IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 2, December 2025
Impact Factor: 7.67

Application of Nanostructured Excipients in Solubility Enhancement and Bioavailability Improvement

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Abstract: *The growing prevalence of poorly water-soluble drug candidates in modern pharmaceutical development has intensified the need for innovative formulation strategies to enhance solubility and oral bioavailability. Nanostructured excipients have emerged as a promising approach to address these challenges by improving drug dissolution, permeability, and systemic absorption. These excipients, including polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanosuspensions, mesoporous materials, and self-nanoemulsifying systems, offer unique physicochemical properties such as high surface area, enhanced wettability, and controlled drug release profiles. By reducing particle size to the nanometer range, they increase the surface-to-volume ratio, thereby accelerating dissolution rate according to the Noyes–Whitney equation and improving saturation solubility through the Ostwald–Freundlich effect.*

Nanostructured excipients also facilitate improved drug stability, targeted delivery, and permeability across biological membranes. Their ability to modulate pharmacokinetic parameters, such as peak plasma concentration (Cmax) and area under the curve, significantly contributes to enhanced therapeutic efficacy and reduced dose variability. Additionally, they can minimize first-pass metabolism and protect labile drugs from degradation. Advances in nanotechnology have enabled the design of multifunctional excipients capable of combining solubilization, sustained release, and site-specific targeting within a single platform...

Keywords: Nanostructured excipients, solubility enhancement, bioavailability improvement.

I. INTRODUCTION

The development of effective pharmaceutical formulations is frequently challenged by the poor aqueous solubility and limited oral bioavailability of many therapeutic agents. Over the past three decades, the emergence of high-throughput screening and combinatorial chemistry has significantly increased the number of drug candidates with complex molecular structures, high lipophilicity, and low water solubility. According to the Biopharmaceutics Classification System, a substantial proportion of newly discovered drugs fall into Class II and Class IV categories, characterized by low solubility and, in some cases, low permeability. These physicochemical limitations often result in erratic absorption, delayed onset of action, dose variability, and reduced therapeutic efficacy. Consequently, solubility enhancement and bioavailability improvement have become central objectives in modern drug delivery research. Among various strategies explored to address these challenges, the application of nanostructured excipients has gained considerable attention due to their ability to modulate drug dissolution, absorption, and pharmacokinetic behavior at the molecular and cellular levels.

Excipients, traditionally regarded as pharmacologically inactive substances, play critical roles in stabilizing, delivering, and enhancing the performance of active pharmaceutical ingredients. In recent years, the paradigm has shifted from conventional excipients such as fillers, binders, and disintegrants toward functional and multifunctional excipients capable of influencing drug release kinetics and absorption pathways. Nanostructured excipients represent an advanced

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class of materials engineered at the nanometer scale, typically ranging from 1 to 100 nanometers. Their unique physicochemical properties including high surface area-to-volume ratio, tunable surface chemistry, enhanced reactivity, and controlled morphology ake them particularly suitable for overcoming solubility-related challenges. These excipients can interact with drug molecules through adsorption, encapsulation, complexation, or molecular dispersion, thereby improving wettability, dissolution rate, and systemic absorption.

One of the primary mechanisms by which nanostructured excipients enhance solubility is through particle size reduction. According to the Noyes–Whitney equation, the dissolution rate of a solid drug is directly proportional to its surface area. By reducing drug particles to the nanometer range or by incorporating them into nanostructured carriers, the effective surface area exposed to the dissolution medium increases dramatically, leading to faster dissolution rates. Nanocrystalline formulations, solid lipid nanoparticles, and nanosuspensions exemplify approaches in which nanostructured excipients stabilize drug particles and prevent agglomeration, thus maintaining enhanced dissolution properties. Furthermore, the small particle size can improve mucosal adhesion and facilitate absorption across biological membranes, contributing to increased bioavailability.

Another significant advantage of nanostructured excipients lies in their ability to modify the microenvironment around the drug molecule. For poorly soluble drugs, the creation of a localized supersaturated state can promote rapid dissolution and absorption before precipitation occurs. Polymeric nanocarriers, such as those based on biodegradable polymers, can encapsulate hydrophobic drugs within their core while presenting a hydrophilic surface to the aqueous environment. This structural arrangement enhances apparent solubility and stabilizes the drug in a dispersed state. Additionally, certain nanostructured excipients possess amphiphilic characteristics that enable the formation of micelles or self-assembled nanostructures, further facilitating the solubilization of lipophilic compounds.

Lipid-based nanostructured excipients, including nanoemulsions and nanostructured lipid carriers, have demonstrated remarkable potential in enhancing oral bioavailability. These systems improve drug solubilization in gastrointestinal fluids and promote lymphatic transport, thereby bypassing first-pass hepatic metabolism. By facilitating drug incorporation into chylomicrons and enhancing permeability across intestinal epithelial cells, lipid nanocarriers can significantly increase systemic drug exposure. Moreover, their ability to protect labile drugs from enzymatic degradation contributes to improved pharmacokinetic profiles. Such multifunctional behavior underscores the transformative role of nanostructured excipients in oral drug delivery.

