



Pharmaceutical Formulation Strategies for Poorly Soluble Drugs: Advanced Techniques for Solubility Enhancement, Bioavailability Optimization, and Controlled Drug Delivery

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Abstract

The bioavailability of orally administered drugs is frequently limited by poor aqueous solubility, a major challenge in modern drug development. A significant proportion of new chemical entities and many existing drugs exhibit low solubility, leading to insufficient dissolution, erratic absorption, and suboptimal therapeutic efficacy. This article comprehensively reviews advanced formulation strategies designed to overcome these critical biopharmaceutical hurdles. The primary aim is to detail the scientific principles, manufacturing considerations, and clinical applications of key enabling technologies. These include amorphous solid dispersions, nanosuspensions, lipid-based delivery systems, and cyclodextrin inclusion complexes. Each strategy employs distinct mechanisms to enhance apparent solubility, dissolution rate, and subsequent absorption, such as particle size reduction, generation of high-energy amorphous states, solubilization within lipid matrices, and molecular complexation. The discussion extends to the stabilization of these systems and their role in enabling controlled and targeted drug delivery. While these technologies have successfully brought numerous poorly soluble drugs to market, challenges in physical stability, scalable manufacturing, and regulatory pathways persist. The future outlook points toward the integration of nanotechnology, intelligent stimuli-responsive carriers, and artificial intelligence in formulation design, paving the way for more predictable development and personalized therapeutic interventions. This review underscores the transformative impact of advanced formulation science on translating challenging drug candidates into viable and effective medicines.

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Introduction

Oral administration remains the most preferred and patient-compliant route for drug delivery, owing to its convenience, cost-effectiveness, and non-invasiveness. For a drug to be effective after oral ingestion, it must dissolve in the gastrointestinal fluids before it can permeate the intestinal membrane and enter systemic circulation. Consequently, aqueous solubility and dissolution rate are fundamental physicochemical properties that dictate the rate and extent of drug absorption, directly influencing bioavailability and therapeutic outcome. The advent of combinatorial chemistry and high-throughput screening has led to a pipeline increasingly populated by lipophilic, highly permeable molecules with intrinsically poor aqueous solubility. It is estimated that up to 90% of new chemical entities in discovery pipelines and approximately 40% of marketed oral drugs are

classified as poorly soluble (Williams *et al.*, 2013; Savjani *et al.*, 2012) ^[1, 2]. This presents a formidable challenge, as poor solubility can lead to low and variable bioavailability, necessitating higher and more frequent dosing, which in turn increases the risk of side effects and reduces patient adherence (Kawabata *et al.*, 2011) ^[4].

The inherent limitations of conventional formulation approaches, such as salt formation or micronization, are often insufficient for modern drug candidates with extremely low solubility (Serajuddin, 1999) ^[21]. This has spurred the development of advanced, engineered formulation strategies that go beyond simple particle size reduction (Brough and Williams, 2013; Kalepu and Nekkanti, 2016) ^[16, 20]. These strategies aim to alter the drug's thermodynamic activity, increase its surface area, or maintain it in a high-energy state to dramatically improve dissolution kinetics (Van den Mooter, 2012; Müller *et al.*, 2011) ^[7, 8]. This article provides a detailed examination of these sophisticated formulation technologies. It will explore their underlying principles, classify the key approaches, analyze their mechanisms of action, and discuss practical manufacturing and regulatory considerations. By integrating scientific rationale with clinical application examples, this review aims to present a holistic perspective on transforming poorly soluble drugs into successful therapeutic products.

Classification of Poorly Soluble Drugs

The Biopharmaceutics Classification System (BCS) provides a valuable framework for categorizing drugs based on their aqueous solubility and intestinal permeability (Amidon *et al.*, 1995) ^[5]. Poorly soluble drugs predominantly fall into BCS Class II (low solubility, high permeability) and BCS Class IV (low solubility, low permeability) (Kawabata *et al.*, 2011) ^[4]. For BCS Class II drugs, the rate-limiting step for absorption is dissolution; therefore, enhancing solubility or dissolution rate can directly and proportionally improve bioavailability (Tsume *et al.*, 2014) ^[28]. BCS Class IV compounds present a dual challenge, requiring strategies that address both solubility and permeability barriers.

