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Improving Oral Bioavailability of Poorly Water-Soluble Drugs: Recent Progress in Solid Dispersions, Lipid Systems, and Nanotechnology

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Abstract:

Poor aqueous solubility remains one of the most significant challenges in pharmaceutical development, affecting approximately 40% of marketed drugs and 70–90% of developmental candidates. This constraint translates directly into inadequate oral bioavailability, reduced therapeutic efficacy, high inter- and intra-subject variability, and compromised dose proportionality. The Biopharmaceutical Classification System (BCS) characterises drugs with low solubility and high permeability (Class II) and those with both low solubility and permeability (Class IV) as particularly problematic for conventional oral formulation. Over the past two decades, three primary technological paradigms have emerged to address this challenge: solid dispersions, lipid-based formulations, and nanotechnology-enabled delivery systems. This review synthesises recent advances (2022–2025) across these platforms, examining their mechanistic basis, formulation strategies, in vivo performance, and regulatory landscape. We demonstrate that hybrid approaches combining multiple technologies now routinely achieve 3–7-fold improvements in oral bioavailability and are increasingly entering clinical practice.

Keywords: Lipid; problematic; solid dispersions; water; drug development

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1. Introduction

1.1 The Bioavailability Crisis in Drug Development

Over the past few decades, pharmaceutical research has made significant progress in the discovery and design of new drug molecules. Advances in molecular biology, computational modelling, high-throughput screening, and structure-based drug design have enabled researchers to identify precise drug targets and develop compounds with potent biological activity [1-2]. As a result, many newly developed drug candidates show excellent potency and selectivity in laboratory studies. However, despite these scientific achievements, a significant challenge has become increasingly evident in later stages of development: a large proportion of new chemical entities exhibit poor water solubility [3-4].

Poor aqueous solubility is now recognised as one of the most common barriers to successful oral drug delivery. Modern medicinal chemistry often focuses on improving target binding, metabolic stability, and receptor selectivity [5-6]. These goals are frequently achieved by increasing the lipophilicity of the drug molecule. While lipophilicity may improve membrane permeability and target interaction, it often comes at the cost of reduced solubility in aqueous environments. As a result, many promising drug candidates dissolve poorly in gastrointestinal fluids after oral administration [7-8].

When a drug does not dissolve sufficiently, its absorption from the gastrointestinal tract becomes limited. In such cases, oral bioavailability depends primarily on the dissolution rate rather than on the molecule's intrinsic pharmacological activity [9-10]. This problem is particularly evident for drugs classified under the Biopharmaceutical Classification System as Class II compounds, which exhibit high permeability but low solubility. Even though these drugs can readily cross intestinal membranes once dissolved, their slow dissolution prevents adequate drug levels from being achieved in systemic circulation. Consequently, the therapeutic potential of otherwise effective molecules remains wholly or partially unrealised [11-12].

From a clinical perspective, poor oral bioavailability has several negative consequences. Patients often need to take higher doses to achieve therapeutic drug concentrations, which increases the risk of dose-related side effects and toxicity [13]. Poor solubility also contributes to variability in drug absorption between patients, leading to inconsistent treatment outcomes. In some cases, food intake can significantly alter drug absorption, resulting in unpredictable pharmacokinetic profiles. These factors reduce patient adherence to therapy and complicate dose optimisation in clinical practice [14].

The impact of poor bioavailability extends beyond patient outcomes and directly affects pharmaceutical development costs. Drug candidates with poor oral absorption often require extensive formulation development to improve performance. This process is time-consuming, expensive, and technically challenging [15-16]. In some cases, companies are forced to discontinue otherwise promising compounds due to formulation difficulties or unfavourable risk–benefit

profiles. As drug development costs continue to rise, poor solubility has become a critical factor contributing to late-stage development failures. Figure 1

Recognising the scale of this problem, regulatory agencies have increasingly acknowledged the importance of advanced formulation strategies. Guidance documents now emphasise the role of formulation science and drug-delivery technologies in enabling the clinical success of poorly soluble drugs [17-18]. In particular, recent regulatory updates highlight nanotechnology-based and complex delivery systems as acceptable and scientifically justified approaches when supported by appropriate characterisation and safety data. This shift reflects a broader understanding that innovative formulation design is often essential to translate potent drug molecules into effective oral therapies [19-20].

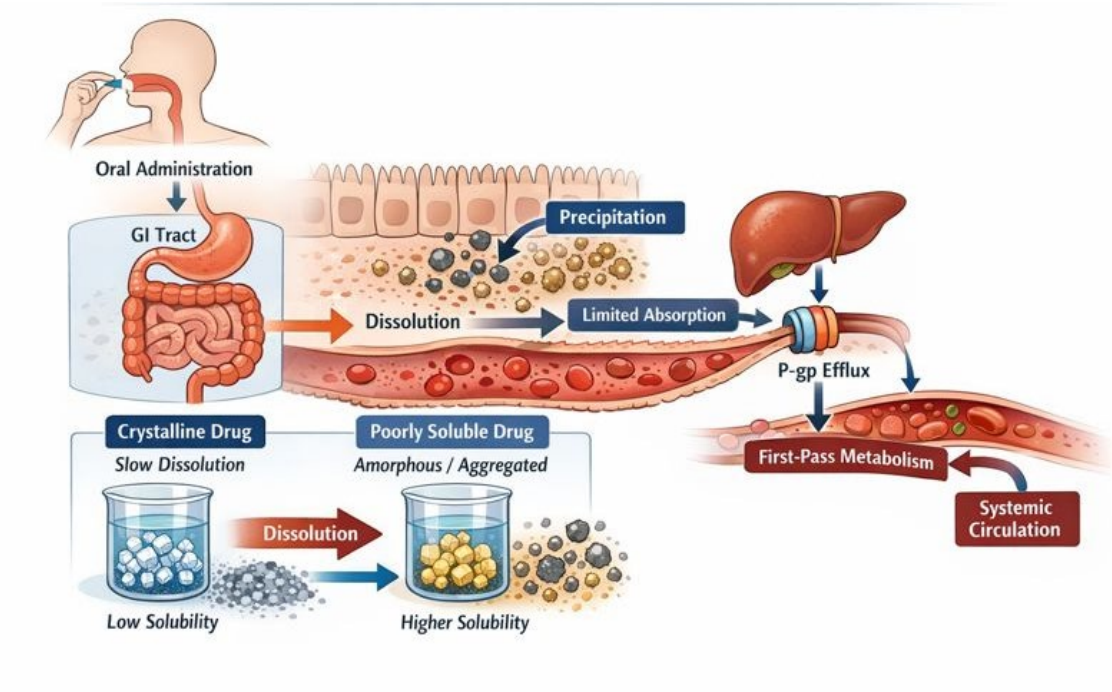

Figure 1: schematically illustrates the key biological and physicochemical barriers responsible for low oral bioavailability of poorly water-soluble drugs following oral administration.

1.2 Biopharmaceutical Classification and Solubility-Driven Absorption

The Biopharmaceutical Classification System provides a widely accepted framework for understanding the relationship between drug properties and oral absorption. This system classifies drugs into four categories based on two key parameters: aqueous solubility and intestinal permeability [21]. By separating these two factors, the BCS helps identify the primary limitation to oral bioavailability for a given drug and guides formulation strategy selection.

Class I drugs exhibit high solubility and high permeability. These drugs generally show good oral bioavailability and minimal formulation challenges. In contrast, Class II drugs are characterised by high permeability but low solubility [22-23]. For these compounds, the rate of drug

dissolution in gastrointestinal fluids becomes the main factor limiting absorption. Once dissolved, the drug readily permeates the intestinal membrane. Therefore, any formulation approach that improves dissolution rate or apparent solubility is likely to result in proportional improvements in oral bioavailability [24].

This principle forms the scientific foundation for many formulation strategies used to improve the performance of poorly soluble drugs. Solid dispersions, lipid-based systems, and nanoscale formulations are specifically designed to increase dissolution rate, maintain drug solubilization, or generate supersaturated drug concentrations in the intestinal environment. By enhancing the concentration gradient across the intestinal membrane, these approaches improve passive diffusion and systemic drug exposure [25-26].

Class IV drugs present an even greater challenge. These compounds exhibit both low solubility and low permeability, meaning that dissolution and membrane transport are both limiting factors. For such drugs, improving solubility alone may not be sufficient to achieve adequate bioavailability [27]. Additional strategies may be required, including permeability enhancement, inhibition of efflux transporters, or targeting alternative absorption pathways such as lymphatic transport. In some cases, non-oral routes of administration may be considered if oral delivery remains ineffective [28-29].

The BCS framework also plays an essential role in regulatory decision-making. It is used to support biowaivers for certain drugs and to guide the design of bioequivalence studies. For formulation scientists, the BCS provides a rational starting point for selecting appropriate delivery technologies. Understanding whether solubility, permeability, or both are limiting allows more efficient allocation of development resources and improves the likelihood of clinical success [30-31].

1.3 Mechanisms of Reduced Bioavailability in Poorly Soluble Drugs

The low oral bioavailability of poorly soluble and lipophilic drugs results from multiple interconnected mechanisms. One of the most essential factors is dissolution-rate limitation. Most poorly soluble drugs exist in a crystalline form, which is thermodynamically stable but dissolves slowly in aqueous environments. In the gastrointestinal tract, slow dissolution limits the amount of drug available in solution for absorption, reducing the driving force for passive diffusion across the intestinal membrane [32].

