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Review Artical

# Nanotechnology-Driven Bioavailability Enhancement: A Critical Review of BCS Class II and IV Drugs

**Arbaz Khan[1], Anu Rai[2], Deepak Rayakwar[3], Soma Sekhar Pulamarasetti[1], Monika Tanwar[1], Anjali Peter[1]**

[1]*B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India*
[2]*Nims Institute of Pharmacy, Nims University Rajasthan, Jaipur, Rajasthan, India*
[3]*Chameli Devi Institute of Pharmacy, Khandwa Road, Umrikheda, Indore, Madhya Pradesh, India*

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ABSTRACT

One of the major hurdles for the oral drug development is poor aqueous solubility. BCS Class II drugs are low solubility and relatively high permeability drugs and Class IV drugs are low solubility and low permeability drugs. Their absorption can thus be limited by dissolution, luminal solubilization, epithelial transport, efflux, metabolism and first pass extraction. Nanotechnology provides a variety of formulation strategies including nanocrystals, nanosuspensions, solid lipid nanoparticles, nanostructured lipid carriers, self-nanoemulsifying systems, nanoemulsions and polymeric or hybrid nanoparticles. We present in this review a mechanism-first framework connecting drug liabilities with gastrointestinal fate and nanocarrier selection. It addresses dissolution enhancement, mucus and unstirred-water-layer transport, epithelial uptake, P-glycoprotein/CYP-mediated presystemic loss and lymphatic transport. Particular attention is paid to formulation development, Quality by Design, biorelevant dissolution and lipolysis, critical quality attributes, scale-up, stability, safety, advanced intestinal models, pharmacokinetic predictability and regulatory translation. The review argues that the most useful oral nanomedicines are not just smaller particles but reproducible systems designed to overcome a defined absorption bottleneck while remaining scalable, stable, safe and clinically interpretable.

## Introduction

Many medicines are convenient to administer orally, but gastrointestinal physiology presents sequential barriers between a dosage form and systemic circulation. Exposure may be determined by a combination of dissolution, luminal solubilization, diffusion through mucus and the unstirred water layer, epithelial permeability, efflux transport, intestinal metabolism and hepatic first-pass extraction. The Biopharmaceutics Classification System (BCS) continues to be a useful first level framework as it discriminates compounds mainly by aqueous solubility and intestinal permeability, but oral absorption is a dynamic process that also depends on transit, food effects, supersaturation, transporter activity and formulation dependent gastrointestinal fate (Amidon et al., 1995; Yu and Amidon, 1999; Wacher et al., 1998;). Thus, nanotechnology has developed from simple particle size reduction to a more general approach to control the physical state, colloidal behavior and biological fate of poorly soluble drugs. Nanocrystals and nanosuspensions mainly enhance dissolution; lipid-based systems can enhance solubilization and, for certain drugs, promote lymphatic transport; polymeric and hybrid systems can

***Corresponding Author:** Omkar Rai

**Address:** Department of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur, Madhya Pradesh, India

**Email ✉:** omkarrai274304@gmail.com

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**Table 1:** BCS-guided formulation logic

| *Feature* | *BCS II* | *BCS IV* | *Main nano-objective* | *Examples* |
|---|---|---|---|---|
| Solubility | Low | Low | Increase apparent solubility/ dissolution | Nanocrystals; nanosuspension |
| Permeability | High | Low | Preserve or selectively increase flux | Lipid/polymeric/hybrid NP |
| Main bottleneck | Dissolution | Dissolution + permeability | Mechanism-matched design | BCS-guided selection |
| Efflux/metabolism | Variable | Often important | Reduce presystemic loss where justified | Lipid excipients; surface engineering |
| Lymphatic route | Drug-dependent | Potentially useful | Increase post-enterocyte transport | NLC/SLN/SNEDDS |

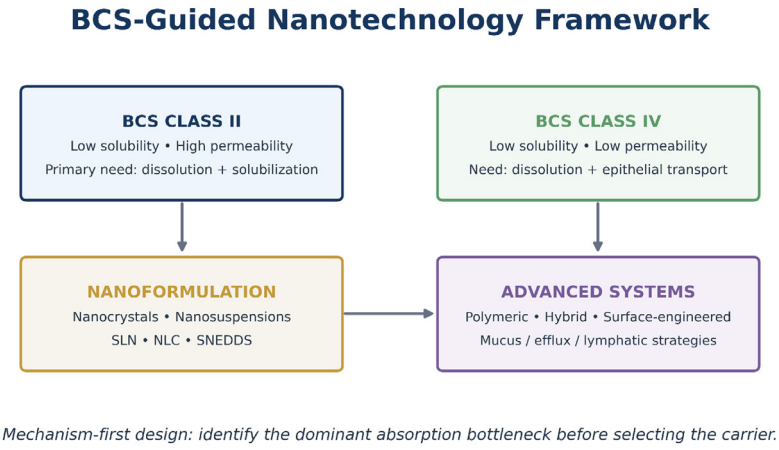


**Figure 1:** BCS-guided mechanistic framework for selecting nanotechnology-based oral bioavailability enhancement strategies

provide protection or modify interactions with mucus and the epithelium. Therefore, a rational review of these platforms requires that the formulation be matched to the dominant absorption bottleneck, rather than being selected solely by carrier popularity (Porter et al., 2007; Müller et al., 2008; Dahan and Hoffman, 2008; Desai et al., 2012; Junyaprasert and Morakul, 2015; Kim, 2023).