Poor solubility is influenced by a complex interplay of molecular properties. Strong intermolecular forces within a crystalline lattice, high melting point, and high lipophilicity, often quantified by a high log P value, are primary contributors (Williams *et al.*, 2013) ^[1]. Many potent therapeutic agents, including antifungal drugs (e.g., itraconazole), chemotherapeutic agents (e.g., paclitaxel), and numerous kinase inhibitors (e.g., nilotinib), exhibit these characteristics (Porter *et al.*, 2007; Gao *et al.*, 2003) ^[12, 25]. These drugs frequently possess a complex, multi-ring molecular structure that packs efficiently into a stable crystal, making disruption of this lattice energetically unfavorable in an aqueous environment (Schultheiss and Newman, 2009) ^[15]. This fundamental physicochemical mismatch between the drug substance and the physiological milieu necessitates intelligent formulation intervention to create a viable product (Singh *et al.*, 2011) ^[38].

Formulation Strategies for Solubility Enhancement

A diverse arsenal of formulation strategies has been developed to address poor solubility (Williams *et al.*, 2013; Singh *et al.*, 2011) ^[1, 38]. The selection of an appropriate technology depends on the drug's physicochemical properties, the intended dose, the target product profile, and practical manufacturing considerations.

Solid dispersions represent one of the most successful and widely applied approaches (Leuner and Dressman, 2000; Dhirendra *et al.*, 2009) ^[3, 6]. This technique involves dispersing the drug molecularly, or as amorphous nano-clusters, within an inert hydrophilic polymer matrix, such as polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), or copolymers of vinylpyrrolidone and vinyl acetate (Van den Mooter, 2012) ^[7].

The result is the formation of an amorphous solid solution or suspension, where the drug is trapped in a high-energy, non-crystalline state (He and Ho, 2015) ^[22]. This state possesses a higher apparent solubility and dramatically faster dissolution rate compared to its crystalline counterpart, as the energy-intensive step of breaking the crystal lattice is circumvented (Serajuddin, 1999; Brough and Williams, 2013) ^[21, 16]. The primary challenge lies in stabilizing the amorphous drug against recrystallization during storage, which is addressed through careful selection of polymers that inhibit molecular mobility and act as crystallization inhibitors (Jermain *et al.*, 2018) ^[37].

Nanosuspensions involve reducing the drug particle size to the nanoscale, typically between 100 and 1000 nanometers, using top-down methods like wet media milling or high-pressure homogenization, or bottom-up approaches like controlled precipitation (Merisko-Liversidge and Liversidge, 2011; Agrawal and Patel, 2011) ^[32, 24]. This reduction increases the particle surface area exponentially, according to the Noyes-Whitney equation, thereby accelerating dissolution (Junghanns and Müller, 2008) ^[9]. Furthermore, for particles below approximately 2 micrometers, the increase in saturation solubility due to the Ostwald-Freundlich effect provides an additional thermodynamic driving force for dissolution (Müller *et al.*, 2011) ^[8]. Nanosuspensions can be administered as liquid suspensions or further processed into solid oral dosage forms like tablets or capsules (Kipp, 2004) ^[26]. They are particularly advantageous for drugs with high crystal lattice energy that are not amenable to amorphization (Kalepu and Nekkanti, 2016) ^[20].

Lipid-based formulations encompass a broad category, including simple lipid solutions, self-emulsifying drug delivery systems (SEDDS), and self-microemulsifying drug delivery systems (SMEDDS) (Pouton, 2006; Hauss, 2007) ^[10, 11]. These systems utilize the drug's inherent solubility in lipids and surfactants (Porter *et al.*, 2007) ^[12]. Upon ingestion and exposure to gastrointestinal fluids, SEDDS and SMEDDS spontaneously form fine oil-in-water emulsions or microemulsions, presenting the drug in a pre-dissolved, readily absorbable form within small lipid droplets (Gershnik and Benita, 2000; Rahman *et al.*, 2013) ^[29, 27]. This process bypasses the dissolution step entirely (O'Driscoll and Griffin, 2008) ^[31]. Furthermore, lipids can stimulate bile secretion and promote intestinal lymphatic transport, which is beneficial for highly lipophilic drugs (Mu *et al.*, 2013) ^[33]. The design of these systems requires a careful balance of oils, surfactants, and co-solvents to ensure robust self-emulsification and drug stability (Gao *et al.*, 2009) ^[36].