Another contributing factor is solubility-limited absorption. Even when sufficient time is available for dissolution, the maximum solubility of some drugs in physiological media remains too low to support efficient absorption. This is particularly problematic for medicines that require relatively high plasma concentrations to achieve therapeutic effects. In such cases, the drug's saturation solubility serves as an upper limit on absorption, regardless of the dose administered [33-34].

Particle size also plays a critical role in dissolution behaviour. Larger drug particles have a lower surface area-to-volume ratio, which slows dissolution. Poorly controlled particle size distribution can therefore contribute to inconsistent drug absorption and high variability between doses and patients. Reducing particle size increases surface area and improves dissolution rate, but microscopic particles may aggregate if not properly stabilised [35-36].

Metabolism and efflux mechanisms further reduce oral bioavailability for certain drugs. Some lipophilic compounds undergo extensive first-pass hepatic metabolism after absorption, significantly reducing the fraction of the drug that reaches systemic circulation. In addition, many drugs are substrates for efflux transporters, such as P-gp, which actively pump them back into the intestinal lumen. These processes reduce net absorption and contribute to low and variable bioavailability [37-38].

Formulation-dependent factors also play an essential role. Poorly soluble drugs often lack consistent solubilization mechanisms in the gastrointestinal tract, leading to variable absorption depending on physiological factors such as pH, bile salt concentration, and food intake. Food effects are common for lipophilic drugs, as dietary lipids can enhance or reduce solubilization depending on formulation design. This variability complicates dose selection and increases the risk of subtherapeutic or excessive drug exposure [39].

Taken together, these mechanisms explain why poorly soluble drugs frequently show low, variable, and unpredictable oral bioavailability. Addressing these challenges requires a comprehensive understanding of drug physicochemical properties, gastrointestinal physiology, and formulation science. Improving dissolution, maintaining solubilization, and controlling drug release are therefore central goals in the development of effective oral formulations for poorly water-soluble drugs [40].

2. Solid Dispersions: Evolution and Current Status

2.1 Generational Classification and Evolution

Solid dispersions are one of the most widely studied and successfully applied formulation strategies for improving the oral bioavailability of poorly water-soluble drugs. In general, a solid dispersion consists of a drug that is molecularly dispersed or finely distributed within a solid carrier matrix, usually a polymer. Over time, solid dispersion technology has evolved through several stages, reflecting progress in polymer science, processing methods, and understanding of drug carrier interactions. Based on formulation composition and functional performance, solid dispersions are commonly classified into four generations [41-42].

The first generation of solid dispersions used crystalline carriers such as urea and succinic acid. In these systems, the drug was physically mixed with the carrier and dispersed at the molecular or microcrystalline level [43]. Although these formulations initially showed improved dissolution compared to the pure crystalline drug, they suffered from poor physical stability. Both the drug and the carrier were crystalline, allowing the drug molecules to reorganise and recrystallise

during storage. Over time, this recrystallisation eliminated the dissolution and bioavailability advantages. Due to these stability issues and limited clinical benefit, first-generation solid dispersions are now rarely used in modern pharmaceutical development [44-46].

Second-generation solid dispersions represented a significant advancement with the introduction of amorphous polymeric carriers. Commonly used polymers include polyvinylpyrrolidone and hydroxypropyl methylcellulose. In these systems, the drug is converted from a crystalline state to an amorphous form and is dispersed within an amorphous polymer matrix [47]. The amorphous form has a higher internal energy than its crystalline counterpart, leading to faster dissolution. At the same time, the polymer matrix reduces the drug's molecular mobility by increasing the overall glass transition temperature of the system. This kinetic stabilisation delays or prevents drug recrystallisation during storage and dissolution [48].

Second-generation solid dispersions remain the most clinically successful and widely used systems. Several marketed oral products use this approach, demonstrating reliable improvements in dissolution rate and oral bioavailability. The combination of improved performance, acceptable stability, and scalable manufacturing has made this generation a standard choice for many poorly soluble drugs [49.]

Third-generation solid dispersions further improved performance by adding surfactants to the drug polymer system, forming ternary formulations. In these systems, surfactants serve multiple roles. They enhance the wetting of drug particles, reduce interfacial tension, and inhibit drug crystallisation during dissolution. Surfactants also help stabilise supersaturated drug solutions formed after dissolution of the amorphous drug [50-51]. As a result, third-generation systems often show faster dissolution, higher peak drug concentrations, and improved physical stability compared to polymer-only dispersions. These formulations are beneficial for drugs with a strong tendency to recrystallise in aqueous media. Figure 2

Fourth-generation solid dispersions represent the most advanced stage of development. These systems use carefully designed combinations of polymers, surfactants, and additional excipients such as polysaccharides or sugar-based materials. The goal of this generation is not only to improve dissolution but also to address specific challenges related to drug chemistry, stability, and site-specific release. Formulation design is often guided by experimental and predictive studies of drug polymer surfactant interactions. This rational approach allows more consistent performance and reduces trial-and-error during development. Fourth-generation systems are increasingly explored for complex drug molecules with challenging solubility and stability profiles [52-53].

Overall, the evolution of solid dispersions reflects a shift from simple physical mixtures toward scientifically designed systems with controlled molecular interactions. Each generation has contributed valuable insights, leading to more reliable and effective oral drug formulations [54].

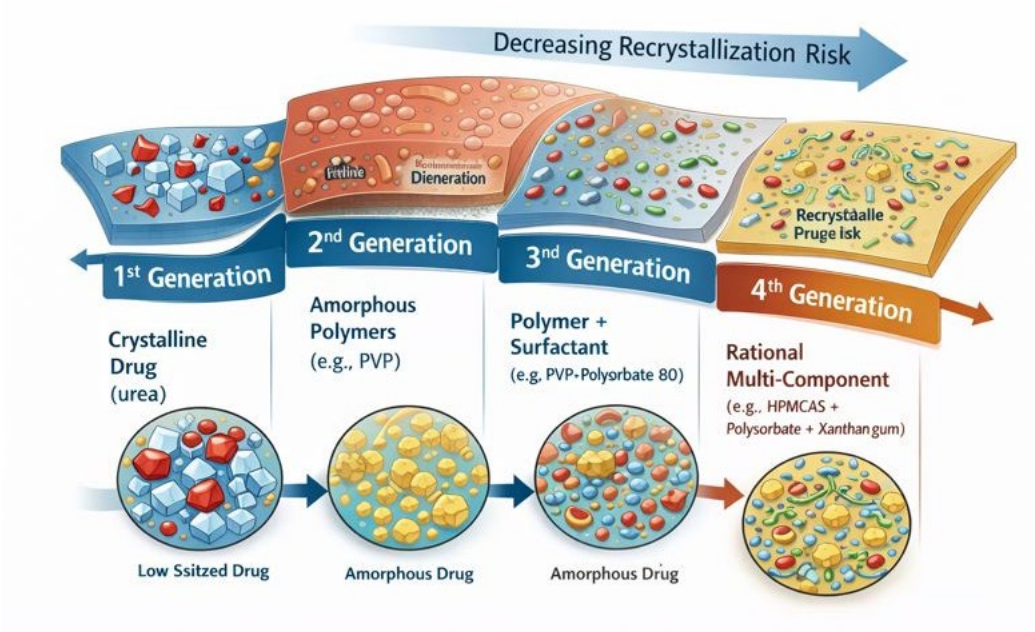

Figure 2: Evolution of solid dispersions across generations

2.2 Mechanistic Basis of Bioavailability Enhancement

Solid dispersions improve oral bioavailability through several complementary mechanisms that act together during drug dissolution and absorption. One of the most important mechanisms is particle size reduction. During the preparation of solid dispersions, the drug is dispersed at the molecular level or as microscopic particles within the carrier matrix. This drastic reduction in adequate particle size greatly increases the surface area available for dissolution, thereby accelerating drug release in gastrointestinal fluids [55-56].

Another key mechanism is the generation of a supersaturated drug solution. In solid dispersions, the drug is often present in an amorphous state, which has higher free energy than the crystalline form. When the amorphous drug dissolves, it can temporarily attain concentrations above its equilibrium solubility. This supersaturated state creates a strong concentration gradient across the intestinal membrane, which enhances passive drug absorption. Supersaturation is therefore a major driver of increased bioavailability in solid dispersion systems [57].

Polymer-mediated stabilisation plays a critical role in maintaining both physical stability during storage and supersaturation during dissolution. Polymers interact with drug molecules through hydrogen bonding and other weak molecular forces. These interactions reduce drug mobility and slow down nucleation and crystal growth. Polymers with high glass transition temperatures further restrict molecular motion, helping prevent drug recrystallisation within the solid matrix. During dissolution, the polymer can also inhibit drug precipitation from the supersaturated solution, thereby extending the absorption time window.

Improved wettability is another crucial contribution of solid dispersions. Many poorly soluble drugs are hydrophobic and do not readily interact with water. Hydrophilic polymers improve

wetting by forming a water-friendly surface around the drug, allowing gastrointestinal fluids to penetrate the formulation more easily. Better wetting leads to faster dissolution and more consistent drug release [58-59].

In some cases, the polymer carrier also protects against harsh gastric conditions. Specific polymers remain intact in acidic environments and dissolve only at higher intestinal pH values. This behaviour can make acid-sensitive drugs less sensitive in the stomach and promote their release in the small intestine, where absorption is more favourable. favourable-specific release further improve adequate bioavailability and reduces drug degradation.

Together, these mechanisms explain why solid dispersions are highly effective for improving the oral delivery of poorly soluble drugs. By combining particle size reduction, polymer stabilisation, improved wetting, and controlled release, solid dispersions address multiple barriers to absorption simultaneously. Simultaneously, this multi-mechanistic action is the primary reason solid dispersions remain one of the most successful and widely adopted formulation strategies in modern pharmaceutical development [60-61].

