue irritation due to reduced surfactant burden (2).
- **Physical Stability:** Superior physical robustness compared to soft nanostructures like liposomes (2).
- **Enhanced Bioavailability:** Marked improvement in the dissolution profile of Class II and IV (BCS) drugs (2).

3. Categories and classification of nanosuspensions

3.1. Based on Carrier Integration

- **Carrier-Free Nanosuspensions:** Consist solely of pure crystalline/amorphous drug particles coated by stabilizing agents.
- **Carrier-Based Nanosuspensions:** Sub-micron drug particles encapsulated or embedded within polymeric matrices or solid lipid nanoparticles.

3.2. Based on Homogenization Environment

- **Aqueous Phase Homogenization (DissoCubes):** Cavitation and shear forces are generated in an aqueous continuous phase.
- **Nonaqueous Phase Homogenization (Nanopure):** Processing occurs in non-aqueous or low-water media to prevent hydrolytic degradation.
- **Hybrid Technology (Nanoedge):** Combines controlled precipitation with rapid high-pressure shearing to refine particle size and prevent recrystallization.

3.3. Based on Route of Administration

- Oral, Parenteral (IV/IM), Ophthalmic, Pulmonary/Inhalation, and Transdermal/Topical systems.

3.4. Based on Stabilizing Architecture

- **Surfactant-Dominant:** Non-ionic or ionic agents (e.g., polysorbates, saponins).
- **Polymer-Dominant:** Steric stabilization matrices (e.g., HPMC, PVA, methacrylate copolymers).
- **Dual/Binary Systems:** Synergistic polymer-surfactant combinations.

4. Preparation methods

4.1. Bottom-Up Techniques (Precipitation)

Bottom-up processing constructs nanostructures starting from molecular solutions. The active drug is dissolved in an organic solvent, which is subsequently introduced into an immiscible or miscible anti-solvent. Rapid supersaturation triggers nucleation and crystallization. Stabilizers must be introduced promptly to control crystal growth and prevent micro-particle aggregation (3).

- **Pros:** Low capital investment and straightforward processing setup (3).
- **Cons:** Requires dual solubility parameters (high solvent solubility vs. low anti-solvent solubility) (3).

4.2. Top-Down Techniques (Size Reduction)

Particle size reduction is achieved through mechanical stress, shear, and attrition (3).

4.2.1.High-Pressure Homogenization (DissoCubes)

DissoCubes utilize piston-gap homogenizers operating at extreme hydraulic pressures (100–1,500 bar for industrial scale; up to 2,000 bar for R&D scale). A coarse pre-dispersion of the API is forced through a narrow orifice gap, generating intense cavitation, shear forces, and impact stresses that fragment drug crystals (3).

- **Pros:** Zero media-wear contamination; highly suited for parenteral drug products.
- **Cons:** High capital equipment costs and pre-milling requirement.

4.2.2.Wet Media Milling

In media milling, coarse drug suspensions are processed in a grinding chamber containing beads (e.g., polystyrene resin or ceramic pearls) driven by a high-shear agitator (3). Operational modes include batch or continuous recirculation. Typical residence times (30–60 minutes) yield narrow size distributions below 200 nm (3).

- **Pros:** Highly scalable and versatile across variable batch sizes (3).
- **Cons:** Potential batch contamination from bead erosion (mitigated using durable cross-linked polystyrene beads with residual monomers <50 ppb and wear debris <0.005% w/w) (3).

4.2.3.Combined Precipitation and Homogenization (Nanoedge)

Nanoedge technology mitigates crystal growth issues inherent in standard precipitation. An initial antisolvent precipitation step creates fragile crystalline nuclei, which are immediately subjected to high-shear homogenization. The process prevents Ostwald ripening and yields narrow, sub-micron particle distributions (3).

4.2.4.Dry Co-Grinding

Dry co-milling involves subjecting active drug crystals to high mechanical shear alongside hydrophilic polymers (e.g., PVP, PEG, HPMC, cyclodextrins) without liquid solvents. Mechanochemical energy alters the crystal lattice, shifting the drug toward an amorphous state with enhanced surface wettability and rapid dispersion properties upon aqueous contact (4).