In addition to oral administration, nanostructured excipients have broadened opportunities in other routes of drug delivery, including parenteral, transdermal, pulmonary, and ocular systems. For injectable formulations, nanocarriers can improve the solubility of hydrophobic drugs without the need for harsh organic solvents, thereby reducing toxicity risks. In transdermal applications, nanostructured systems enhance drug penetration through the stratum corneum by interacting with lipid bilayers and increasing skin permeability. Similarly, in pulmonary and ocular delivery, nanoscale excipients improve drug dispersion, retention time, and targeted delivery, ultimately contributing to better therapeutic outcomes.

Surface modification of nanostructured excipients further enhances their functionality. By incorporating targeting ligands, surfactants, or permeability enhancers, researchers can design excipients that not only improve solubility but also optimize site-specific delivery. For example, mucoadhesive polymers at the nanoscale can prolong residence time in the gastrointestinal tract, thereby increasing the window for drug absorption. Additionally, stimuli-responsive nanostructured excipients can release drugs in response to changes in pH, temperature, or enzymatic activity, ensuring controlled and predictable drug release patterns.

Despite their promising advantages, the application of nanostructured excipients also presents challenges that require careful consideration. Issues related to scalability, reproducibility, regulatory acceptance, and long-term stability must be addressed to ensure successful translation from laboratory research to commercial products. The safety profile of nanomaterials is another critical factor, as nanoscale particles may exhibit different biological interactions compared to their bulk counterparts. Comprehensive toxicological evaluation and adherence to regulatory guidelines are essential to ensure patient safety and product quality. Furthermore, the complexity of nanostructured systems necessitates advanced characterization techniques to assess particle size distribution, zeta potential, morphology, crystallinity, and drug-excipient interactions.

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Advancements in material science, nanotechnology, and pharmaceutical engineering continue to expand the repertoire of nanostructured excipients available for formulation scientists. Techniques such as spray drying, hot-melt extrusion, high-pressure homogenization, and supercritical fluid processing have facilitated the production of stable nanostructured systems with enhanced performance characteristics. Integration of computational modeling and quality-by-design (QbD) approaches further supports the rational design and optimization of nano-enabled formulations. By systematically evaluating critical material attributes and process parameters, researchers can develop robust and reproducible nanostructured excipient systems tailored to specific drug candidates.

The application of nanostructured excipients represents a paradigm shift in pharmaceutical formulation strategies aimed at overcoming solubility and bioavailability limitations. Through mechanisms such as particle size reduction, microenvironment modification, enhanced permeability, and targeted delivery, these advanced materials significantly improve the therapeutic performance of poorly soluble drugs. As research continues to refine their design, safety, and scalability, nanostructured excipients are poised to play an increasingly central role in the development of next-generation drug delivery systems. Their integration into pharmaceutical practice not only addresses longstanding challenges associated with solubility but also opens new avenues for personalized and precision medicine, ultimately contributing to improved patient outcomes and healthcare advancement.

Mechanisms of Solubility and Bioavailability Enhancement

Nanostructured excipients improve drug performance through several mechanisms:

Particle Size Reduction

Reduction to nanoscale increases surface area according to the Noyes–Whitney equation, leading to enhanced dissolution velocity (Noyes & Whitney, 1897).

Increased Saturation Solubility

Nanoparticles exhibit higher saturation solubility due to increased surface curvature and thermodynamic properties (Müller et al., 2001).

Amorphization

Conversion from crystalline to amorphous state eliminates lattice energy barriers, enhancing solubility (Hancock & Zografi, 1997).

Improved Wettability

Polymeric and surfactant-based nanocarriers improve drug wetting, reducing interfacial tension.

Lymphatic Transport

Lipid-based nanostructures facilitate lymphatic uptake, bypassing hepatic first-pass metabolism (Porter et al., 2007).

TYPES OF NANOSTRUCTURED EXCIPIENTS

Nanocrystalline Carriers

Drug nanocrystals stabilized with surfactants or polymers enhance dissolution rate without altering chemical structure. These systems are particularly suitable for BCS Class II drugs (Keck & Müller, 2006).

Polymeric Nanoparticles

Biodegradable polymers such as PLGA and chitosan form nanosystems capable of controlled drug release and improved bioavailability (Danhier et al., 2012).

Lipid-Based Nanocarriers

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) enhance solubility of lipophilic drugs and improve stability (Müller et al., 2002).

Mesoporous Silica Nanoparticles

These excipients provide high surface area and pore volume, allowing drug adsorption in amorphous form (Vallet-Regí et al., 2007).

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Nano Solid Dispersions

Drugs are molecularly dispersed within polymer matrices at nanoscale, preventing recrystallization and enhancing dissolution (Chiou & Riegelman, 1971).