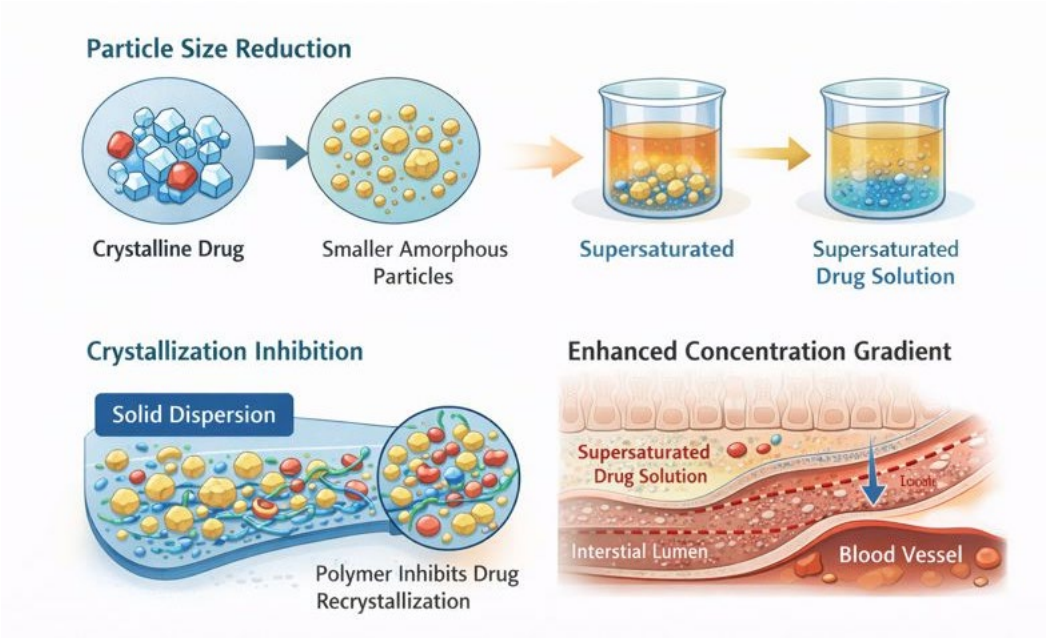

Figure 3: Enhancing drug bioavailability mechanisms

2.3 Polymer Selection and Rational Design

Polymer selection constitutes the critical design variable in solid dispersion formulation. Polymers must satisfy multiple, sometimes competing requirements:

Property	Clinical Impact	Preferred Characteristics
Glass transition temperature (Tg)	Determines molecular mobility and storage	High Tg (>100°C) for improved stability; must be modified by drug

	stability	plasticization [62]
Hygroscopicity	Affects water uptake and moisture-induced crystallisation	Low to moderate (PVP is more hygroscopic than HPMCAS) [63]
Solubility in aqueous media	Enables polymer dissolution and supersaturation stabilisation	Water-soluble polymers are preferred for rapid drug release [64]
Molecular weight	Influences viscosity, dissolution rate, and mechanical properties	Moderate MW (20,000–150,000 Da) balances processing and performance [65]
Surface chemistry/Functional groups	Enables hydrogen bonding with polar drugs	Polymers with carbonyl, hydroxyl, or carboxyl groups are beneficial [66]
pH-dependent solubility	Controls site-specific drug release	HPMCAS dissolves above pH 5.0; Eudragit L100 above pH 6.0; Eudragit S100 above pH 7.0, [67]

Common polymers and their characteristics are summarised in the table below:

Polymer Class	Example	Tg (°C)	Solubility Profile	MW Range (Da)	FDA Status
Vinyl lactam copolymers	PVP K25, PVP K30, PVP K90	153–177	Water-soluble	2,000–1,500,000	Approved (many products) [68]
	PVP/VA 64 (Kollidon VA64)	105	Water-soluble	45,000–70,000	Approved [69]
	Soluplus®	72	Water-soluble	90,000–140,000	Approved [70]
Cellulosic polymers	HPMC (Methocel)	147–173	Water-soluble	10,000–150,000	Approved [71]
	HPC (Klucel)	0	Water-soluble	~95,000	Approved [72]
	HPMCAS	122–147	pH-dependent (pH>5.0)	18,000–45,600	Approved [73]
	HPMCP (HP-55)	147	pH-dependent (pH>5.0)	45,600	Approved [74]
Acrylate/methacrylate copolymers	Eudragit E PO	52	pH-dependent (pH<5.0)	47,000	Approved [75]

	Eudragit L100	195	pH-dependent (pH>6.0)	125,000	Approved [76]
	Eudragit S100	173	pH-dependent (pH>7.0)	125,000	Approved [77]
PEG-based polymers	PEG, Poloxamer (Pluronic)	55–66	Water-soluble	1,000–7,000,000	Approved [78]

Drug-polymer miscibility constitutes the thermodynamic prerequisite for successful solid dispersion formation. Miscibility can be predicted through Flory-Huggins theory, but empirical assessment via differential scanning calorimetry (DSC) and modulated DSC remains standard. High drug loading often compromises miscibility; therefore, optimal formulations typically employ drug loadings of 20- 40% to balance bioavailability benefit with stability robustness [79].

2.4 Manufacturing Technologies: Comparative Analysis

The performance and stability of solid dispersions are strongly influenced by the manufacturing method used. Among the available techniques, spray drying and hot-melt extrusion are the most widely applied at both laboratory and commercial scales. Solvent evaporation and freeze-drying are also used in specific situations, particularly during early formulation development or for heat-sensitive drugs. Each method has distinct advantages and limitations, and the choice of technique depends on drug properties, polymer selection, scalability requirements, and regulatory considerations.

2.4.1 Spray Drying

Spray drying is the most commonly used solvent-based method for the production of solid dispersions. In this process, the drug and polymer are first dissolved in a suitable solvent system to form a clear solution. This solution is then atomised into fine droplets using a nozzle or rotary atomiser. The droplets are brought into contact with a stream of hot drying gas, leading to rapid solvent evaporation. As the solvent evaporates, solid particles are formed and subsequently collected using cyclone separation.

One of the main advantages of spray drying is its high scalability. The same basic process can be applied from small laboratory dryers to large commercial-scale equipment with minimal changes in formulation composition. Spray drying is also well suited for thermolabile drugs, as the actual exposure time to elevated temperatures is very short, despite the use of hot drying gas. Rapid solvent removal limits the time available for drug molecules to reorganise and crystallise, thereby favouring the formation of amorphous solid dispersions. In addition, particle size, shape, and density can be adjusted by modifying process conditions, allowing some control over downstream processing behaviour.

Spray drying is compatible with a wide range of organic solvents and solvent mixtures, allowing flexibility in dissolving both the drug and the polymer. This is particularly useful for drugs with limited solubility in common solvents. However, the method also has several limitations. Large volumes of solvent are often required, increasing cost, waste generation, and environmental burden. In some cases, rapid solvent evaporation can lead to the formation of a polymer-rich outer layer, which may trap residual solvent inside the particles. This can complicate drying efficiency and residual solvent control.

Another challenge in spray drying is product stickiness, particularly when operating near the polymer's glass transition temperature. Sticky particles may adhere to the drying chamber or cyclone walls, leading to yield loss and poor process reproducibility. Spray drying also has a relatively narrow operating window. Excessively high inlet temperatures may cause thermal degradation of the drug or polymer, while low temperatures may result in incomplete drying and wet, aggregated product.

Successful spray drying requires careful control of several key process parameters. Inlet temperature typically ranges from 80 to 140°C and must remain below the degradation temperature of formulation components. Feed rate affects droplet drying time and particle morphology, while outlet temperature provides a practical indication of drying efficiency. Atomization pressure determines droplet size distribution, which directly influences particle size. Solvent selection is critical and must ensure complete solubilization of both drug and polymer. Commonly used solvents include ethanol, acetone, and dichloromethane [80-81].

Recent studies have shown that spray-dried amorphous solid dispersions formulated with appropriate polymers can achieve significant bioavailability improvement. In particular, systems based on hydroxypropyl methylcellulose acetate succinate have demonstrated sustained supersaturation and improved in vivo performance. Animal studies have reported three- to seven-fold increases in systemic drug exposure compared to crystalline drug, along with higher peak plasma concentrations, confirming the clinical relevance of spray-dried solid dispersions.

2.4.2 Hot-Melt Extrusion

Hot-melt extrusion is the most widely used thermal-based manufacturing method for solid dispersions and is increasingly favoured for large-scale production. Unlike spray drying, this technique does not require solvents. In hot-melt extrusion, the drug and polymer are fed into an extruder barrel using controlled feeders. Inside the barrel, the materials are exposed to elevated temperatures and mechanical shear generated by rotating screws. This combination of heat and mixing forces the drug to disperse uniformly within the molten polymer matrix. The molten mass is then pushed through a die to form strands or pellets, which are cooled to obtain a solid amorphous dispersion.

A significant advantage of hot-melt extrusion is the absence of solvents, which eliminates concerns related to solvent toxicity, residual solvent limits, and solvent disposal. The process is continuous, making it inherently scalable and suitable for commercial manufacturing. Processing

times are short, often measured in minutes, and residence time and temperature can be precisely controlled along different zones of the extruder. Rapid cooling of the extrudate can further reduce the risk of drug recrystallisation.