Cyclodextrin inclusion complexes offer a molecular-level solution (Loftsson and Brewster, 2010; Brewster and Loftsson, 2007) ^[13, 14]. Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a hydrophobic central cavity. Poorly soluble drug molecules can be partially or fully incorporated into this cavity, forming

a non-covalent inclusion complex (Loftsson and Brewster, 2010) ^[13]. This molecular encapsulation enhances apparent solubility by masking the hydrophobic drug surface with the cyclodextrin's hydrophilic shell (Brewster and Loftsson, 2007) ^[14]. Commonly used derivatives like hydroxypropyl-beta-cyclodextrin (HP-β-CD) and sulfobutylether-beta-cyclodextrin (SBE-β-CD) offer improved solubility and safety profiles compared to native cyclodextrins (Loftsson and Brewster, 2010) ^[13]. This technology is especially useful for low-dose, potent drugs.

Co-crystallization involves forming a crystalline material comprising two or more different molecules, typically the active drug and a co-former (e.g., a food-grade acid or base), held together by non-ionic interactions like hydrogen bonds (Schultheiss and Newman, 2009) ^[15]. Pharmaceutical co-crystals can modify critical properties such as solubility, dissolution rate, and physical stability without altering the drug's chemical structure or pharmacological activity (Schultheiss and Newman, 2009) ^[15]. This provides a targeted crystal engineering approach to fine-tune performance. Polymeric carriers and micellar systems represent another avenue (Djordjevic *et al.*, 2003) ^[30].

Block copolymers or surfactants can self-assemble into micelles in aqueous solutions, with hydrophobic cores that solubilize poorly soluble drugs (Gupta *et al.*, 2013) ^[35]. These systems can also be designed for controlled release or targeted delivery (Denning and Taylor, 2018) ^[39].

Mechanisms of Improved Drug Delivery

The success of the aforementioned strategies hinges on their ability to manipulate the drug's biopharmaceutical profile through specific physical and chemical mechanisms, ultimately leading to enhanced bioavailability and therapeutic performance (Williams *et al.*, 2013; Kawabata *et al.*, 2011) ^[1, 4].

The central mechanism for most strategies is the enhancement of dissolution rate and apparent solubility (Amidon *et al.*, 1995) ^[5]. Amorphous solid dispersions achieve this by presenting the drug in a high-energy state with no crystal lattice to overcome (He and Ho, 2015; Serajuddin, 1999) ^[22, 21]. Nanosuspensions leverage increased surface area and the curvature effect on solubility (Junghanns and Müller, 2008; Müller *et al.*, 2011) ^[9, 8]. Lipid-based systems eliminate the dissolution step in aqueous media by delivering the drug pre-dissolved in a digestible lipid vehicle (Porter *et al.*, 2007; Gershanik and Benita, 2000) ^[12, 29]. Cyclodextrins increase the concentration of molecularly dissolved drug in solution through complexation (Loftsson and Brewster, 2010) ^[13]. Each method accelerates the critical step of getting the drug into solution in the gastrointestinal tract, as summarized in Table 3. Beyond simple dissolution, stabilization of the drug in its absorbed state is crucial (Jermain *et al.*, 2018) ^[37]. Polymers in solid dispersions not only inhibit crystallization in the solid state but can also maintain supersaturation in the gastrointestinal fluid by inhibiting drug precipitation after dissolution (Van den Mooter, 2012; He and Ho, 2015) ^[7, 22]. This prolonged period of supersaturation, where the drug concentration exceeds its thermodynamic solubility, creates a stronger concentration gradient for passive diffusion across the intestinal membrane (Tsume *et al.*, 2014) ^[28]. This "spring and parachute" effect—where the drug rapidly dissolves

("springs") into a supersaturated state and is then prevented from precipitating by polymers ("parachute")—is a key contributor to the success of solid dispersion technologies (Brough and Williams, 2013) ^[16].