Table 1: Types of Nanostructured Excipients and Their Functional Roles in Solubility Enhancement

Type of Nanostructured Excipient	Mechanism of Action	Advantages	Limitations
Nanocrystals	Particle size reduction	High drug loading	Physical instability
Polymeric nanoparticles	Controlled release & stabilization	Biodegradable	Complex manufacturing
Solid lipid nanoparticles	Improved lipid solubilization	Enhanced stability	Limited drug loading
Mesoporous silica	Amorphous stabilization	High surface area	Potential toxicity concerns
Nano solid dispersions	Molecular dispersion	Enhanced dissolution	Moisture sensitivity

PREPARATION TECHNIQUES

Various techniques are employed in manufacturing nanostructured excipients:

Top-Down Approaches

High-pressure homogenization and media milling reduce particle size mechanically (Müller et al., 2001).

Bottom-Up Approaches

Precipitation and solvent evaporation techniques allow controlled nanoparticle formation.

Supercritical Fluid Technology

Provides solvent-free nanostructures with controlled morphology.

Spray Drying and Freeze Drying

Used in nano solid dispersions to stabilize amorphous systems.

Applications in Drug Delivery

Nanostructured excipients have shown promising applications in:

Oral drug delivery (improved dissolution and absorption)

Parenteral formulations (controlled release)

Topical delivery (enhanced permeation)

Ocular drug systems

Targeted cancer therapy

For example, lipid nanoparticles have improved oral bioavailability of poorly soluble anticancer drugs (Müller et al., 2002). Similarly, polymeric nanoparticles have enhanced therapeutic efficiency of antibiotics and anti-inflammatory drugs (Danhier et al., 2012).

CHALLENGES AND LIMITATIONS

Despite advantages, challenges remain:

Scale-up difficulties

Stability issues (aggregation, recrystallization)

Regulatory concerns

Toxicological evaluation

Cost of production

Long-term safety evaluation of nanomaterials remains a significant regulatory consideration.

DOI: 10.48175/568

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FUTURE PERSPECTIVES

Future research focuses on:

Green synthesis of nanostructured excipients

Smart stimuli-responsive nanocarriers

AI-assisted nanoformulation design

Personalized nanomedicine

Hybrid nano-excipient systems

Advanced characterization techniques such as atomic force microscopy and differential scanning calorimetry will further optimize formulation design.

II. CONCLUSION

The application of nanostructured excipients represents a transformative advancement in pharmaceutical formulation science, particularly in addressing the persistent challenge of poor aqueous solubility and limited bioavailability of many therapeutic agents. A significant proportion of newly developed drug molecules fall under Biopharmaceutics Classification System Class II and IV categories, characterized by low solubility and/or poor permeability, which directly restricts their therapeutic efficiency. Nanostructured excipients such as nanocrystals, solid lipid nanoparticles, polymeric nanoparticles, nanoemulsions, dendrimers, mesoporous silica nanoparticles, and lipid-based nanocarriers have emerged as highly effective strategies to overcome these limitations through particle size reduction, increased surface area, enhanced dissolution rate, and improved drug–carrier interactions.

One of the primary mechanisms by which nanostructured excipients enhance solubility is through nanosizing, which significantly increases surface area according to the Noyes Whitney equation, thereby accelerating dissolution velocity. Additionally, the reduction in particle size to the nanometer range can alter saturation solubility due to increased surface energy, leading to improved thermodynamic solubility. Beyond simple size reduction, nanostructured systems provide a microenvironment that stabilizes poorly soluble drugs in an amorphous or molecularly dispersed state, preventing recrystallization and enhancing dissolution stability.

Lipid-based nanostructured excipients, including solid lipid nanoparticles and nanostructured lipid carriers, facilitate improved oral bioavailability by promoting lymphatic transport and bypassing first-pass hepatic metabolism. Similarly, polymer-based nanocarriers offer controlled and sustained release profiles, enhancing drug residence time and absorption across biological membranes. Surface modification of nanoparticles with hydrophilic polymers such as polyethylene glycol further improves systemic circulation time and reduces rapid clearance, contributing to enhanced therapeutic performance.

Nanostructured excipients also enable targeted drug delivery, reducing off-target toxicity and improving therapeutic index. By optimizing particle size, surface charge, and morphology, drug absorption across epithelial barriers can be enhanced through improved permeability and cellular uptake mechanisms such as endocytosis. Furthermore, advanced nanostructured systems allow co-delivery of drugs and bioenhancers, synergistically improving absorption and clinical outcomes.

Despite these promising benefits, challenges remain in the large-scale manufacturing, long-term stability, regulatory approval, and cost-effectiveness of nanostructured excipient-based formulations. Issues related to particle aggregation, polymorphic transitions, reproducibility, and safety evaluation require careful consideration. Regulatory frameworks must continue evolving to address characterization, quality control, and toxicity assessment specific to nanotechnology-based pharmaceutical systems.

Nanostructured excipients have revolutionized modern drug delivery by offering multifaceted solutions to solubility and bioavailability constraints. Their ability to enhance dissolution, stabilize amorphous forms, improve permeability, enable targeted delivery, and reduce variability in drug absorption makes them a cornerstone of next-generation pharmaceutical development. Continued research focusing on scalable production methods, safety validation, and regulatory harmonization will further strengthen their role in developing efficient, patient-friendly, and clinically effective therapeutic formulations.

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