Hot-melt extrusion often produces solid dispersions with good physical stability due to potent drug–polymer mixing and improved molecular-level dispersion. However, the method also has limitations. High processing temperatures may not be suitable for heat-sensitive drugs or polymers. Some drug–polymer combinations exhibit limited miscibility at high drug loadings, restricting formulation flexibility. The equipment required for hot-melt extrusion is expensive, and process optimisation requires specialised expertise. In addition, exposure to oxygen during processing may lead to oxidation of sensitive drugs or polymers that are inadequately controlled [83-84].

Comparative studies have shown that hot-melt extruded solid dispersions often exhibit superior physical stability compared to spray-dried systems, particularly for drugs with a strong tendency to recrystallise. Improved miscibility between the drug and polymer in the molten state contributes to higher glass transition temperatures and reduced molecular mobility. As a result, hot-melt extrusion is often preferred when long-term stability is critical.

2.4.3 Solvent Evaporation and Freeze-Drying

Solvent evaporation remains a helpful technique for early-stage formulation development and for drugs that cannot tolerate elevated temperatures. In this approach, the drug and polymer are dissolved in a common solvent, followed by slow solvent removal under reduced pressure or ambient conditions. Inflexible and straightforward, solvent overchallenging's difficult to scale and often results in heterogeneous products.

Freeze-drying offers an alternative for moisture- or heat-sensitive drugs. In this method, the solvent is removed by sublimation after freezing the solution. Freeze-drying can produce highly porous materials with rapid dissolution, but it is expensive, time-consuming, and not well-suited for large-scale manufacturing. As a result, both solvent evaporation and freeze-drying are mainly limited to research and early development stages [85-86].

2.5 Supersaturation Maintenance and Recrystallisation Prevention

The formation of a supersaturated drug solution is the primary mechanism by which solid dispersions enhance oral bioavailability. When an amorphous drug dissolves, it can reach concentrations above its equilibrium solubility. However, such supersaturated states are thermodynamically unstable and tend to revert to the crystalline form unless stabilised. Preventing recrystallisation during dissolution is therefore essential for maintaining improved absorption.

Polymers act as precipitation inhibitors by interacting with drug molecules in solution. They reduce nucleation by adsorbing onto forming crystal surfaces and slow crystal growth by

increasing solution viscosity and limiting molecular diffusion. Drug–polymer hydrogen bonding also plays a key role in maintaining the drug in solution. In addition, smaller drug particles dissolve faster than larger ones, and this size-dependent behaviour can delay crystal growth in supersaturated systems [87].

pH-dependent polymers provide an additional mechanism for stabilisation by maintaining a local environment that discourages crystallisation. Cyclodextrins can further stabilise supersaturation through inclusion complex formation and hydrophobic interactions. Studies comparing different polymers have shown that carrier selection strongly influences supersaturation duration. Polymers such as HPMCAS are able to maintain elevated drug concentrations for several hours, whereas PVP-based systems often show rapid precipitation shortly after dissolution.

2.6 Physical and Chemical Stability Considerations

Despite their advantages, solid dispersions face significant stability challenges. Intrinsic factors influencing recrystallisation include the strength of drug–polymer interactions, drug loading level, molecular mobility, and the drug's inherent crystallisation tendency. Lower drug loading generally improves stability by reducing the driving force for crystallisation. Polymer glass transition temperature and moisture content also strongly affect molecular movement within the matrix.

Environmental factors such as humidity, temperature, light exposure, and oxygen availability further impact stability. Moisture acts as a plasticiser, lowering the glass transition temperature and accelerating crystallisation. Elevated temperature increases molecular mobility, while light and oxygen may cause chemical degradation. Packaging materials also play an important role by controlling moisture and oxygen exposure.

For these reasons, solid dispersions must undergo rigorous stability testing according to international guidelines. Experimental data consistently show that formulations with moderate drug loading exhibit better long-term stability than highly loaded systems. This highlights the importance of conservative formulation design to ensure acceptable shelf life and reliable clinical performance [88-89].

3. Lipid-Based Formulations: Mechanisms and Applications

3.1 Classification and Composition

Lipid-based drug delivery systems encompass a diverse group of formulations ranging from simple triglyceride solutions to sophisticated self-emulsifying and self-nanoemulsifying systems. The FDA's classification of lipid-based oral formulations distinguishes four types based on composition and self-emulsification properties:

Type	Composition	Surfactant Content (%)	Self-Emulsification Droplet Size	Clinical Examples
Type I	Oil only; drug dissolved in oil	0	100–500 nm upon dispersion	Soft gelatin capsules (Sandimmune®) [90]
Type II	Oil + surfactant	20–50	100–300 nm (SEDDS)	Fortovase®, Agenerase® [91]
Type IIIA	Oil + hydrophilic surfactant (HLB 10–16) + hydrophobic surfactant	40–80	50–100 nm (SMEDDS)	Kaletra®, Aluvia®[92]
Type IIIB	Water-soluble surfactant + co-solvent + minimal oil	40–80	50–100 nm (SNEDDS)	Triglide®, Celexa® [93]
Type IV	Aqueous surfactant solution; no oil	>90	N/A	Limited oral applications [94]

3.2 Formulation Components and Rational Selection

Lipid-based drug delivery systems rely on the careful selection of formulation components to achieve effective solubilization, stable dispersion, and enhanced intestinal absorption. The main components include lipid vehicles, surfactants, and cosurfactants, or co-solvent components, which play specific roles, and their combined performance determines the overall success of the formulation. Rational selection is therefore essential to balance drug solubility, physical stability, digestion behaviour, and patient safety [95].

3.2.1 Lipid Vehicles (Oils)

Lipid vehicles serve two primary functions in lipid-based formulations. First, they dissolve lipophilic drugs and maintain them in a solubilised state before and after oral administration. Second, they promote the transport of highly lipophilic drugs via the intestinal lymphatic system, thereby allowing partial or complete avoidance of first-pass hepatic metabolism. The choice of oil strongly influences drug solubility, digestion rate, and the risk of drug precipitation during gastrointestinal dilution.

Medium-chain triglycerides are commonly used lipid vehicles and include triglycerides of caproic, caprylic, and capric acids. These lipids are rapidly digested by pancreatic lipase, forming digestion products that support drug solubilization. Due to their fast digestion, medium-chain triglycerides often provide rapid drug release and absorption. However, rapid dilution and

digestion in gastrointestinal fluids can cause a sudden drop in drug solubility, increasing the risk of precipitation. This limitation must be carefully evaluated during formulation development.

Long-chain triglycerides, such as derivatives of oleic and linoleic acids, are digested more slowly than medium-chain triglycerides. Their slower digestion reduces the risk of drug precipitation after oral administration and promotes the formation of chylomicrons in intestinal cells. This process enhances lymphatic transport, which is particularly beneficial for drugs that undergo extensive first-pass metabolism. While long-chain triglycerides generally provide better precipitation resistance, slow digestion may delay drug release, and high intestinal lipase activity can still lead to solubility challenges in some cases.

Semi-synthetic lipids, including fatty acid esters of propylene glycol such as caprylic-capric triglycerides, are designed to combine the favourable properties of medium- and long-chain lipids. These materials offer a balanced profile of solubilization capacity and digestibility, making them suitable for many lipid-based systems. They are widely used for their reproducibility and good compatibility with surfactants.

Monoglycerides and diglycerides are essential critical components in lipid formulations. Their amphiphilic nature allows them to act as both lipid vehicles and mild surfactants. These molecules facilitate emulsion formation and enhance self-emulsifying behaviour. Their hydrophilic–lipophilic balance values are generally low, making them effective at stabilising oil phases and enhancing formulation performance.

Comparative studies consistently show that long-chain lipids are more effective than medium-chain lipids in preventing drug precipitation after dilution. As a result, formulations containing long-chain lipids often exhibit improved, more consistent oral bioavailability [96-97].

3.2.2 Surfactants

Surfactants are essential components of lipid-based drug delivery systems. Their primary role is to reduce interfacial tension between the oil and aqueous phases, allowing the formulation to form acceptable emulsions upon contact with gastrointestinal fluids. Surfactants also help maintain colloidal stability and prevent phase separation during storage and dilution.

Selection of surfactants primarily based on their hydrophilic–lipophilic balance value. For oil-in-water emulsions, surfactants with intermediate to high HLB values are required. In self-emulsifying drug delivery systems, surfactants with moderate HLB values are typically used, whereas in self-micro emulsifying systems, more hydrophilic surfactants are needed to achieve spontaneous formation of small droplets.

Commonly used surfactants include polysorbates, sorbitan esters, ionic surfactants, and vitamin E-based materials. Polysorbate 80 and polysorbate 20 are widely applied due to their good safety profile and strong emulsifying capacity. Sorbitan monooleate is more lipophilic and is often

combined with hydrophilic surfactants to achieve an optimal balance. Sodium lauryl sulphate provides strong emulsification but may cause gastrointestinal irritation at higher concentrations.

Vitamin E polyethene glycol succinate is a multifunctional surfactant that not only improves emulsification but also inhibits intestinal enzymes and efflux transporters. This additional activity can further enhance drug absorption and reduce variability.

Surfactant concentration is a critical formulation parameter. Self-emulsifying systems generally require moderate surfactant levels, while micro emulsifying systems may need much higher concentrations to achieve spontaneous emulsification. However, excessive surfactant content can irritate the gastrointestinal tract and negatively affect patient tolerance. Therefore, careful optimisation is required to balance performance and safety [98-99].

3.2.3 Cosurfactants and Co-solvents

Cosurfactants and co-solvents are used to support surfactant function and improve formulation flexibility. These components enhance drug solubility in the lipid phase and facilitate rapid emulsification upon dilution. They reduce interfacial tension and increase interfacial fluidity, thereby helping form stable emulsions with small droplet sizes.