The objective of this review is to organize the major nanotechnology-based approaches for BCS Class II and IV drugs around three linked questions: which gastrointestinal barrier is limiting exposure, which nanoarchitecture can address that barrier, and which experiments can demonstrate a reproducible mechanistic benefit. The emphasis is on oral formulation design and translation rather than on a broad catalogue of nanomaterials (Wu and Benet, 2005; Salah et al., 2020; Babadi et al., 2021; Khan et al., 2022; Liu et al., 2024).

## Bcs Class II and IV: Distinct Biopharmaceutical Problems

### BCS Class II

BCS Class II drugs have low aqueous solubility and relatively high permeability. Their absorption is therefore often dissolution-limited, so increasing the rate and extent of drug dissolution can increase the concentration gradient available for epithelial uptake. Gastric emptying, intestinal pH, bile secretion, precipitation after dilution and food effects can nevertheless determine whether an apparent formulation improvement becomes a meaningful increase in systemic exposure (Amidon et al., 1995; Porter et al., 2007; Wu and Benet, 2005; O\'Driscoll and Griffin, 2008).

### BCS Class IV

BCS Class IV drugs have both low solubility and low permeability. For these compounds, increasing dissolution alone may not produce a proportional increase in exposure because epithelial transport can remain rate limiting. A useful formulation may therefore need to combine solubilization with controlled improvement of epithelial access, protection from presystemic loss, or an alternative transport route such as intestinal lymphatic uptake (Wu and Benet, 2005; Constantinides and Wasan, 2007; Caliph et al., 2000; Porter and Charman, 2001; Trevaskis et al., 2008).

### Beyond the BCS: A Mechanistic Framework

The same BCS class can contain drugs with markedly different gastrointestinal behavior. A compound that rapidly precipitates after dilution requires a different

strategy from one whose main problem is crystal lattice energy; similarly, a BCS IV drug with substantial P-glycoprotein liability is unlikely to benefit fully from dissolution enhancement alone. Formulation development should therefore begin with drug profiling and identification of the dominant absorption bottleneck (Yu and Amidon, 1999; Cummins et al., 2002; Benet and Cummins, 2001; Benet et al., 2004; Tiwari and Pathak, 2011).

The practical implication is that particle engineering should be selected after identifying the rate-limiting step. This approach reduces empirical screening and creates a clearer link between formulation attributes, mechanistic assays and pharmacokinetic outcomes (Patel and Patel, 2021; Kim et al., 2023; Agarwal et al., 2021; Liu et al., 2024).

### Gastrointestinal Absorption Mechanisms

After oral administration a nanocarrier suffers dilution, change in pH, bile salts, phospholipids, digestive enzymes, mucus, the unstirred water layer and intestinal motility before drug reaches the epithelial surface. Particle size, surface chemistry, lipid digestion, drug loading and stabilizer identity is what ultimately determines the species that delivers the drug to the epithelium (Thomson et al., 1993; Read et al., 1977; Porter et al., 2007; Dahan and Hoffman, 2008; Dahan and Hoffman, 2006) .

### Dissolution and Apparent Solubility

Nanocrystals increase the specific surface and can aid dissolution . Nanosuspensions provide a versatile dispersed form of poorly soluble APIs . Aggregation of particles, growth of crystal or change of polymorphic state during storage or redispersion can result in loss of benefit. The nanoscale dimensions should be regarded as a critical quality attribute and not as an end point per se (Junyaprasert and Morakul, 2015; Agarwal et al., 2021; Wang and et, 2022; Shegokar and Müller, 2010).

### Mucus and Unstirred-Water-Layer Transport

The mucus and unstirred water layer provides diffusional resistance between luminal drug and epithelial membrane. Surface charge, hydrophilicity, particle size and protein adsorption can affect the retention or penetration of mucus. Therefore, the formulations should be formulated to have a prolonged residence or efficient penetration depending on the mechanism of absorption (Thomson et al., 1993; Read et al., 1977; Banerjee et al., 2016).

### Epithelial Uptake

Transcellular uptake of nanoparticles by enterocytes may be mediated by specialized intestinal pathways and by paracellular transport under controlled conditions. Physiological lipid digestion and chylomicron-associated transport can be also exploited by lipid systems. However, increased cellular association should not be automatically interpreted as increased systemic bioavailability; barrier integrity and pharmacokinetic evidence should still be considered paramount (Caliph et al., 2000; Porter and Charman, 2001; Pridgen et al., 2014; Kim et al., 2023).

