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REVIEW ARTICLE

Strategies to Enhance Oral Bioavailability of Poorly Water-Soluble Drugs: From Formulation Design to Nanotechnology

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Abstract

Oral administration remains the preferred route for most systemically acting drugs, yet many compounds emerging from discovery programmes displays low aqueous solubility, which restricts dissolution in gastrointestinal fluids and can limit both the rate and the extent of absorption. This review examines the physicochemical and biopharmaceutical determinants of poor oral bioavailability and appraises the strategies available to address them, from conventional techniques to nanoscale systems. Salt formation, pH adjustment, cosolvency, surfactant solubilisation and cyclodextrin complexation act largely by altering the drug environment or its ionisation state. Solid-state approaches, particularly amorphous solid dispersions, and lipid-based systems exploit supersaturation and digestion-mediated solubilisation respectively. Particle-size reduction and nanocrystals increase surface area and dissolution rate without changing equilibrium solubility. Nanocarriers, including polymeric nanoparticles, lipid nanoparticles, nanoemulsions, liposomes and polymeric micelles, offer additional mechanisms such as protection from degradation and altered mucosal interaction, although their translational record is mixed and intact intestinal uptake is limited. The review argues that no single approach is universally superior; selection depends on dose, solubility, permeability, solid-state behaviour, stability and manufacturing feasibility. Enduring challenges of scale-up, physical stability, reproducibility and regulatory characterization are discussed, together with emerging directions in rational design and continuous manufacturing.

Keywords: Poorly Water-Soluble Drugs; Oral Bioavailability; Dissolution Rate; Biopharmaceutics Classification System; Lipid-Based Drug Delivery; Amorphous Solid Dispersion; Nanocrystals; Nanocarriers

Introduction

Oral administration is preferred for most systemically acting drugs because it is non-invasive, convenient and inexpensive.¹ After oral dosing, the drug must dissolve in the gastrointestinal fluids and then cross the intestinal epithelium; the interplay of dissolution and permeability, modified by dose and luminal conditions, determines the rate and extent of entry into the systemic circulation.^{1,2} The Biopharmaceutics Classification System (BCS) formalised this relationship by grouping drug substances according to aqueous solubility and intestinal permeability.¹

Solubility, dissolution, permeability and bioavailability are distinct properties that are often used interchangeably. Solubility is an equilibrium property describing the maximum concentration of dissolved drug at a given temperature, pH and medium. Dissolution is a kinetic process governed by the surface area available and by the difference between saturation and bulk concentration. Permeability describes passage across the

intestinal membrane, absorption is the net transfer across that membrane, and bioavailability denotes the fraction of the dose reaching the systemic circulation unchanged.^{1,2} A formulation that accelerates dissolution, for instance by reducing particle size, need not change equilibrium solubility, and an increase in solubility does not guarantee improved absorption when permeability or first-pass extraction is limiting.³

Low aqueous solubility is a frequent obstacle in contemporary development, although estimates of its prevalence vary with the compound set and the definition of solubility used; the trend towards higher molecular weight and greater lipophilicity among discovery compounds has contributed to the problem.⁴ When dissolution is slow or incomplete, the concentration presented to the absorptive epithelium may remain below that required for efficient permeation, producing variable and dose-limited exposure. This review traces the available approaches from conventional

methods through solid-state and lipid-based strategies to nanoscale systems, and evaluates them critically.

Biopharmaceutical Basis of Poor Oral Bioavailability

Aqueous solubility reflects the balance between solvation and crystal lattice energy, and is also influenced by molecular size and lipophilicity. Dissolution rate, described by the Noyes-Whitney relationship, depends on surface area, diffusion coefficient and the concentration gradient across the diffusion layer, so it can be increased by enlarging surface area or improving wetting without altering equilibrium solubility.^{5,6} Permeability depends on partitioning across the enterocyte membrane and on influx and efflux transporters. Efflux systems such as P-glycoprotein, together with presystemic metabolism by cytochrome P450 enzymes, limit the fraction of absorbed drug reaching the systemic circulation.⁴

The gastrointestinal environment is neither uniform nor static. Gastric pH varies between fasting and fed states, and the stepwise rise in pH along the small intestine alters the ionisation, and hence solubility, of weak acids and bases. Bile salts and phospholipids secreted after a meal form mixed micelles that increase the solubilising capacity of intestinal fluids for lipophilic drugs, one reason for the positive food effects seen with many poorly soluble compounds.^{7,8} Crystallinity and solid-state form influence dissolution through lattice energy, and polymorphs or solvates of the same compound can differ in solubility and dissolution rate.¹⁰