For lipid-based systems, the mechanism extends to interaction with physiological pathways (O'Driscoll and Griffin, 2008) ^[31]. The formed lipid droplets undergo digestion by pancreatic lipases, producing mono- and diglycerides and free fatty acids (Mu *et al.*, 2013) ^[33]. These products, along with bile salts, form mixed micelles and vesicles that can further solubilize the drug, facilitating its absorption (Porter *et al.*, 2007) ^[12]. Furthermore, some lipids can promote intestinal lymphatic transport, which bypasses first-pass hepatic metabolism—a significant advantage for drugs with high pre-systemic clearance (Hauss, 2007) ^[11]. Many of these advanced formulations also serve as platforms for controlled and targeted drug delivery (Kalepu and Nekkanti, 2016) ^[20]. Nanosuspensions and nanoparticles can be surface-modified with ligands for active targeting (Müller *et al.*, 2011) ^[8]. Lipid-based and polymeric systems can be engineered for sustained release, mitigating peak-trough fluctuations and improving tolerability (Djordjevic *et al.*, 2003; Gupta *et al.*, 2013) ^[30, 35]. This multifunctionality transforms a simple solubility-enabling technology into a comprehensive drug delivery platform.

Manufacturing Considerations

The translation of a promising laboratory-scale formulation into a robust, commercially viable product requires meticulous attention to manufacturing processes (Singh *et al.*, 2011) ^[38]. Scale-up presents significant challenges. For instance, the process parameters for producing an amorphous solid dispersion via hot-melt extrusion or spray drying—such as temperature

profiles, screw design, feed rates, atomization pressure, and drying kinetics—must be tightly controlled to ensure consistent product quality, including the maintenance of the amorphous state and desired particle morphology (Brough and Williams, 2013; He and Ho, 2015) ^[16, 22]. Similarly, media milling for nanosuspensions requires optimization of milling time, bead size and density, and stabilizer concentration to achieve a reproducible particle size distribution without excessive Ostwald ripening or aggregation (Merisko-Liversidge and Liversidge, 2011; Junghanns and Müller, 2008) ^[32, 9].

Stability is a paramount concern (Jermain *et al.*, 2018) ^[37]. Amorphous systems are inherently metastable and must be formulated and packaged to prevent moisture uptake and temperature excursions that could induce crystallization over the product's shelf life (Van den Mooter, 2012; Serajuddin, 1999) ^[7, 21]. Nanosuspensions in liquid form must be stabilized against particle growth (Ostwald ripening) and aggregation through the use of appropriate stabilizers like polymers and surfactants (Müller *et al.*, 2011; Agrawal and Patel, 2011) ^[8, 24]. Lipid-based formulations require protection from oxidation and hydrolysis (Hauss, 2007) ^[11]. Long-term stability studies under International Council for Harmonisation (ICH) conditions are essential to define appropriate storage conditions and shelf life.

Regulatory compliance and quality assurance demand a thorough understanding of the critical quality attributes (CQAs) of these complex products (Williams *et al.*, 2013) ^[1].

These may include the degree of crystallinity for solid dispersions, particle size distribution for nanosuspensions, emulsification performance for SEDDS, and complexation efficiency for cyclodextrins (Leuner and Dressman, 2000; Junghanns and Müller, 2008; Gershanik and Benita, 2000; Loftsson and Brewster, 2010) [3, 9, 29, 13]. Analytical methods must be developed and validated to monitor these CQAs (Singh *et al.*, 2011) [38]. Furthermore, the regulatory submission must provide a robust scientific rationale for the chosen technology and demonstrate that the manufacturing process is well-understood, controlled, and capable of consistently producing a product that meets its predefined quality standards (Kawabata *et al.*, 2011) [4].

Challenges and Limitations

Despite their proven success, advanced formulation strategies are not without limitations (Singh *et al.*, 2011; Kalepu and Nekkanti, 2016) [38, 20]. Physical and chemical instability remains the most significant hurdle for amorphous systems and nanosuspensions (Jermain *et al.*, 2018; Müller *et al.*, 2011) [37, 8]. Recrystallization can negate solubility advantages, while chemical degradation may be accelerated in high-energy states or at interfaces in nanosystems (Serajuddin, 1999; Junghanns and Müller, 2008) [21, 9]. The excipients required for these formulations, such as high levels of polymers, surfactants, or novel lipids, can introduce toxicity or biocompatibility concerns that must be thoroughly evaluated (Haus, 2007; Loftsson and Brewster, 2010) [11, 13]. Gastrointestinal irritation from surfactants or the osmolarity effects of cyclodextrins are examples of such considerations (Brewster and Loftsson, 2007) [14].