### P-glycoprotein and CYP-Mediated Loss

P-glycoprotein can return absorbed drug to the intestinal lumen, while CYP3A4 and other enzymes can metabolize drug within enterocytes. Selected surfactants, polymers and lipids may modify transporter activity, but intentional transporter modulation carries drug–drug interaction and safety implications. Mechanistic transporter assays should therefore accompany claims of improved absorption when efflux liability is important (Wacher et al., 1998; Wacher et al., 2001; Cummins et al., 2002; Benet and Cummins, 2001; Batrakova et al., 2004; Dabholkar et al., 2006; Cornaire et al., 2004).

### Lymphatic Transport and Gastrointestinal Fate

Long-chain lipids can stimulate chylomicron formation and promote lymphatic transport for sufficiently lipophilic drugs, potentially reducing direct hepatic first-pass extraction. Lipid formulations also undergo digestion, generating fatty acids, monoglycerides and mixed colloidal structures that can change drug solubilization. Consequently, lipid formulations should be characterized under physiologically relevant digestion conditions rather than in water alone (Porter et al., 2007; Dahan and Hoffman, 2008; Dahan and Hoffman, 2006; Caliph et al., 2000; O\'Driscoll, 2002; Porter and Charman, 2001; Trevaskis et al., 2008).

## Nanotechnology-Based Formulation Strategies

### Drug Nanocrystals and Nanosuspensions

Drug nanocrystals are mainly composed of the API with stabilizing agents and offer high drug loading and a direct correlation between particle size and dissolution. The usual ways of producing them are top-down milling or homogenization and bottom-up precipitation or crystallization. Dried redispersible systems and nanocrystal-in-microparticle approaches allow for improved handling and solid-dose conversion, provided that redispersibility and solid-state stability are maintained (Junyaprasert and Morakul, 2015; Agarwal et al., 2021; Che et al., 2024; Wang et al., 2021; Wang and et, 2022; Shegokar and Müller, 2010) (Abuzar et al., 2018; Roberts and Zhang, 2013).

### Solid Lipid Nanoparticles

Solid lipid nanoparticles encapsulate poorly soluble drugs in a solid lipid matrix. They can improve solubilization, shield payloads and alter intestinal absorption but drug loading, lipid polymorphism and drug expulsion during storage can impair performance. The choice of these is most rational when the drug is sufficiently lipophilic and the formulation provides a definite edge over simpler

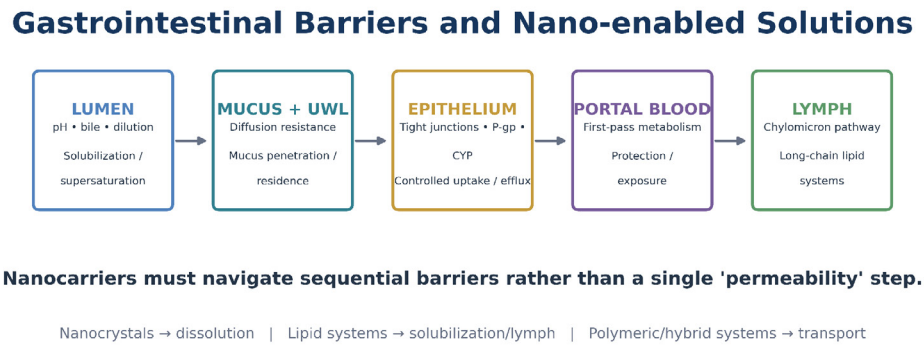


**Figure 2:** Major gastrointestinal barriers encountered by orally administered drugs and representative nano-enabled solutions

approaches based on dissolution (Müller et al., 2008; Müller et al., 2000; Muchow et al., 2008; Salah et al., 2020).

### Nanostructured Lipid Carriers

NLCs are composed of a mixture of solid and liquid lipids resulting in a less ordered matrix with a higher potential for drug loading than highly crystalline SLNs. Their value may lie in solubilization, mixed-micelle formation, and, in the case of appropriate drugs, lymphatic transport. The lipid ratio and the digestion behavior are important, since increasing the complexity of the formulation can change the physical stability and the in vivo behavior (Müller et al., 2002; Muchow et al., 2008; Zhuang et al., 2010; Tiwari and Pathak, 2011; Khan et al., 2015; Beloqui et al., 2017) (Poonia et al., 2016).

### SNEDDS and Nanoemulsions

Self-nanoemulsifying systems spontaneously form fine dispersions on dilution in gastrointestinal fluid and have the potential to maintain lipophilic drugs in a solubilized state. Nanoemulsions also have large interfacial areas. Key development risks include precipitation after dilution, surfactant burden, phase behavior and food dependence, so dispersion size alone is not an adequate performance criterion (Narang et al., 2007; Gursoy and Benita, 2004; Gangavarapu et al., 2024; Arshad et al., 2024; Babu and Prajapati, 2026).

### Polymeric and Hybrid Nanoparticles

Polymeric nanoparticles can be designed for interaction with mucus, controlled release or ligand-mediated uptake, and can protect the payloads. Hybrid systems by combining a nanocrystal, lipid phase and polymeric or surface layer can overcome multiple barriers. Multifunctionality is particularly attractive for BCS IV drugs, but every added component increases complexity in analytical, manufacturing and regulatory issues (Dabholkar et al., 2006; Pridgen et al., 2014; Pridgen et al., 2015; Kim et al., 2023; Babadi et al., 2021) (Mei et al., 2013).