Where a supersaturated solution is generated, for example by dissolution of an amorphous solid or a lipid formulation, precipitation may follow dilution or a change in pH, and precipitation inhibitors are often needed to sustain the transiently elevated concentration long enough for absorption.⁹ Distinguishing thermodynamic solubility from apparent, transient supersaturation is therefore central to understanding these systems. The BCS defines four classes: class I (high solubility, high permeability), class II (low solubility, high permeability), class III (high solubility, low permeability) and class IV (low solubility, low permeability).¹ Poorly soluble compounds of interest are most often class II, for which absorption is dissolution-rate-limited and formulation can markedly affect bioavailability; class IV compounds combine solubility

and permeability limitations and are generally harder to develop.³ Poorly soluble drugs do not, however, behave identically: the Developability Classification System separates dissolution-rate-limited (IIa) from solubility-limited (IIb) compounds, since the former may respond to particle-size reduction while the latter usually require approaches that raise the dissolved concentration itself.¹¹

Conventional Formulation Strategies

Micronisation and nanonization reduce particle size to increase surface area and hence dissolution rate; the principle is kinetic rather than thermodynamic, because saturation solubility is essentially unchanged except at very small dimensions.⁶ Wet-milling, high-pressure homogenisation and controlled precipitation generate particles in the micron and sub-micron range, and nanocrystal suspensions exploit this directly.¹² Limitations include poor wettability of fine powders, aggregation, and a ceiling once dissolution is no longer rate-limiting. The approach suits dissolution-rate-limited, high-dose, chemically stable compounds.

Salt formation converts an ionisable drug into a more soluble salt, exploiting the higher aqueous solubility of the ionised species; it applies to weakly acidic and weakly basic compounds possessing a suitable ionisable group.¹³ Salts offer inexpensive, well-characterised counterions and can raise dissolution rate within the gastrointestinal pH range, but they may disproportionate to the free form in vivo and are unsuitable for neutral compounds.¹³ Adjusting pH through buffering excipients can increase the solubility of ionisable drugs, but its usefulness is constrained by gastrointestinal tolerability and by the risk of precipitation as pH shifts on transit.⁵

Cosolvents such as propylene glycol, ethanol and polyethylene glycol increase solubility by reducing vehicle polarity and are widely used in liquid products. After oral dosing they are diluted by gastrointestinal fluids and the loss of solvent power can precipitate the drug, while tolerability and the volumes sometimes required further limit applicability.^{5,14} Surfactants and wetting agents improve dissolution by lowering surface tension and, above the critical micelle concentration, solubilising drug within micelles. This raises apparent solubility, but dilution below the critical micelle concentration, or destabilisation by bile salts and lipids, can cause precipitation, and gastrointestinal tolerance

constrains surfactant concentration.^{5,14} Complexation with cyclodextrins produces inclusion complexes in which the lipophilic drug sits within a hydrophilic cavity, raising aqueous solubility and improving dissolution and stability.¹⁵ Cyclodextrins are most effective when the drug dimensions match the cavity and the dose does not exceed the complexation capacity of a tolerable amount of excipient; high-dose drugs may need impractically large quantities, and complexation does not address permeability-limited absorption.^{15,16}

Solid-State and Physical Formulation Approaches

The amorphous state offers the highest apparent solubility of a solid form because the absence of a crystal lattice lowers the energy required for dissolution; it is, however, metastable and tends to crystallise, which can abolish the solubility advantage during storage or dissolution.^{17,18} Amorphous solid dispersions stabilise the drug by dispersing it molecularly within a polymeric carrier, usually a hydrophilic polymer with which the drug interacts. The polymer inhibits nucleation and crystal growth and maintains supersaturation in the dissolution medium, allowing a transiently high concentration to be presented to the absorptive epithelium.^{9,18}

Polymorphism, cocrystals, eutectic systems and solid solutions modify solid-state properties in different ways. Cocrystals are crystalline multi-component solids in which drug and coformer are held together by non-covalent interactions; they can improve solubility and dissolution rate while retaining crystallinity and may suit neutral compounds lacking ionisable groups.^{20,21} Spray drying and hot-melt extrusion are the principal manufacturing routes to amorphous solid dispersions; hot-melt extrusion is solvent-free and continuous, whereas spray drying suits thermally labile drugs but requires solvent handling.^{19,22} The critical limitations are crystallisation risk, moisture sensitivity and manufacturing reproducibility.