Commonly used cosurfactants and co-solvents include ethanol, propylene glycol, and polyethene glycol. These materials improve drug loading capacity and reduce the amount of surfactant required. However, volatile co-solvents may evaporate during storage or after capsule filling, thereby affecting formulation stability. Their concentration must therefore be carefully controlled [100].

3.3 Mechanisms of Bioavailability Enhancement

Lipid-based drug delivery systems enhance oral bioavailability through multiple complementary mechanisms that act during digestion and absorption in the gastrointestinal tract. These mechanisms allow lipid formulations to overcome dissolution-limited absorption associated with poorly soluble drugs.

3.3.1 Solubilization in the Lipid Phase

In lipid-based formulations, the drug is already dissolved in the lipid vehicle before administration. This eliminates the need for solid-state drug dissolution, a significant barrier in conventional oral dosage forms. After ingestion, the formulation remains as a uniform mixture until it encounters digestive fluids. Enzymatic digestion of triglycerides produces monoglycerides and fatty acids, which maintain the drug in a solubilised state [101].

3.3.2 Mixed Micelle Formation

During digestion, lipid breakdown products interact with bile salts and phospholipids naturally present in the intestine. This interaction leads to the formation of small mixed micelles. These micelles effectively solubilise the drug, thereby creating a high local drug concentration at the intestinal surface. The resulting concentration gradient strongly favours drug absorption and reduces the impact of poor aqueous solubility.

3.3.3 Lymphatic Transport and First-Pass Bypass

Highly lipophilic drugs can associate with chylomicrons formed during lipid digestion and be transported through the intestinal lymphatic system. This pathway allows drugs to enter systemic circulation without passing through the liver, thereby avoiding first-pass metabolism. Lipid-based formulations containing suitable lipid vehicles are particularly effective in promoting this mechanism and can dramatically increase bioavailability for drugs with high hepatic clearance [102].

3.3.4 Epithelial Transport Enhancement

Recent studies suggest that lipid-based formulations may also enhance drug transport across the intestinal epithelium. Lipid components can modify membrane fluidity, inhibit efflux transporters, and increase drug residence time in the intestine. These effects further support improved and consistent oral absorption.

components may enhance epithelial permeability through:

- Tight junction modulation
- P-glycoprotein inhibition (particularly TPGS)
- CYP3A4 inhibition (reducing intestinal first-pass metabolism)
- Increased residence time in the small intestine

3.4 Self-Emulsifying Drug Delivery Systems (SEDDS) and Their Variants

3.4.1 SEDDS vs. SMEDDS vs. SNEDDS

SEDDS (Self-emulsifying drug delivery systems): Form conventional emulsions with droplet size 100–300 nm upon dilution in aqueous media. The self-emulsification process is triggered by digestive motility and water diffusion into the formulation.

SMEDDS (Self-micro emulsifying drug delivery systems): Generate transparent or translucent microemulsions with droplet size <50 nm. These formulations typically contain higher surfactant concentrations (50–80% w/w) and exhibit spontaneous emulsification.

SNEDDS (Self-nanoemulsifying drug delivery systems): Represent the most advanced formulation type, forming fine nano emulsions (<100 nm) even upon mild aqueous dilution. SNEDDs often incorporate lipophilic surfactants, hydrophilic polymers, and solid carriers to enhance physical stability.

Comparative clinical data demonstrate that SEDDS/SMEDDS/SNEDDS formulations consistently outperform conventional tablets in oral bioavailability. A meta-analysis comparing microemulsions and SMEDDS with liposomal formulations found that both approaches enhance oral bioavailability comparably, with no significant differences in AUC [103-104].

3.4.2 Formulation Development and Pseudo-Ternary Phase Diagrams

Rational formulation design employs pseudo-ternary phase diagrams mapping the oil-surfactant-aqueous system composition space. The diagram identifies:

- Emulsification region: Composition space yielding stable emulsions
- Microemulsion window: Narrower region producing transparent microemulsions
- Crystallisation boundary: Formulation compositions exhibiting phase separation or drug crystallisation

Pre-formulation studies establish optimal oil: surfactant: cosurfactant ratios, validate drug solubility in each component, and confirm the absence of undesired drug-excipient interactions via HPLC, XRPD, and DSC.

A representative case study: Bosentan (BOS), a poorly soluble antihypertensive, was formulated into SNEDDS using pseudo-ternary diagrams. Optimisation via Box-Behnken design yielded a formulation with droplet size ~80 nm, robustness to pH and viscosity variations, long-term stability (>12 months at 25°C/60% RH), and a 2–3-fold improvement in in vitro dissolution and ex vivo permeability compared to the commercial product (Tracleer®) [105-106].

3.5 Clinical Performance and Marketed Products

Multiple lipid-based formulations have achieved regulatory approval and clinical success:

- Fortovase® (saquinavir soft gelatin capsules): Type II SEDDS; 12-fold oral bioavailability improvement vs. crystalline drug
- Kaletra® (lopinavir-ritonavir capsules): Type IIIA SEDDS; improved therapeutic drug levels
- Aluvia® (lopinavir-ritonavir tablets): Enhanced formulation with improved stability and food-effect reduction
- Triglide® (fenofibrate): Type III lipid-based system; marked food-effect mitigation
- Viread® (tenofovir): Lipid-based delivery; improved bioavailability

Docetaxel microemulsion demonstrates dramatic bioavailability enhancement: oral bioavailability 34.42% in rats versus 6.63% for Taxotere® intravenous formulation when administered orally-a >5-fold improvement [107].

4. Nanotechnology-Based Drug Delivery Systems

4.1 Nanocrystals: Rationale, Preparation, and Clinical Application

4.1.1 Definition and Mechanism

Nanocrystals are defined as carrier-free, submicron colloidal drug delivery systems with a mean particle size typically between 10–800 nm (more commonly 100–400 nm). Unlike solid dispersions, which require polymeric stabilisers, nanocrystals consist of pure drug particles, minimally stabilised with surface-active agents (surfactants, polymers) solely to prevent aggregation.

The bioavailability enhancement mechanism in nanocrystals is elegantly straightforward: reduction of particle size dramatically increases surface area. According to the Noyes-Whitney equation, the dissolution rate is directly proportional to the surface area (A) and the concentration gradient (Cs - C):

$$\frac{dC}{dt} = \frac{D \times A \times (C_s - C)}{h}$$

Where:

- D = drug diffusion coefficient
- A = particle surface area
- Cs = saturation concentration
- C = concentration in bulk solution
- h = boundary layer thickness

Reducing particle size from 10 µm to 200 nm increases surface area ~50-fold, thereby accelerating dissolution by a commensurate factor.

4.1.2 Manufacturing Technologies

Top-down methods (particle size reduction):

- High-pressure homogenization (HPH): Drug suspension forced through a microfluidiser at 1,500–4,000 bar; creates cavitation phenomena that disrupt particle agglomerates
- Media milling: Drug suspended in liquid vehicle with ceramic beads; collision comminates particles to nanosized
- Sonication: Ultrasonic energy disrupts particle agglomerates [108-109].

Bottom-up methods (controlled precipitation):

- Supercritical antisolvent (SAS) precipitation: Drug dissolved in organic solvent; supercritical CO2 (scCO2) added as antisolvent, inducing controlled precipitation
- Nanoprecipitation: Rapid mixing of drug solution in organic solvent with aqueous surfactant solution; diffusion-driven precipitation yields nanoparticles
- Combination HME + sonication: Hot-melt extrusion of drug-lipid nanoparticles followed by probe sonication for size reduction

Representative bioavailability improvements achieved with nanocrystal formulations:

Drug	Particle Size	Bioavailability vs. Coarse Powder	Metric
Lutein	150–200 nm	26.3-fold ↑ saturation solubility	3–4-fold ↑ in vitro release [110]
Apigenin	400–800 nm	3.6-fold ↑ Cmax; 3.4-fold ↑ AUC	Significant ↓ tmax [111]
Bexarotene	<200 nm	↑ AUC, ↓ Cmax → reduced side effects	Improved in vivo efficacy [112]
Oridonin	Nano vs. commercial	Dramatically ↑ different solubility vs. physical mixture	Stabilized with Pluronic F68, Brij 78, PVP K25 [113]

4.1.3 Stabilisation and Surface Modification

While theoretically "carrier-free," nanocrystals require surface stabilisation to prevent Ostwald ripening, defined as the preferential growth of larger particles at the expense of smaller ones, and colloidal aggregation. Surfactants used for stabilisation include Poloxamer 188 (Pluronic F68), which protects through steric hindrance; polysorbates such as Tween 20 and Tween 80, which provide ionic and steric stabilisation; lecithin, which forms a phospholipid coating and is biocompatible; and sodium dodecyl sulfate (SDS), which offers ionic stabilisation but has potential for GI irritation. Surface modification for targeting involves coating nanocrystals with polymers or conjugating them with targeting ligands such as antibodies and peptides to achieve tissue-specific delivery, passive or active accumulation in tumours through the enhanced permeation and retention (EPR) effect, or cellular internalisation via receptor-mediated endocytosis.

4.2 Polymeric Nanoparticles

4.2.1Classification and Composition

Polymeric nanoparticles encompass nanospheres, which are matrix systems, and nanocapsules, which exhibit core-shell architectures. Common polymers include PLGA (poly(lactide-co-glycolide)), an FDA-approved biodegradable copolymer suitable for hydrophobic cargo encapsulation; chitosan, a biopolymer with mucoadhesive properties whose cationic charge enables cellular uptake; polycaprolactone (PCL), a hydrophobic polyester that provides a

sustained release profile; and PEG-modified polymers, which enhance circulation time and reduce reticuloendothelial system (RES) uptake.