### Nano-Cocrystals and Amorphous Nanoparticles

Nano-cocrystals combine crystal engineering and nanosizing and may alter the dissolution and physical properties when a suitable coformer is available. Amorphous nanoparticles can lead to high apparent solubility but tend to recrystallize. The formulation goal should be to control supersaturation, rather than to achieve maximum supersaturation, as rapid precipitation may offset the initial dissolution advantage (Tan et al., 2021; Liu et al., 2024).

## Comparative Platform Selection

No platform is intrinsically superior across all BCS II/IV compounds. Selection should be driven by the dominant liability, the required dose, the physical state of the API, expected gastrointestinal transformations and the feasibility of manufacturing the final dosage form (Patel and Patel, 2021; Gangavarapu et al., 2024; Kim et al., 2023; Khan et al., 2022; Arshad et al., 2024; Darwish et al., 2022). The platform coverage and mechanism groupings are illustrated in Figures 4 and 5.

## Formulation Development and Characterization

A rational development program should begin with drug profiling rather than carrier screening. Solubility across physiological pH, pKa, logP/logD, dose, melting point, crystal form, intrinsic dissolution rate, permeability, efflux liability, metabolic stability and food effect should be considered before selecting the nanoarchitecture. The resulting formulation should then be evaluated for particle attributes, solid state, drug loading, redispersibility, storage stability and biorelevant performance (Amidon et al., 1995; Wu and Benet, 2005; Babadi et al., 2021; Khan et al., 2022; Liu et al., 2024).

### Quality by Design Framework

Quality by Design is particularly useful for nanoformulations because small changes in process conditions can alter

**Table 2:** Comparative assessment of major nanotechnology platforms

| *Platform* | *Primary strength* | *Dominant mechanism* | *Best fit* | *Major limitation* | *Critical attributes* |
|---|---|---|---|---|---|
| Nanocrystals | High drug loading | Surface area/dissolution | BCS II; selected IV | Aggregation | Size, PDI, crystallinity, redispersibility |
| Nanosuspension | Flexible nanosizing | Dissolution/dispersion | BCS II/IV | Physical instability | Size, PDI, zeta potential |
| SLN | Lipid matrix | Solubilization + uptake | Lipophilic II/IV | Drug expulsion | Size, lipid state, EE |
| NLC | Higher loading than SLN | Solubilization + lymphatic effects | Lipophilic II/IV | Composition complexity | Lipid ratio, size, EE |
| SNEDDS | Rapid self-emulsification | Solubilization + possible lymphatic uptake | Lipophilic II/IV | Precipitation/surfactants | Dispersion size, phase behavior |
| Polymeric NP | Protection/engineering | Mucus interaction + uptake | Selected IV | Low epithelial transport | Size, polymer, surface |
| Nanoemulsion | Large interfacial area | Solubilization/dispersion | II; selected IV | Dilution stability | Droplet size, PDI |
| Hybrid NP | Multifunctionality | Combined barriers | Complex IV | High CMC burden | Component-specific CQAs |

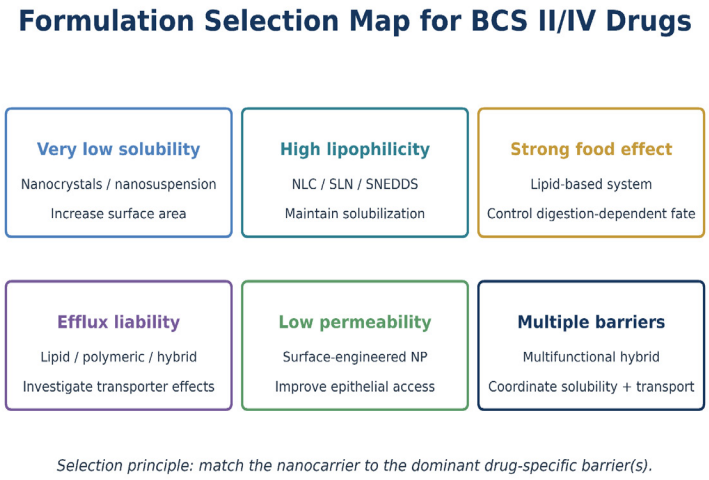


**Figure 3:** Practical formulation-selection map linking drug liabilities to candidate nanocarrier platforms.

particle size, morphology, solid state and surface characteristics. The Quality Target Product Profile should define the intended dose, release behavior, stability and clinical performance. Critical Quality attributes could include particle dimensions, polydispersity index, zeta potential, crystallinity, polymorphism characteristics, encapsulation efficacy, drug loading capacity, residual solvent levels, moisture content, redispersibility, and dissolution or lipolysis characteristics. Critical Material Attributes encompass API crystalline structure, lipid formulation, polymer molecular weight, and surfactant quality, whereas Critical Process Parameters may involve mixing vigor, homogenization pressure, milling energy, temperature, feed rate, and drying conditions (Patel and Patel, 2021; Kim et al., 2023; Babadi et al., 2021; Agarwal et al., 2021).