Lipid-Based Formulation Strategies

Lipid formulations range from simple lipid solutions to self-emulsifying systems that generate fine dispersions on contact with gastrointestinal fluids. The lipid formulation classification system groups them by composition and behaviour on dispersion, distinguishing

simple lipid solutions, self-emulsifying and self-microemulsifying systems containing water-soluble surfactants, and formulations containing hydrophilic cosolvents.^{7,23} Self-nanoemulsifying systems form nanoscale droplets on dilution and are a subgroup of the self-emulsifying family.^{23,24} After administration, the formulation is dispersed and digested; pancreatic lipases hydrolyse triglycerides, and the resulting fatty acids and monoglycerides, with bile salts, form mixed micelles and vesicles that accommodate the drug and keep it solubilised as it traverses the intestine.^{7,8} The choice of lipid, for example medium- versus long-chain triglycerides, influences digestion kinetics and the extent of lymphatic transport.^{8,25} Lymphatic transport can bypass hepatic first-pass metabolism for highly lipophilic drugs that associate with lipoprotein particles, but this pathway is available only to compounds of sufficient lipophilicity and is difficult to predict reliably from *in vitro* data.²⁶

Lipid systems suit highly lipophilic, potent, low-dose drugs and compounds that partition strongly into mixed micelles; they are less suited to high-dose drugs, because drug load is limited by the solubilising capacity of the vehicle.²⁷ Physical and chemical stability of the lipid excipients, susceptibility to oxidation, and the potential for food effects to alter exposure are additional considerations. Precipitation of drug after aqueous dispersion is a recognised failure mode, and its prediction requires dispersion and digestion testing rather than simple solubility measurement.²⁴

Polymer-Based and Advanced Drug-Delivery Systems

Polymeric nanoparticles and polymeric micelles solubilise or encapsulate poorly soluble drugs within a hydrophobic core or matrix formed from amphiphilic block copolymers, increasing apparent solubility and, in some cases, protecting the drug from degradation.^{28,29} Polymeric micelles are well suited to parenteral delivery but have also been studied orally, where their stability under gastrointestinal conditions determines effectiveness; direct absorption of intact micelles is limited and, in many cases, drug is released within the gut and absorbed conventionally.²⁹ Dendrimers possess a highly branched architecture with internal cavities that can host hydrophobic drugs and increase solubility, and

their tunable surface chemistry permits biocompatible derivatives, although regulatory and toxicological questions remain for high-generation systems.^{30,31}

Solid lipid nanoparticles and nanostructured lipid carriers are lipid-based colloidal systems with a solid or mixed solid-liquid lipid matrix. Solid lipid nanoparticles may exhibit limited drug loading and a tendency to expel drug as the lipid lattice reorganises, whereas the inclusion of liquid lipids in nanostructured lipid carriers disrupts the crystalline matrix, accommodating more drug and reducing expulsion on storage.^{32,33} Liposomes have been explored orally, but instability in the gastrointestinal environment and susceptibility to bile salt disruption limit their application, and evidence for benefit is strongly formulation- and model-dependent.³⁴

Nanotechnology for Oral Delivery

A distinction is often blurred in the literature: nanosizing and nanocarrier-based delivery are different strategies addressing different problems. Nanocrystals are essentially pure drug particles reduced to the nanometre range and stabilised by surfactant or polymer; their purpose is to increase dissolution rate and, to a lesser degree, apparent solubility through surface area and curvature.^{12,35} Nanocrystals retain the drug in its crystalline state & do not encapsulate it, so their mechanism is dissolution-related rather than membrane-transport-related. Nanocarriers, by contrast, encapsulate, solubilise or complex the drug within a vehicle and may protect it from degradation, alter its interaction with mucus, epithelium, and modify release.^{36,37}

Claims that nanoparticles cross the intestinal barrier intact and release their contents systemically are not generally supported; the evidence indicates that intact particle uptake by healthy intestinal epithelium is limited and that, for many formulations, drug is released in the gut and subsequently absorbed in the usual manner.^{36,37} The contribution of lymphatic transport to overall absorption is likewise compound- and formulation-dependent and not easily generalised.²⁶