4.2.2 Bioavailability Enhancement Mechanisms Polymeric nanoparticles enhance oral bioavailability through multiple mechanisms, including particle uptake via M cells and antigen-sampling intestinal pathways, where particles smaller than 1000 nm readily penetrate Peyer's patches and bypass traditional enterocyte absorption; mucoadhesion, as chitosan nanoparticles adhere to the intestinal mucosa, prolonging residence time and increasing absorption opportunity; permeability enhancement through modulation of tight junctions or facilitation of paracellular transport; protection from enzymatic degradation by shielding drugs from intestinal proteases within the polymer matrix; and lymphatic targeting, where particle size and surface chemistry direct transport to gut-associated lymphoid tissue (GALT). A landmark study evaluated PLGA nanoparticles loaded with cyclosporine, a BCS Class II immunosuppressant with P-glycoprotein efflux liability, and demonstrated that PLGA nanoparticles with a size of 143 nm enhanced oral cyclosporine bioavailability in rats compared to a free drug suspension, likely due to increased intestinal permeability, reduced efflux, and protection against enzymatic degradation [114–115]. Figure 4

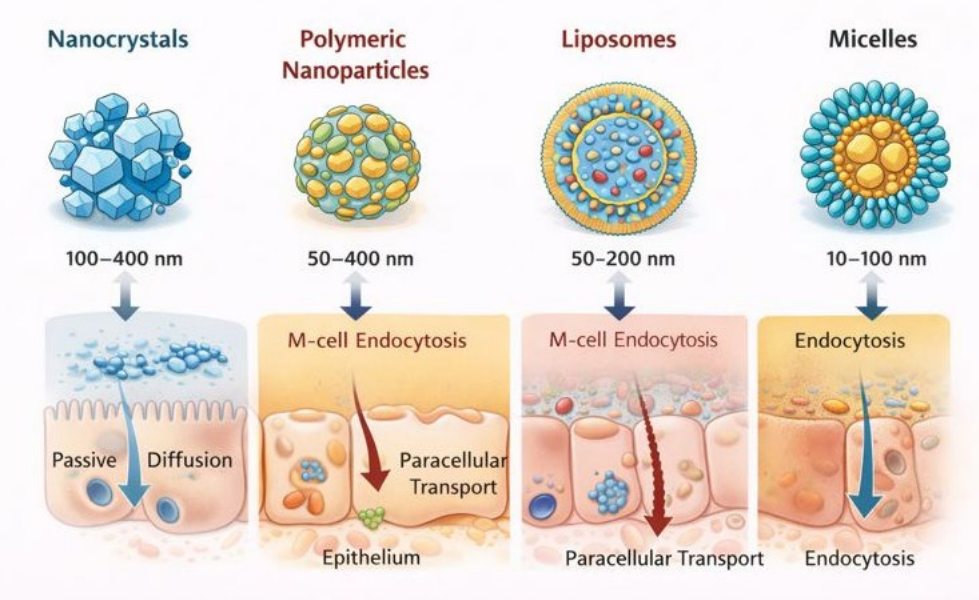

Figure 4. Nanotechnology Platforms for Oral Delivery

4.3 Liposomes and Other Vesicular Systems

4.3.1 Liposomal Architecture and Composition Liposomes are bilayered phospholipid vesicles with an aqueous interior capable of encapsulating both hydrophilic and lipophilic cargo. They mimic biological membranes, providing inherent biocompatibility and biodegradability. Lipid composition variables include phosphatidylcholine derived from egg or soy lecithin, which is zwitterionic and forms stable bilayers; cholesterol, which modulates membrane fluidity; PEG-lipid conjugates, which enhance circulation time and reduce immunogenicity; and cationic

lipids, which facilitate cellular uptake and enable targeting. Drug loading strategies include passive encapsulation using co-extrusion or thin-film hydration methods, active loading through pH gradient or ammonia gradient techniques to achieve higher loading efficiency, and supercritical fluid loading, which produces smaller particles with higher drug loading.

4.3.2 Clinical Application and Performance

Liposomal formulations have achieved widespread clinical adoption, with Doxil® (pegylated liposomal doxorubicin) remaining a first-line cancer therapeutic since FDA approval in 1995. For poorly soluble compounds, liposomes enable improved performance, as demonstrated by curcumin liposomes with a particle size of 263 nm that showed approximately a two-fold oral bioavailability enhancement in rats, and efavirenz liposomes that achieved a two-fold bioavailability improvement over the free drug with reduced CD4+ T cell toxicity. A representative study demonstrated that liposomal preparations of poorly soluble therapeutic agents produced via supercritical fluid technology exhibited superior physical stability and bioavailability, with liposomes prepared through supercritical fluids showing a 4.8-fold increase in in vivo AUC compared to conventional formulations [116–117].

4.4 Polymeric Micelles

4.4.1 Architecture and Mechanism

Polymeric micelles are self-assembled nanostructures formed by amphiphilic block copolymers in aqueous solution. Above the critical micelle concentration (CMC), these copolymers spontaneously aggregate, with hydrophobic blocks forming a core and hydrophilic blocks extending into the aqueous phase. Common block copolymers include PEO-PPO-PEO such as Pluronic F68, F77, and F87, which are non-ionic, FDA-approved, and employed in Abraxane; poloxamines (Tetronic), which are dendritic poloxamers with enhanced solubilization; chitosan-based copolymers that are cationic and promote cellular uptake; and PEG-poly(lactide) or PEG-poly(ε-caprolactone) systems that are biodegradable and provide sustained release.

4.4.2 Performance and Clinical Examples Polymeric micelles typically exhibit a size of approximately 300 nm, enabling passive tumour targeting through the EPR effect. They solubilise hydrophobic drugs via hydrophobic interactions, prevent drug crystallisation, and allow sustained release governed by core degradation kinetics. Paclitaxel polymeric micelles marketed as Abraxane® are based on PEG-poly(lactide) copolymers, have a particle size of 80–130 nm, and are FDA-approved for breast cancer in 2005 and pancreatic cancer in 2013. Compared with Taxol®, a cremophor-formulated paclitaxel, Abraxane eliminates hypersensitivity reactions, increases Cmax by 27%, and improves antitumor efficacy without increasing toxicity [118–119].

5. Advanced Nanotechnology Platforms

5.1 Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC)

5.1.1 Architecture and Preparation Solid lipid nanoparticles (SLN) represent a hybrid approach combining lipid chemistry with nanotechnology. They consist of drug-loaded lipid cores (60–500 nm) stabilised by stabilising layers, physically resembling fat globules. Unlike liposomes, the lipid matrix is solid at body temperature, providing superior drug encapsulation and stability. Preparation methods include high-pressure homogenization, in which the drug-lipid mixture is forced through a microfluidiser with temperature maintained above the lipid melting point to ensure melt formation; ultrasonication, where a lipid-drug dispersion is sonicated and cavitation effects generate nanoparticles; and spray cooling, in which a hot lipid-drug solution is atomised into cold air and rapid cooling solidifies droplets. Nanostructured lipid carriers (NLC) represent next-generation refinements, incorporating a liquid lipid component alongside solid lipids, creating an imperfect crystal structure that enhances drug loading and reduces burst release [120].

5.1.2 Bioavailability Enhancement Mechanism

SLN/NLC formulations enhance bioavailability through improved lymphatic uptake, where the lipid matrix promotes chylomicron-mediated transport; enhanced intestinal absorption due to intimate contact with enterocytes via mucosal penetration; P-glycoprotein inhibition, as some lipids such as lecithin and oleic acid inhibit drug efflux; reduced enzymatic degradation because the lipid matrix shields the drug from proteases; and increased residence time, as bioadhesive lipids prolong GI transit. A representative case is Vinpocetine, a poorly soluble cerebrovascular drug, formulated as SLN with a glyceryl monostearate (GMS) core (70–200 nm), which demonstrated enhanced oral bioavailability in Wistar rats compared to free drug suspensions and conventional formulations [121–122].

5.2 Mesoporous Silica Nanoparticles (MSN)

5.2.1 Rationale and Unique Properties Mesoporous silica nanoparticles represent an inorganic platform offering distinct advantages for poorly soluble drug delivery. They provide a large pore volume that can accommodate substantial drug quantities (20–40% w/w drug loading), controlled pore size with a narrow pore distribution (2–10 nm typical) that stabilises drugs in an amorphous state, and a high specific surface area of 500–1000 m^2/g that enables strong drug adsorption. Their tunable surface chemistry allows silanol groups to enable silanization, surface coating, and targeting ligand attachment. Silica demonstrates biocompatibility and is GRAS (Generally Recognised as Safe) at appropriate dose ranges, and stimuli-responsive release can be achieved through gatekeeper concepts enabling pH-, temperature-, or enzyme-triggered release [121].

5.2.2 Drug Loading and Release Mechanisms Drug loading can be achieved through impregnation, where a drug solution contacts MSN and capillary forces fill the pores; solvent evaporation, in which the drug is dissolved in a volatile solvent with MSN and solvent removal leaves the drug in the pores; and supercritical CO_2 loading, which enables rapid and uniform pore filling without thermal degradation. Release mechanisms include diffusion-controlled release, where the drug gradually diffuses from hydrophobic pores into the

aqueous dissolution medium; pore-sealing with gates, in which polymeric gates such as pH-sensitive polymers maintain pores sealed in acidic gastric fluid and open in neutral or basic small intestinal pH; and enzymatic release, where protease-cleavable linkers enable intestinal-specific release.