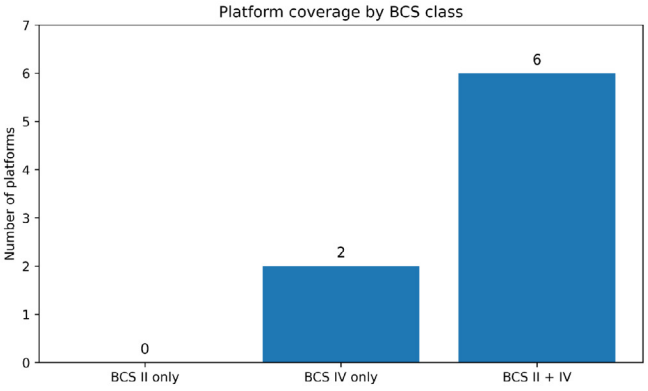


**Figure 4:** Platform coverage by BCS class, derived from the "Best fit" classifications in Table 2

## Biorelevant In Vitro Testing

Dissolution in deionized water or a simple buffer is generally insufficient for oral nanoformulations. Biorelevant media containing physiologically relevant bile salts and phospholipids can better describe drug solubilization. Dynamic in vitro lipolysis is valuable for lipid systems, because digestion changes the colloidal environment and can shift the balance between drug precipitation and solubilization. Where applicable, supersaturation should be assessed as a moderate concentration maintained over

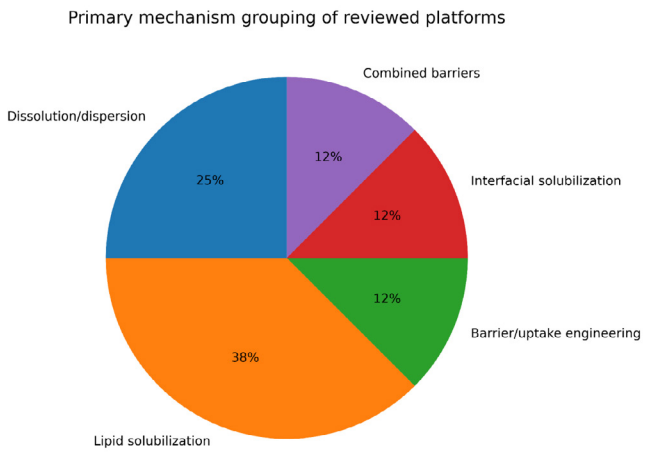


**Figure 5:** Primary mechanism grouping of the eight reviewed platforms, classified from the dominant mechanisms reported in Table 2

a useful interval may be more meaningful than a transient concentration spike (Dahan and Hoffman, 2008; Dahan and Hoffman, 2006; Gangavarapu et al., 2024; Babadi et al., 2021; Liu et al., 2024).

## Translational Challenges

### Scale-Up, Stability and Solid-Dosage Conversion

The sonication, precipitation and milling conditions developed in the laboratory may not be directly transferable to manufacturing, due to changes in mixing, shear, heat transfer, solvent removal and nucleation kinetics that can change size and solid state. Aqueous nanosuspensions may also need to be converted into tablets, capsules or powders, and drying can cause irreversible aggregation or crystallinity changes. Therefore, scale-up and solid-dose conversion should be considered during platform selection rather than after proof of concept (Patel and Patel, 2021; Agarwal et al., 2021; Wang and et, 2022; Shegokar and Müller, 2010).

### Safety and Excipient Exposure

Cellular interactions can be altered by nanoscale materials, and toxicity or drug–drug interactions can be affected by surfactants, polymers, lipid digestion products and surface ligands. Special attention should be paid to class IV formulations when permeability enhancers are used. Enhancement of epithelial flux is of no benefit if barrier integrity is compromised. Hence, the final product should be evaluated as a complete formulation and not only by taking into account the active ingredient (Batrakova et al., 2004; Dabholkar et al., 2006; Cornaire et al., 2004; Wandel et al., 2003; Banerjee et al., 2016).

### IVIVC and Clinical Predictability

Traditional dissolving assays might not accurately replicate bile, lipid degradation, mucus formation, precipitation, and intestinal movement. Dynamic lipolysis, biorelevant medium, mechanistic absorption models, and sophisticated intestinal cultures can enhance predictive accuracy, although their efficacy is contingent upon establishing a correlation with pharmacokinetic results. In vivo investigations must differentiate between exposure augmentations resulting from dissolution and those stemming from modified permeability, metabolism, or lymphatic transport (Dahan and Hoffman, 2008; Dahan and Hoffman, 2006; Kim et al., 2023; Babadi et al., 2021; Liu et al., 2024).

### Advanced Preclinical Models

Caco-2 monolayers are still useful for screening apparent permeability and transporter effects but do not recreate the full intestinal environment. Mucus-producing co-cultures, intestinal organoids, microphysiological systems and gut-on-chip platforms may provide information on mucus penetration, epithelial integrity and transporter biology. These models should complement existing assays and should be considered alongside pharmacokinetic evidence (Pridgen et al., 2014; Kim et al., 2023; Babadi et al., 2021; Banerjee et al., 2016).