Mechanisms by Which Nanotechnology May Improve Bioavailability

Several distinct mechanisms may be distinguished, and their relative importance is formulation-specific. Increased surface area accelerates dissolution, and improved wetting of hydrophobic surfaces raises the effective area available.^{6,12} Enhanced apparent solubility

arises where the vehicle, such as micelles or the lipid phase of an emulsion, solubilises the drug, which is an effect of the medium rather than of the drug substance. Supersaturation maintenance, in which a polymer or other excipient retards precipitation, extends the period over which a high concentration is available.⁹ Protection from chemical or enzymatic degradation within the gut lumen preserves intact drug for absorption, and altered residence time or mucus interaction may change the opportunity for uptake.³⁷ Modulation of absorptive pathways has been proposed for some systems, but the evidence is largely mechanistic or preclinical and should not be extended to human absorption without direct confirmation.^{4,36}

Comparative Analysis of Formulation Strategies

Table 1 sets out the principal strategies, their mechanisms and their limitations side by side. The comparison shows that these approaches are not interchangeable: they act on different rate-limiting steps and are therefore suited to different drugs. Particle-size reduction addresses dissolution-limited absorption; complexation, cosolvency and lipid systems increase the dissolved or apparent concentration; solid dispersions exploit supersaturation; and nanocarriers add functions such as protection, controlled release and modified mucosal interaction. A strategy effective for one drug may be irrelevant for another whose absorption is limited by permeability or first-pass metabolism.

Formulation Selection: A Decision-Making Perspective

Selection should begin from the properties of the drug and of the dose rather than from a preferred technology. Dose number, aqueous solubility across the physiological pH range, permeability, melting point, LogP and LogD, ionisation behaviour and solid-state properties define the feasible options. A weakly basic drug with an ionisable centre may be considered for salt formation; a high-melting, lipophilic, dissolution-rate-limited compound may respond to particle-size reduction or an amorphous dispersion; and a very lipophilic drug may suit a lipid formulation, particularly if lymphatic transport is desirable and the dose is modest.^{3,4,11} Chemical and gastrointestinal stability constrain the choice, since a strategy that increases exposure only to a rapidly degraded or precipitated drug offers little benefit. Preformulation studies, including solubility and

dissolution profiling in biorelevant media, solid-state characterisation and stability assessment, provide the evidence on which this selection rests; such frameworks are conceptual aids to development and are not validated regulatory decision tools.¹¹

Characterization and Evaluation

Different techniques establish different things, and their combination depends on the strategy. Equilibrium solubility studies define thermodynamic solubility, whereas dissolution testing under sink and non-sink conditions probes release kinetics &, for supersaturating systems, the maintenance of elevated concentrations.^{16,18} Particle-size analysis and the polydispersity index characterise the size distribution of nanocrystals, nanosuspensions, nanoemulsions, and zeta potential indicates surface charge &, indirectly, colloidal stability.^{12,33} Solid-state characterisation distinguishes crystalline from amorphous material and identifies polymorphs: differential scanning calorimetry detects thermal transitions, powder X-ray diffraction reveals long-range crystalline order, & Fourier-transform infrared spectroscopy on molecular interactions.^{10,18}

Encapsulation efficiency indicates how much drug is associated with a carrier, while physical stability studies and, for lipid systems, in vitro digestion testing assess behaviour under simulated gastrointestinal conditions.^{24,27} Permeability studies & pharmacokinetic evaluation provide the integrated measures of absorption & exposure, but no single method suffices & in vitro surrogates must not be equated with in vivo behaviour.¹¹

Translational and Regulatory Challenges

The transition from an effective laboratory formulation to a robust product exposes problems not evident at small scale. Scale-up of high-energy processes, whether milling, homogenisation or hot-melt extrusion, can alter particle size, drug distribution and, for amorphous systems, the physical state, so batch-to-batch consistency must be demonstrated rather than assumed.^[19,38,39] Long-term physical stability remains a principal concern for amorphous and lipid systems, which may crystallise or undergo drug expulsion on storage, and for nanosystems, whose large surface area makes them sensitive to aggregation. Nanomaterial characterisation requires methods that establish size, size distribution, surface properties and, where relevant, the state of the

drug within the carrier.⁴⁰

The regulatory environment is developing. The United States Food and Drug Administration has issued guidance on drug products containing nanomaterials, describing the risk-based characterisation expected during development.⁴⁰ The International Council for Harmonisation guideline M9 provides recommendations for biopharmaceutics classification and for waiving in vivo bioequivalence studies for certain immediate-release products, and the FDA has published corresponding guidance on bioavailability and bioequivalence waivers based on the BCS.^{41,42} For products whose performance depends on the carrier as well as the drug substance, the European Medicines Agency has issued reflection papers on data requirements.⁴³