5.2.3 Clinical Performance A representative case is Prednisolone, a glucocorticoid with variable bioavailability, loaded into MSN and incorporated into orodispersible films, which achieved more than 90% drug release within 2 minutes, dramatically faster than free drug formulations, enabling immediate-release applications and precise low-dose therapies.

5.3 Advanced Nanoplatforms and Emerging Technologies

5.3.1 Metal-Organic Frameworks (MOF) Metal-organic frameworks combine metal ions or clusters with organic ligands, forming porous crystalline structures. Their application to poorly soluble drug delivery is emerging, with advantages including exceptionally high surface areas greater than 5000 m^2/g, diverse chemical tunability, and potential for active targeting. Challenges include potential metal ion toxicity, biocompatibility concerns, and regulatory uncertainty, while applications remain at the early-stage research level for pH-responsive release and combination drug delivery [122].

5.3.2 Carbon Nanostructures (Nanotubes, Fullerenes) Carbon nanotubes (CNTs) and fullerenes offer unique properties for drug delivery, including high drug loading capacity due to hydrophobic drug binding within the tube structure, targeted delivery through functionalization that enables targeting ligand attachment, and permeability enhancement, as carbon-based structures may enhance transcellular transport. Limitations include potential pulmonary and hepatic toxicity, bioaccumulation concerns, and limited clinical translation to date.

5.3.3 Hybrid Lipid-Polymer Nanoparticles Hybrid systems combine polymeric and lipid components, synergising advantageous properties. PEG-lipid-polymer nanoparticles utilise PEG to increase circulation time, lipid to facilitate cellular uptake, and polymer to enable controlled release. Lipid-substituted PLGA nanoparticles use surface lipid coating to reduce immunogenicity and enhance intestinal uptake. mRNA lipid nanoparticles (LNP), composed of an ionizable lipid, structural lipid, cholesterol, and PEG-lipid, have shown remarkable clinical success, as demonstrated by Comirnaty® and Spikevax®, highlighting their therapeutic potential [123].

6. Comparative Analysis and Technology Selection

6.1 Decision Tree for Formulation Strategy Selection among solid dispersions, lipid systems, and nanotechnology requires systematic evaluation of drug physicochemical properties, regulatory precedent, and commercial viability. The decision algorithm considers drug properties such as LogP (lipophilicity), where high LogP values greater than 3 favour lipid formulations and nanocrystals, while low LogP drugs may require supersaturation stabilisation; molecular

weight, as huge molecules greater than 600 Da may prefer a nanoparticle or micellar approach; ionizability, since ionizable drugs that are weak acids or bases may benefit from salt formation or complexation; and stability, because heat-labile drugs require spray drying or solution-based methods rather than hot-melt extrusion (HME). Regulatory precedent is also evaluated, with solid dispersions having more than 50 FDA-approved products and well-established guidance, SEDDS and SMEDDS having 10–15 approved products with growing acceptance, nanocrystals having 3–5 approved products including Abraxane® with an emerging regulatory pathway, and liposomes having 10–15 approved products with an established regulatory framework. Manufacturing scalability and cost are critical considerations, where spray drying is established and scalable with moderate cost, HME offers superior scalability at large scale with lower solvent waste, lipid-based systems require specialised equipment with moderate cost, and nanoparticles are equipment-dependent with potentially higher cost but increasing efficiency. Finally, the bioavailability improvement target guides selection, as BCS Class II drugs with high permeability typically require only dissolution rate enhancement, making solid dispersions often optimal, whereas BCS Class IV drugs with low permeability require combined dissolution and permeability enhancement, making lipid systems or absorption enhancers necessary [124]. Figure 5

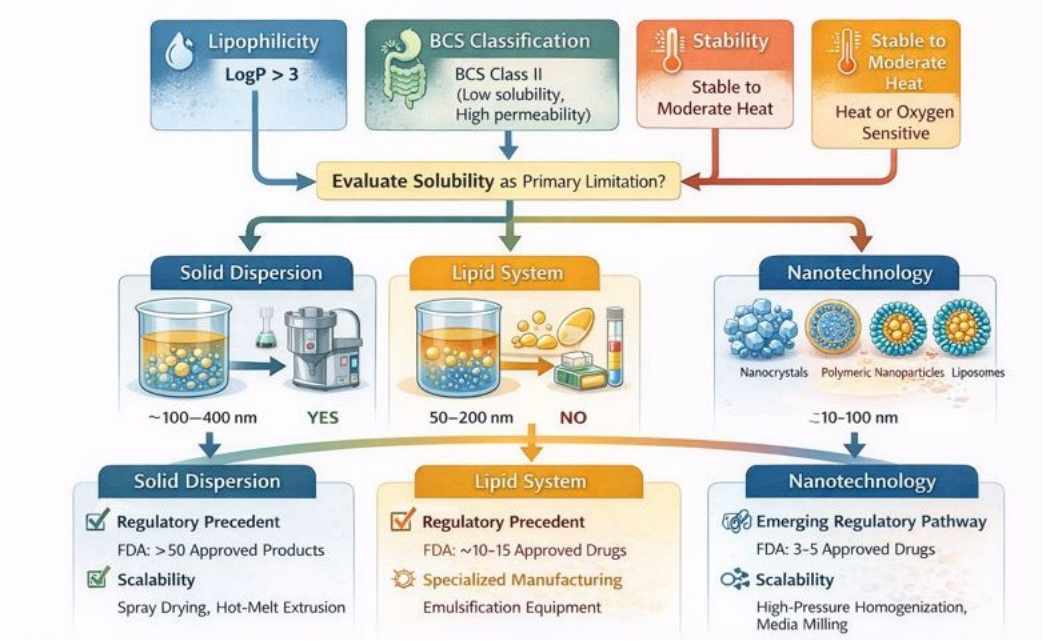

Figure 5 . Decision Tree for Selecting Oral Bioavailability Enhancement Strategy

6.2 Comparative Efficacy: Case Study Analysis

Case 1: Itraconazole (Triazole Antifungal)

Formulation Type	Oral Bioavailability	Food Effect	Regulatory Status	Commercial Product

Crystalline drug	~5%	Minimal	N/A	Sporanox® IV only (pre-2001) [125]
HPMC solid dispersion	~50–60%	Minimal	FDA approved (2001)	Sporanox® oral capsule
SEDDS lipid formulation	~40–50%	Minimal	N/A	Alternative research formulation [126]

Conclusion: HPMC solid dispersion proved superior, achieving ~10-fold bioavailability enhancement. HPMC's pH-dependent solubility aligns with the weakly basic pKa of itraconazole, enabling targeted release in the small intestine, where absorption is optimal.

Case 2: Saquinavir (HIV Protease Inhibitor)

Formulation Type	Oral Bioavailability	Food Effect	Regulatory Status	Commercial Product
Crystalline drug	~4%	Extreme	Not developed	N/A
SEDDS (soft gelatin)	~48%	Requires a high-fat meal	FDA approved (1997)	Fortovase®
Enhanced formulation (tablet)	~22%	Reduced with a light meal	FDA approved (2005)	Invirase® tablet [127]

SEDDS formulation dramatically improved bioavailability through lymphatic transport and enhanced intestinal permeability. A subsequent tablet formulation with improved absorption enhancers partially matched SEDDS performance while enabling dose reduction through enhanced compliance and stability.

7. Regulatory Landscape and Clinical Translation

7.1 Regulatory Framework for Poorly Soluble Drug Formulations The regulatory environment has evolved substantially, recognising the legitimate need for sophisticated formulation science to enable therapeutic advancement. Key regulatory guidances include FDA Guidance for Industry (2018, updated 2024), “Considerations for Drug Products that Contain Nanomaterials,” which establishes a framework for evaluating characterisation including particle size distribution, morphology, surface area, and composition, stability including physical, chemical, and colloidal stability, toxicology with nanoparticle-specific concerns such as organ accumulation and inflammation, and manufacturing scale-up feasibility. ICH Guideline M9 (2023) addresses nanoparticles in regulatory submissions and requires physico-chemical characterisation by multiple independent methods, stability data under ICH conditions,

bioavailability and bioequivalence assessment, and in vivo performance correlation with in vitro dissolution [128].

7.2 Approved Products and Market Penetration Solid dispersion formulations represent the majority of approved poorly soluble drug products, including itraconazole with HPMC for fungal infections approved in 1992 as Sporanox® in oral capsule form, tacrolimus with HPMC for immunosuppression approved in 1994 as Prograf® in oral capsule form, griseofulvin with PEG for fungal infections approved in 2000 as Gris-PEG™ in oral tablet form, rosuvastatin with HPMC for hyperlipidemia approved in 2002/2004 as Crestor® in oral tablet form, lopinavir–ritonavir with PVP-VA for HIV infection approved in 2001/2005 as Kaletra® in oral capsule and tablet forms, etravirine with HPMC for HIV infection approved in 2008 as Intelence® in oral tablet form, vemurafenib with HPMCAS for melanoma approved in 2011 as Zelboraf® in oral tablet form, and ivacaftor with HPMCAS for cystic fibrosis approved in 2012 as Kalydeco® in oral tablet form. Lipid-based formulations remain limited in number but clinically impactful, including lopinavir–ritonavir (Kaletra®, Aluvia®), saquinavir (Fortovase®, Invirase®), fenofibrate (Triglide®), and tenofovir (Viread®). Nanocrystal and polymeric micellar formulations include paclitaxel (Abraxane®, protein-bound nanoparticles), aprepitant (Emend®, nanocrystalline suspension), and itraconazole/hydroxypropyl-β-cyclodextrin (Sporanox® IV) [129-130].