Cost and scalability can be prohibitive (Brough and Williams, 2013) [16]. Many enabling technologies require specialized, capital-intensive equipment and complex processing steps, leading to higher manufacturing costs compared to conventional tablets (Merisko-Liversidge and Liversidge, 2011) [32]. The requirement for strict control over processing parameters and the potential for batch-to-batch variability add further complexity (He and Ho, 2015) [22]. Additionally, the intellectual property landscape for many advanced carriers and processes is dense, which can impact freedom to operate (Schultheiss and Newman, 2009) [15]. Finally, there is no universal solution (Williams *et al.*, 2013) [1]. The selection and optimization of a formulation strategy are highly drug-specific (Kawabata *et al.*, 2011) [4]. A technology that works brilliantly for one molecule may fail for another due to subtle differences in melting point, log P, chemical stability, or dose (Amidon *et al.*, 1995) [5]. This necessitates an iterative, resource-intensive development process (Singh *et al.*, 2011) [38].

Future Perspectives

The future of formulating poorly soluble drugs lies in the integration of cutting-edge scientific disciplines (Williams *et al.*, 2013) [1]. Nanotechnology will continue to evolve beyond simple nanosuspensions to include sophisticated nanocarriers

like mesoporous silica particles, which can load and stabilize amorphous drugs within their pores, and solid lipid nanoparticles, which combine lipid and nanoparticle advantages (Denig and Taylor, 2018; Müller *et al.*, 2011) [39, 8]. The emergence of "smart" or stimuli-responsive systems—such as those that release drug in response to specific pH, enzymes, or redox conditions in the target tissue—promises to add a new layer of spatial and temporal control (Kalepu and Nekkanti, 2016) [20].

Personalized medicine and precision formulation are converging (Singh *et al.*, 2011) [38]. The understanding of patient-specific factors, such as genetics, diet, and gut microbiome, which influence drug absorption and metabolism, may lead to tailored formulations for sub-populations (Tsume *et al.*, 2014) [28]. Three-dimensional (3D) printing of pharmaceuticals offers the potential to fabricate complex dosage forms with precise geometry and composition to control release profiles on-demand (Brough and Williams, 2013) [16].

Perhaps one of the most transformative trends is the application of artificial intelligence (AI) and machine learning (ML) in formulation design (Kalepu and Nekkanti, 2016) [20]. AI models can predict the solubility of drug candidates, recommend suitable formulation strategies based on molecular descriptors, and optimize complex mixtures of excipients (Williams *et al.*, 2013) [1]. This data-driven approach has the potential to drastically reduce the number of trial-and-error experiments, accelerate development timelines, and improve the success rate of formulating challenging molecules (Singh *et al.*, 2011) [38].

Conclusion

The challenge of poor solubility represents a significant bottleneck in drug development, but it has also catalyzed remarkable innovation in pharmaceutical formulation science. Strategies such as amorphous solid dispersions, nanosuspensions, lipid-based systems, and cyclodextrin complexation have established themselves as powerful tools to enhance dissolution, improve bioavailability, and enable the delivery of otherwise impractical drug candidates. Each technology operates on distinct physicochemical principles and offers a unique set of advantages and trade-offs regarding stability, manufacturability, and therapeutic application. While challenges in physical stability, scalable manufacturing, and regulatory navigation persist, ongoing research is actively addressing these limitations. The convergence of formulation science with nanotechnology, advanced materials, and computational intelligence heralds a future where the delivery of poorly soluble drugs will become more predictable, efficient, and tailored to individual patient needs. The continued evolution of these advanced formulation strategies is essential for unlocking the full therapeutic potential of modern drug discovery pipelines and improving clinical outcomes across a wide spectrum of diseases.

Figures



Fig 1



Fig 2

Tables

Table 1: Comparison of different formulation strategies for poorly soluble drugs, including advantages and limitations.