Reproducibility of manufacture, the establishment of in vitro-in vivo relationships and the variability of pharmacokinetics for absorption-dependent formulations remain practical obstacles. The cost of goods, the complexity of quality control and the limited number of established manufacturing routes for some nanocarriers further restrict translation.^{36,37,38}

Future Directions

Rational formulation design guided by preformulation data and by an explicit understanding of the rate-limiting step is likely to improve development efficiency, and quality-by-design approaches provide a systematic framework for linking formulation and process variables to product performance.^{11,22} Advanced solid-state engineering, including mesoporous carriers & cocrystals, continues to expand options for improving dissolution while retaining crystallinity, and computational approaches are increasingly used to predict drug-polymer miscibility and formulation stability.^{20,21,22}

Continuous manufacturing, exemplified by hot-melt extrusion, offers tighter process control and may improve consistency compared with batch routes.^{38,39} More predictive in vitro models, including biorelevant dissolution and digestion testing, are needed to narrow the gap between laboratory performance and clinical outcome, and reliable in vitro-in vivo correlations remain a priority.^{24,39} For nanomedicines, clearer characterisation requirements & harmonised regulatory expectations would support translation, but the evidence linking carrier to human absorption is still limited.^{36,40}

Table 1. Major Formulation Strategies for Improving Oral Bioavailability of Poorly Water-Soluble Drugs

Strategy	Principal mechanism	Major advantages	Important limitations	Typical application
Particle-size reduction (micronisation, nanonization)	Increases surface area and wetting, accelerating dissolution rate	Simple; broadly applicable; no change to the drug molecule; chemically stable crystalline product	No change to equilibrium solubility; poor wettability, aggregation and a ceiling once dissolution is no longer rate-limiting	Dissolution-rate-limited, high-dose, chemically stable compounds
Salt formation	Raises aqueous solubility of the ionised species	Inexpensive, well-characterised counterions; improved crystallinity and processability	Requires an ionisable group; risk of disproportionation or instability; unsuitable for neutral drugs	Weakly acidic or weakly basic, ionisable drugs
pH modification	Shifts ionisation and hence solubility of the drug	Conceptually simple; applicable to weakly basic compounds	Limited by gastrointestinal tolerability; precipitation on pH change	Weakly basic drugs whose solubility rises sharply at acidic pH
Cosolvent systems	Reduces solvent polarity to increase solubility	Effective in liquid products; simple to prepare	Dilution and precipitation on gastrointestinal transit; tolerability and volume constraints	Liquid and low-dose oral products
Surfactants and wetting agents	Wetting plus micellar solubilisation above the critical micelle concentration	Increases apparent solubility and improves wetting of hydrophobic particles	Loss of solubilisation on dilution or bile salt interaction; tolerance limits on surfactant concentration	Lipophilic drugs requiring enhanced wetting or solubilisation
Cyclodextrin complexation	Forms inclusion complexes that raise aqueous solubility	Well-established excipients; improves solubility, dissolution and stability	Cavity-size and dose dependence; large excipient quantities for high doses; does not address permeability	Low-to-moderate dose drugs with suitable molecular geometry
Amorphous solid dispersion	Molecular dispersion in polymer raises apparent solubility and maintains supersaturation	High apparent solubility; polymer stabilises the amorphous form and inhibits precipitation	Crystallisation and moisture sensitivity; manufacturing and storage complexity	High-melting, lipophilic, dissolution- or solubility-limited compounds
Co-crystals	Crystalline multi-component solid with improved solid-state properties	Improves solubility and dissolution while retaining crystallinity; suits neutral drugs	Requires a suitable coformer; limited solubility improvement; regulatory considerations	Neutral, non-ionisable, poorly soluble compounds
Lipid-based systems (solutions)	Presents drug in a lipid vehicle and leverages digestion-mediated solubilisation	Improved intestinal solubilisation; potential for lymphatic transport	Load limited by lipid capacity; oxidation and food-effect considerations	Highly lipophilic, potent, low-dose drugs
SEDDS / SMEDDS / SNEDDS	Forms fine or nanoemulsion on dispersion with lipids and surfactants	Spontaneous emulsification; improved solubilisation and absorption	Drug precipitation on dispersion; complex excipient selection; scale-up	Lipophilic drugs with high LogP and modest dose
Nanocrystals	Pure drug nanoparticles with high surface area increasing dissolution rate	High drug loading; chemically simple; no carrier required	Stabilisation against aggregation; no encapsulation or protection	Dissolution-rate-limited drugs, including high dose
Polymeric nanoparticles / micelles	Encapsulation or solubilisation within a polymer matrix or micellar core	Protection from degradation; controlled release; tunable surface chemistry	Limited intact particle uptake; stability under gastrointestinal conditions; variability	Lipophilic drugs requiring protection or modified release
Solid lipid nanoparticles	Drug dispersed in a solid lipid matrix	Biocompatible lipids; protection against degradation; controlled release	Low drug loading; drug expulsion on lipid lattice reorganisation	Lipophilic drugs requiring a lipid carrier
Nanostructured lipid carriers	Mixed solid-liquid lipid matrix with disrupted crystallinity	Higher loading than solid lipid nanoparticles; reduced drug expulsion	Colloidal stability; manufacture and characterisation complexity	Lipophilic drugs needing higher loading or stability
Nanoemulsions	Dispersed lipid droplets carrying dissolved drug	Improved solubilisation and dissolution; scalable preparation	Physical stability; dilution and digestion effects; surfactant load	Lipophilic drugs compatible with lipid excipients