### Regulatory, CMC and Clinical Translation

Translation necessitates a definitive sequence of proof connecting material characteristics to biological efficacy. A formulation gains credibility when a specific alteration in particle size, lipid content, or surface chemistry results in a foreseeable modification in dissolution, intestinal absorption, and pharmacokinetics. Consistent critical quality attributes, resilient analytical techniques,

**Table 4:** Characterization domains and failure signals

| *Domain* | *Recommended test* | *Purpose* | *Failure signal* |
|---|---|---|---|
| Physical | DLS/TEM/SEM; PDI; zeta | Dispersion quality | Aggregation |
| Solid state | XRPD; DSC; Raman/FTIR | Polymorphism/crystallinity | Crystal growth |
| Biorelevant | FaSSIF/FeSSIF; supersaturation | Luminal availability | Rapid precipitation |
| Lipid systems | Dynamic lipolysis | Digestion-dependent solubilization | Drug precipitation |
| Barrier models | Mucus; Caco-2; HT29-MTX; organoids | Transport mechanism | Poor epithelial access |
| PK | AUC; Cmax; Tmax; food effect | Clinical exposure | High variability |
| Safety | Cytotoxicity; barrier integrity; histology | Therapeutic window | Barrier damage |

**Table 6:** Translational decision matrix for BCS II and IV drugs.

| *Drug profile* | *Likely bottleneck* | *Preferred first-line platform* | *Key experiment* | *Translation risk* |
|---|---|---|---|---|
| Very low solubility; high permeability | Dissolution | Nanocrystal/ nanosuspension | Biorelevant dissolution + PK | Crystal growth |
| High lipophilicity; food effect | Luminal solubilization | SNEDDS/NLC/ nanoemulsion | Dynamic lipolysis | Precipitation after dilution |
| Low solubility + low permeability | Dual barrier | Surface-engineered/hybrid NP | Permeability + transporter + PK | Barrier toxicity |
| High P-gp liability | Efflux | Lipid/polymeric system with justified modulation | Efflux assay + metabolite PK | Drug–drug interaction |
| Lymphatically transportable drug | First-pass extraction | Long-chain lipid system | Chylomicron/lymphatic evidence | Food dependence |
| High dose; poor loading | Dose/formulation burden | Nanocrystal or high-loading lipid system | Dose feasibility + stability | Large dosage form |

scalable production, permissible excipient exposure, and a feasible final dosage form are imperative, even when the formulation offers a compelling mechanistic justification (Gangavarapu et al., 2024; Kim et al., 2023; Babadi et al., 2021; Hosszú et al., 2026; Sharma et al., 2026; Noor and Alsaad, 2026).

## Future Perspectives

The next generation of BCS II/IV nanomedicines is likely to be more precision-oriented. Instead of empirically screening large libraries of carriers, developers can map drug properties to predicted gastrointestinal fate and select a formulation that addresses the dominant bottleneck. Mechanistic absorption models, biorelevant dissolution and lipolysis, intestinal organoids and mucus-containing co-cultures can strengthen translational prediction, while data-assisted formulation development may help prioritize excipients and process conditions. Computational approaches should, however, remain experimentally anchored because small changes in aggregation, surface chemistry or solid state can produce nonlinear biological effects.

Continuous production and process analytical technologies might decrease batch to batch variability. Quality by Design can associate material qualities and process factors with clinical performance. The best future systems for tackling Class IV molecules will be multifunctional but not unmanufacturable: they should solubilize the drug, maintain useful supersaturation, promote epithelial transfer or lymphatic transport where appropriate, and limit presystemic loss with an acceptable safety margin. Patient-centric development should also consider dose burden, food dependence, dosing frequency, excipient exposure and long-term tolerability. Sustainability considerations such as solvent use, energy-intensive processing and packaging may become increasingly relevant for chronic therapies. The development goal should therefore be the lowest necessary material burden that provides a reproducible therapeutic exposure.

## Conclusion

Nanotechnology is best viewed as a mechanism-matching toolbox rather than a universal solution. For BCS Class II drugs, nanocrystals, nanosuspensions and lipid systems can address dissolution and luminal solubilization. For Class IV drugs, meaningful gains are more likely when solubility enhancement is coordinated with epithelial transport, efflux, metabolism or lymphatic pathways. Successful translation depends on reproducible critical quality attributes, physiologically relevant testing, scalable manufacturing, safety and credible clinical predictability. The central development principle is therefore simple: design the nanomedicine around the absorption bottleneck, then demonstrate that the selected formulation resolves that bottleneck without creating a larger manufacturing or safety problem.