Formulation Strategy	Key Advantages	Key Limitations
Amorphous Solid Dispersions	High dissolution rate; significant bioavailability enhancement; potential for controlled release.	Risk of physical instability (recrystallization); requires specialized manufacturing (spray drying, HME).
Nanosuspensions	Applicable to virtually all poorly soluble drugs; can increase both dissolution rate and saturation solubility.	Potential for particle growth (Ostwald ripening); physical stability of suspension; may require sterile manufacturing for parenteral routes.
Lipid-Based Systems (SEDDS/SMEDDS)	Bypasses dissolution step; enhances lymphatic transport; reduces food effect.	Limited drug loading; potential for excipient toxicity; stability issues (oxidation, hydrolysis).
Cyclodextrin Complexes	Molecular encapsulation; well-characterized; can improve chemical stability.	Limited capacity for high-dose drugs; can be costly; some renal toxicity at high intravenous doses.
Co-crystals	Modifies properties without chemical change; can improve solubility and physical stability.	Requires identification of suitable co-former; regulatory path can be complex.

Table 2: Key excipients and carrier materials used in solubility enhancement approaches.

Formulation Approach	Typical Excipient/Carrier Classes	Examples
Solid Dispersions	Hydrophilic Polymers	Polyvinylpyrrolidone (PVP), Hydroxypropyl methylcellulose (HPMC), Copovidone, Soluplus
Nanosuspensions	Stabilizers (Polymers & Surfactants)	Polyvinyl alcohol (PVA), Poloxamers, Polysorbates, Cellulose derivatives (HPMC)
Lipid-Based Systems	Oils, Surfactants, Co-surfactants	Medium-chain triglycerides, Oleic acid, Tween 80, Cremophor EL, PEGylated lipids, Ethanol, Propylene glycol
Cyclodextrin Complexes	Cyclodextrin Derivatives	Hydroxypropyl- β -cyclodextrin (HP- β -CD), Sulfobutylether- β -cyclodextrin (SBE- β -CD), Randomly methylated- β -cyclodextrin (RM- β -CD)
Polymeric Micelles	Block Co-polymers	Pluronics (Poloxamers), PEG-PLA, PEG-PCL

Table 3: Mechanisms of solubility improvement and bioavailability enhancement for various formulation types.

Formulation Type	Primary Solubility/Dissolution Mechanism	Secondary Bioavailability Enhancement Mechanisms
Solid Dispersions	Conversion to amorphous state (higher energy, no crystal lattice).	Polymer-mediated supersaturation stabilization; potential for modified release.
Nanosuspensions	Increased surface area (Noyes-Whitney); increased saturation solubility (Ostwald-Freundlich).	Adhesion to gut wall; potential for targeted delivery.
Lipid-Based Systems	Delivery in pre-dissolved state; solubilization in mixed micelles post-digestion.	Stimulation of lymphatic transport (reduces first-pass metabolism); inhibition of efflux transporters.
Cyclodextrin Complexes	Molecular inclusion, increasing apparent solubility of drug-CD complex.	Protection from degradation; possible modulation of membrane permeability.
Co-crystals	Altered crystal lattice energy and hydrogen bonding, improving dissolution.	Improved physical stability compared to amorphous forms.

Table 4: Examples of commercially available poorly soluble drugs and the formulation strategies applied.

Drug (Therapeutic Class)	Formulation Strategy	Commercial Product Example(s)
Itraconazole (Antifungal)	Amorphous Solid Dispersion (Spray Dried)	Sporanox
Sirolimus (Immunosuppressant)	Amorphous Solid Dispersion (TAB)	Rapamune
Fenofibrate (Lipid-lowering)	Nanocrystal	Tricor, Triglide
Aprepitant (NK1 antagonist)	Nanocrystal	Emend
Cyclosporine A (Immunosuppressant)	Self-Microemulsifying Drug Delivery System (SMEDDS)	Neoral, Gengraf
Ritonavir (Antiretroviral)	Amorphous Solid Dispersion (Melt Extrusion)	Norvir
Nilotinib (Anticancer)	Amorphous Solid Dispersion	Tasigna
Voriconazole (Antifungal)	Cyclodextrin Complex (IV), Solid Dispersion (Oral)	Vfend

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