8. Recent Advances and Emerging Trends (2023–2025)

8.1 Hybrid and Multi-Modal Formulation Approaches Contemporary pharmaceutical development increasingly employs hybrid strategies that combine the advantages of multiple technologies. Polymer–surfactant–lipid ternary systems, representing third-generation amorphous solid dispersions augmented with lipid components such as MCT and LCT and surfactants, enable superior supersaturation maintenance, enhanced lymphatic uptake potential, improved physical stability, and synergistic bioavailability enhancement of 3–7-fold compared with crystalline drug. Nanocrystal–polymer composites, in which nanocrystals are stabilised within polymeric matrices such as spray-dried nanocrystal–polymer composites, combine high drug loading from the nanocrystal phase, enhanced stability from the polymer matrix, improved wettability from the polymeric coating, and reduced Ostwald ripening potential.

8.2 Stimuli-Responsive and Triggered Release Systems Recent advancement in gatekeeper-concept delivery enables pH-responsive triggers using acid-labile linkers in the gastric environment with release in neutral intestinal pH and polymer gates such as Eudragit L-100 and HPMCAS dissolving at pH greater than 5.0–7.0. Enzyme-triggered release includes protease-cleavable peptide sequences, β-galactosidase-mediated release in the colon, and bacteria-triggered systems for colonic targeting. Physically triggered release includes ultrasound-responsive microbubbles, temperature-sensitive polymers above body temperature, and magnetic field-responsive systems using iron oxide nanoparticles.

8.3 Personalised Medicine Approaches Emerging pharmacogenomic understanding enables personalised formulation selection. CYP3A4 polymorphisms indicate that individuals with

reduced CYP3A4 expression may benefit from formulations bypassing first-pass metabolism such as lipid-based and lymphatically transported systems. P-glycoprotein genetic variation suggests that patients with high P-gp expression benefit from formulations incorporating P-gp inhibitors such as TPGS or lymphatic routing. Genetic prediction of absorption involves machine learning models predicting optimal formulation based on individual genetic and physiological markers.

8.4 Artificial Intelligence and In Silico Formulation Design AI-assisted drug development accelerates formulation optimisation through machine learning models predicting bioavailability by training on historical formulation–bioavailability data and predicting optimal excipient combinations and drug loading, molecular dynamics simulation predicting drug–polymer interactions and miscibility before empirical synthesis, and high-throughput screening automation using robotic systems to screen hundreds of formulation variants in parallel. A representative study demonstrated that in silico prediction of solid dispersion performance using machine learning accurately identified HPMCP HP-55, CAP, and Eudragit L-100 as optimal polymers for specific model drugs, with predictions subsequently confirmed by in vitro and animal pharmacokinetic studies, demonstrating the validity of computational approaches [131-132].

9. Challenges, Limitations, and Future Perspectives

9.1 Persistent Technical Challenges Despite decades of research, recrystallisation remains the Achilles heel of amorphous formulations, as supersaturated solutions exhibit inherent thermodynamic instability and prevention requires continuous inhibition through polymer-mediated mechanisms. Current mitigation strategies include polymer selection optimisation with HPMCAS being superior to PVP for crystallisation inhibition, conservative drug loading of 20–30% rather than 40–50%, surfactant incorporation to inhibit nucleation and growth, moisture control below 3% w/w for most polymers, and temperature stability through cool-chain maintenance. Future perspectives include novel polymers with enhanced crystallisation inhibition capacity, computational prediction of optimal polymer–drug combinations, and in situ crystallisation monitoring during formulation development. Drug–polymer miscibility and phase separation remain critical issues, as not all drug–polymer combinations form stable, miscible systems and poor interactions result in phase separation and crystallisation during storage or dissolution. Approaches to predict miscibility include Flory–Huggins interaction parameter calculation, Hansen solubility parameter matching, thermal analysis using DSC and modulated DSC, and spectroscopic characterisation using Raman, NMR, and FTIR.

9.2 Manufacturing and Scale-Up Issues Spray drying challenges include stickiness near Tg causing products to adhere to cyclone walls and yield loss, solvent residues requiring regulatory limits below 5 ppm with critical residual solvent removal, thermal degradation of labile drugs or polymers at high inlet temperatures, and batch-to-batch consistency requiring careful control of process parameters and essential GMP documentation. HME limitations include temperature constraints where thermolabile drugs are incompatible with an upper processing limit of approximately 220°C, shear forces that may cause polymer degradation or drug oxidation,

pressure spikes due to blockages causing extrusion interruptions, and die design considerations where pellet versus strand geometry impacts downstream processing [133-134].

9.3 Physical and Chemical Instability Hygroscopic instability arises because PVP and some other hydrophilic polymers absorb substantial moisture at elevated humidity, and water acts as a plasticiser, reducing Tg and accelerating molecular motion and crystallisation. Solutions include desiccant packaging using silica gel or molecular sieves, moisture-barrier container closure systems, polymer selection with HPMCAS being less hygroscopic than PVP, and moisture-resistant coating. Oxidative stability issues occur as lipophilic drugs in formulations containing lipid components are prone to oxidative degradation, particularly when unsaturated lipids are present. Mitigation strategies include antioxidant addition such as butylated hydroxytoluene, butylated hydroxyanisole, and mixed tocopherols, oxygen-barrier packaging, nitrogen or argon flushing, and headspace control.

9.4 Regulatory and Commercialisation Challenges Regulatory agencies acknowledge insufficient standardisation for nanoparticle characterisation, particularly for particle size distribution where multiple methods such as laser diffraction, dynamic light scattering, and transmission electron microscopy yield different results and harmonisation is lacking, surface area measurement where the BET method is standard for powders but less established for suspensions, colloidal stability assessment where no universally accepted protocol exists, and bioavailability prediction where IVIVC development is challenging for nanosystems. Cost and commercial viability remain concerns, as nanoformulations requiring sophisticated equipment and manufacturing command premium pricing, and Abraxane®, despite being clinically superior to conventional paclitaxel, faced reimbursement challenges in some healthcare systems due to cost despite evident clinical advantages.

9.5 Future Directions Emerging technologies on the horizon include self-assembling peptides and proteins as biopolymer-based nanocarriers offering superior biocompatibility, exosome-mimetic nanoparticles leveraging cell-derived vesicle technology for enhanced cellular targeting, microfluidic formulation for continuous production of nanoparticles with precise control, blockchain-enabled quality control using distributed ledger technology to ensure manufacturing traceability, and quantum dots and optomagnetic systems enabling simultaneous imaging and therapy in theranostics. Translational priorities include accelerated regulatory pathways such as FDA expedited designation for innovative formulations, bioavailability prediction modelling with robust IVIVC models reducing animal testing, sustainable manufacturing using green chemistry approaches to reduce environmental impact, combination formulations for co-delivery of multiple poorly soluble drugs in a single formulation, and personalised dosing using adaptive formulations responding to individual pharmacogenomic profiles [135-136.]

10. Conclusion

Oral bioavailability enhancement of poorly water-soluble drugs has matured from an empirical art into a rigorous science underpinned by a mechanistic understanding of drug dissolution, supersaturation phenomena, and cellular absorption. Three primary technological platforms solid

dispersions, lipid-based formulations, and nanotechnology systems offer complementary advantages.

Solid dispersions, leveraging polymeric carriers and manufacturing innovations (spray drying, HME), remain the most clinically prevalent approach, with >50 FDA-approved products. Their success stems from demonstrated physical and chemical stability, scalability, and predictable bioavailability enhancements (2–10-fold).

Lipid-based formulations (SEDDS/SMEDDS/SNEDDS) shine for lipophilic drugs where lymphatic bypass of first-pass metabolism becomes advantageous. Their evolution toward Type IIIB and IV systems reflects pharmaceutical ingenuity in optimising carrier composition. Performance improvements rival or exceed solid dispersions in selected applications, though regulatory precedent remains more limited.

Nanotechnology-based systems**,** including nanocrystals, polymeric nanoparticles, liposomes, and mesoporous silica, represent the frontier of innovation. Nanocrystal and polymeric micellar formulations (clearede®) have regulatory hurdles, validating this approach. Ongoing miniaturisation, surface functionalization, and stimuli-responsive release mechanisms promise even more sophisticated performance in the coming decade.

Hybrid approaches combining multiple technologies (polymer-surfactant-lipid ternary systems, nanocrystal-polymer composites) now routinely achieve improvements and represent the future trajectory of formulation science.

From a translational perspective, systematic evaluation of drug physicochemical properties, regulatory precedent, manufacturing for g scalability, and bioavailability improvement remains essential. The pharmaceutical industry's embrace of innovative formulation science, evidenced by >100 FDA-approved products that leverage technologies, demonstrates the clinical and commercial value of addressing this persistent development challenge.

As pharmaceutical discovery increasingly yields lipophilic, bioactive compounds, the formulation technologies reviewed herein will remain central to drug development strategy. Continued investment in mechanistic understanding, manufacturing innovation, and regulatory harmonisation will expand the arsenal of tools available to practitioners, enabling the clinical translation of novel therapeutics previously considered "undruggable" due to poor solubility. The convergence of artificial intelligence, personalised medicine, and sustainable manufacturing promises a future in which oral bioavailability challenges become increasingly manageable, delivering benefits to patients globally through improved therapeutic efficacy, reduced side effects, and enhanced medication compliance.

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