## References


1. Amidon GL, Lennernäs H, Shah VP, Crison JR. (1995). A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. DOI: 10.1023/A:1016212804288.
2. Yu LX, Amidon GL. (1999). A compartmental absorption and transit model for estimating oral drug absorption. Int J Pharm. DOI: 10.1016/S0378-5173(99)00147-7.
3. Thomson AB, Schoeller C, Keelan M, Smith L, Clandinin MT. (1993). Lipid absorption: Passing through the unstirred layers, brush-border membrane, and beyond. Can J Physiol Pharmacol. DOI: 10.1139/y93-078.
4. Read NW, Barber DC, Levin RJ, Holdsworth CD. (1977). Unstirred layer and kinetics of electrogenic glucose absorption in the human jejunum in situ. Gut. DOI: 10.1136/gut.18.11.865.
5. Wacher VJ, Silverman JA, Zhang Y, Benet LZ. (1998). Role of P-glycoprotein and cytochrome P450 3A in limiting oral absorption of peptides and peptidomimetics. J Pharm Sci. DOI: 10.1021/js980082d.
6. Wacher VJ, Salphati L, Benet LZ. (2001). Active secretion and enterocytic drug metabolism barriers to drug absorption. Adv Drug Deliv Rev. DOI: 10.1016/S0169-409X(00)00126-5.
7. Cummins CL, Jacobsen W, Benet LZ. (2002). Unmasking the dynamic interplay between intestinal P-glycoprotein and CYP3A4. J Pharmacol Exp Ther. DOI: 10.1124/jpet.300.3.1036.
8. Benet LZ, Cummins CL. (2001). The drug efflux-metabolism alliance: Biochemical aspects. Adv Drug Deliv Rev. DOI: 10.1016/S0169-409X(01)00178-8.