5. Evaluation parameters

- **Particle Size Distribution:** Measured via dynamic light scattering (DLS) or digital optical microscopy to confirm mean droplet/particle size and polydispersity index (PDI) (5).
- **Total Drug Content:** Evaluated by dissolving a known aliquot of nanosuspension in a suitable solvent (e.g., methanol) followed by spectrophotometric analysis at the characteristic wavelength 238nm (5).
- **Entrapment / Inclusion Efficiency:** Unbound drug in the continuous phase is separated via centrifugation (e.g., 1,000 rpm for 10 minutes). The supernatant is analyzed via UV spectroscopy to quantify unencapsulated drug using a standard expression (5).
- **Saturation Solubility:** Samples are spun at high speed (e.g., 10,000 rpm for 10 minutes) to isolate the saturated phase, which is measured spectrophotometrically to quantify maximum solubility improvements compared to unprocessed drug (5).
- **Accelerated Stability Testing:** Formulations are stored under ICH-accelerated conditions 40°C ± 2°C and 75% ± 5% RH over 30 days. Physical integrity, chemical degradation, particle size shift, and entrapment changes are re-evaluated post-storage (5).

6. Clinical applications

- **Oral Administration:** Significantly boosts absorption kinetics for low-solubility drugs like atovaquone, bupravaquone, naproxen, and danazol (2).
- **Parenteral Administration:** Enables targeted tissue accumulation (e.g., clofazimine targeting pulmonary and splenic tissue) and eliminates toxic solubilizing surfactants (2).
- **Pulmonary Delivery:** Enables uniform aerosolization via nebulization for targeted lung deposition of hydrophobic drugs (e.g., budesonide) (2).
- **Ocular Delivery:** Increases precorneal residence time and bioavailability in the conjunctival sac (e.g., anti-inflammatory ocular suspensions of ibuprofen).
- **Topical Formulations:** Boosts saturation solubility on the stratum corneum, driving dermal penetration without systemic over-exposure.
- **Targeted Systems:** Allows surface-modified nanocarriers to cross specialized biological barriers, such as the blood–brain barrier, using scalable manufacturing protocols (3).
- **Bioavailability Enhancement:** Solves BCS Class II/IV limitations by synchronously driving dissolution rates and biological membrane permeation (e.g., oleanolic acid) (3).

7. Conclusion

In conclusion, nanosuspensions represent a highly effective and versatile formulation strategy to address the long-standing challenge of poor aqueous and lipophilic solubility in pharmaceutical development. By reducing active pharmaceutical ingredient (API) particles to the sub-micron range, this technology dramatically amplifies the total surface area, thereby driving rapid dissolution kinetics and significantly boosting systemic bioavailability. Whether manufactured through mechanical top-down attrition like high-pressure homogenization and media milling, or bottom-up molecular precipitation, each methodology offers distinct manufacturing advantages that can be tailored to the specific physicochemical properties of the drug. Hybrid techniques, such as Nanoedge technology, further bridge these approaches to yield systems with exceptional physical stability while successfully mitigating the risks of crystal growth and Ostwald ripening.

Furthermore, the integration of targeted stabilizers and functional excipients ensures that these colloidal dispersions remain robust against aggregation and local tissue irritation, outperforming traditional soft nanostructures. Beyond traditional oral delivery, the clinical adaptability of nanosuspensions extends across multiple specialized administration routes, including parenteral, pulmonary, ocular, and transdermal pathways, even facilitating targeted transport across complex biological barriers like the blood–brain barrier. Rigorous evaluation of critical quality attributes—ranging from particle size distribution to saturation solubility and accelerated stability testing—guarantees the reproducible performance of these systems under real-world conditions. Ultimately, nanosuspensions emerge as an economically viable, highly scalable, and robust platform that holds the potential to unlock the therapeutic value of previously challenging Biopharmaceutics Classification System (BCS) Class II and IV drug candidates.

Compliance with ethical standards

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Disclosure of conflict of interest

I, Simran, declare no conflicts of interest, financial or otherwise, with any institution, organization, or product mentioned in this manuscript. There are no commercial or personal affiliations that could influence the outcomes or discussion presented in this review article

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