Table 2. Comparison of Nanotechnology-Based Approaches for Oral Delivery

Nanotechnology approach	Basic principle	Potential bioavailability benefit	Major formulation challenges	Translational considerations
Nanocrystals	Pure drug nanoparticles stabilised by surfactant or polymer	Faster dissolution and some increase in apparent solubility	Aggregation and particle growth; stabiliser selection; drying to a solid form	Relatively simple manufacture; established routes for some products
Polymeric nanoparticles	Drug dispersed or encapsulated in a polymer matrix	Protection from degradation, controlled release, modified mucosal interaction	Drug loading and encapsulation efficiency; stability in the gut; particle fate	Limited intact particle uptake; scale-up and characterisation demands
Lipid nanoparticles (SLN/NLC)	Drug dispersed in a solid or mixed solid-liquid lipid matrix	Improved solubilisation and dissolution; protection from degradation	Loading capacity, drug expulsion, colloidal and storage stability	Requires lipid digestion and stability testing; drying and scale-up
Nanoemulsions	Lipid droplets stabilised by surfactants	Enhanced intestinal solubilisation and dissolution	Physical stability, dilution and digestion behaviour, surfactant load	Scalable but sensitive to composition and processing
Liposomes	Phospholipid bilayers surrounding an aqueous core	Solubilisation of lipophilic drug; possible protection from degradation	Instability in the gastrointestinal environment; bile salt disruption	Evidence for oral benefit is formulation- and model-dependent
Polymeric micelles	Amphiphilic block copolymer micelles with a hydrophobic core	Increased apparent solubility; possible protection and release control	Stability on dilution; limited intact micelle absorption	Fate after oral administration not well established across drugs

Conclusion

Improving the oral bioavailability of poorly water-soluble drugs is a formulation problem with several possible solutions, and the appropriate choice is governed by the properties of the drug and the demands of the dose. Salt formation, cosolvency and complexation remain effective where the drug possesses the requisite ionisable groups or the dose permits; amorphous solid dispersions and lipid-based systems exploit supersaturation and digestion-mediated solubilisation for less tractable compounds; and nanocrystals provide a dissolution-oriented solution that is chemically simple but requires careful stabilisation. Nanocarrier systems extend the available mechanisms to include protection, controlled release and altered mucosal interaction, yet the evidence does not support the view that they are universally superior, since intact particle absorption is limited, their behaviour is highly formulation-dependent, and their manufacture and regulatory characterisation are demanding. Progress will come not from adopting a single technology but from matching the strategy to the molecule, supported by rigorous preformulation, appropriate characterisation and models that predict human absorption more faithfully.

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Conflicts of Interest

There are no conflicts of interest.

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