9. Benet LZ, Cummins CL, Wu CY. (2004). Unmasking the dynamic interplay between efflux transporters and metabolic enzymes. Int J Pharm. DOI: 10.1016/j.ijpharm.2002.12.002.
10. Porter CJ, Trevaskis NL, Charman WN. (2007). Lipids and lipid-based formulations: Optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discov. DOI: 10.1038/nrd2197.
11. Müller RH, Runge SA, Ravelli V, Thünemann AF, Mehnert W, Souto EB. (2008). Cyclosporine-loaded solid lipid nanoparticles (SLN): Drug-lipid physicochemical interactions and characterization of drug incorporation. Eur J Pharm Biopharm. DOI: 10.1016/j.ejpb.2007.07.006.
12. Narang AS, Delmarre D, Gao D. (2007). Stable drug encapsulation in micelles and microemulsions. Int J Pharm. DOI: 10.1016/j.ijpharm.2007.08.057.
13. Dahan A, Hoffman A. (2008). Rationalizing the selection of oral lipid based drug delivery systems by an in vitro dynamic lipolysis model for improved oral bioavailability of poorly water soluble drugs. J Control Release. DOI: 10.1016/j.jconrel.2008.03.021.
14. Müller RH, Mäder K, Gohla S. (2000). Solid lipid nanoparticles (SLN) for controlled drug delivery - A review of the state of the art. Eur J Pharm Biopharm. DOI: 10.1016/S0939-6411(00)00087-4.
15. Müller RH, Radtke M, Wissing SA. (2002). Nanostructured lipid matrices for improved microencapsulation of drugs. Int J Pharm. DOI: 10.1016/S0378-5173(02)00180-1.
16. Muchow M, Maincent P, Müller RH. (2008). Lipid nanoparticles with a solid matrix (SLN, NLC, LDC) for oral drug delivery. Drug Dev Ind Pharm. DOI: 10.1080/03639040802130061.
17. Zhuang CY, Li N, Wang M, Zhang XN, Pan WS, Peng JJ, et al. (2010). Preparation and characterization of vinpocetine loaded nanostructured lipid carriers for improved oral bioavailability. Int J Pharm. DOI: 10.1016/j.ijpharm.2010.05.005.
18. Tiwari R, Pathak K. (2011). Nanostructured lipid carrier versus solid lipid nanoparticles of simvastatin: Comparative analysis of characteristics, pharmacokinetics and tissue uptake. Int J Pharm. DOI: 10.1016/j.ijpharm.2011.05.044.
19. Wu CY, Benet LZ. (2005). Predicting drug disposition via application of BCS: Transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res. DOI: 10.1007/s11095-004-9004-4.
20. Constantinides PP, Wasan KM. (2007). Lipid formulation strategies for enhancing intestinal transport and absorption of P-glycoprotein substrate drugs. J Pharm Sci. DOI: 10.1002/jps.20780.
21. O\'Driscoll CM, Griffin BT. (2008). Biopharmaceutical challenges associated with drugs with low aqueous solubility - the potential impact of lipid-based formulations. Adv Drug Deliv Rev. DOI: 10.1016/j.addr.2007.10.012.
22. Batrakova EV, Li S, Li Y, Alakhov VY, Kabanov AV. (2004). Effect of pluronic P85 on ATPase activity of drug efflux transporters. Pharm Res. DOI: 10.1007/s11095-004-7675-5.
23. Dahan A, Hoffman A. (2006). Use of a dynamic in vitro lipolysis model to rationalize oral formulation development for poor water soluble drugs. Pharm Res. DOI: 10.1007/s11095-006-9054-x.
24. Caliph SM, Charman WN, Porter CJ. (2000). Effect of fatty acid-based vehicles on oral bioavailability and intestinal lymphatic transport of halofantrine. J Pharm Sci. DOI: 10.1002/1520-6017(200008)89:8\<1073::AID-JPS12\>3.0.CO;2-V.
25. O\'Driscoll CM. (2002). Lipid-based formulations for intestinal lymphatic delivery. Eur J Pharm Sci. DOI: 10.1016/S0928-0987(02)00051-9.
26. Porter CJ, Charman WN. (2001). Intestinal lymphatic drug transport: An update. Adv Drug Deliv Rev. DOI: 10.1016/S0169-409X(01)00151-X.
27. Trevaskis NL, Charman WN, Porter CJ. (2008). Lipid-based delivery systems and intestinal lymphatic drug transport: A mechanistic update. Adv Drug Deliv Rev. DOI: 10.1016/j.addr.2007.09.007.
28. Dabholkar RD, Sawant RM, Mongayt DA, Devarajan PV, Torchilin VP. (2006). PEG-PE mixed micelles and modulation of P-glycoprotein-mediated efflux. Int J Pharm. DOI: 10.1016/j.ijpharm.2006.02.018.
29. Desai P, Date A, Patravale B. (2012). Overcoming poor oral bioavailability using nanoparticle formulations-opportunities and limitations. Drug Discov Today Technol. DOI: 10.1016/j.ddtec.2011.12.001.
30. Gursoy RN, Benita S. (2004). Self-emulsifying drug delivery systems for improved oral delivery of lipophilic drugs. Biomed Pharmacother. DOI: 10.1016/j.biopha.2004.02.001.
31. Cornaire G, Woodley J, Hermann P, Cloarec A, Arellano C, Houin G. (2004). Impact of excipients on the absorption of P-glycoprotein substrates in vitro and in vivo. Int J Pharm. DOI: 10.1016/j.ijpharm.2004.03.001.
32. Wandel C, Kim RB, Stein CM. (2003). Inactive excipients such as Cremophor can affect in vivo drug disposition. Clin Pharmacol Ther. DOI: 10.1016/S0009-9236(03)00010-9.
33. Mei L, Zhang Z, Zhao L, et al. (2013). Pharmaceutical nanotechnology for oral delivery of anticancer drugs. Adv Drug Deliv Rev. DOI: 10.1016/j.addr.2012.11.005.
34. Junyaprasert VB, Morakul B. (2015). Nanocrystals for enhancement of oral bioavailability of poorly water-soluble drugs. Asian J Pharm Sci. DOI: 10.1016/j.ajps.2014.08.005.
35. Salah E, Abouelfetouh MM, Pan Y, Chen D, Xie S. (2020). Solid lipid nanoparticles for enhanced oral absorption: A review. Colloids Surf B Biointerfaces. DOI: 10.1016/j.colsurfb.2020.111305.
36. Patel P, Patel M. (2021). Nanostructured Lipid Carriers- A Versatile Carrier for Oral Delivery of Lipophilic Drugs. Recent Pat Nanotechnol. DOI: 10.2174/1872210514666200909154959.
37. Gangavarapu A, Tapia-Lopez LV, Sarkar B, Pena-Zacarias J, Badruddoza AZM, Nurunnabi M. (2024). Lipid nanoparticles for enhancing oral bioavailability. Nanoscale. DOI: 10.1039/D4NR01487A.
38. Pridgen EM, Alexis F, Farokhzad OC. (2014). Polymeric Nanoparticle Technologies for Oral Drug Delivery. Clin Gastroenterol Hepatol. DOI: 10.1016/j.cgh.2014.06.018.
39. Kim KS, Na K, Bae YH. (2023). Nanoparticle oral absorption and its clinical translational potential. J Control Release. DOI: 10.1016/j.jconrel.2023.06.024.
40. Babadi D, Dadashzadeh S, Osouli M, Abbasian Z, Daryabari MS, Sadrai S, Haeri A. (2021). Biopharmaceutical and pharmacokinetic aspects of nanocarrier-mediated oral delivery of poorly soluble drugs. J Drug Deliv Sci Technol. DOI: 10.1016/j.jddst.2021.102324.
41. Khan KU, Minhas MU, Badshah SF, Suhail M, Ahmad A, Ijaz S. (2022). Overview of nanoparticulate strategies for solubility enhancement of poorly soluble drugs. Life Sci. DOI: 10.1016/j.lfs.2022.120301.
42. Agarwal V, Kaushik N, Sharma PK. (2021). Nanocrystal Approaches for Poorly Soluble Drugs and their Role in Development of Marketed Formulation. Drug Dev Ind Pharm. DOI: 10.2174/2210303111666210616115543.
43. Liu Y, Liang Y, Yuhong J, et al. (2024). Advances in Nanotechnology for Enhancing the Solubility and Bioavailability of Poorly Soluble Drugs. Drug Des Devel Ther. DOI: 10.2147/DDDT.S447496.
44. Che J, Fu Y, Li Y, Zhang Y, Yin T, Gou J, Tang X, Wang Y, He H. (2024). Eudragit L100-coated nintedanib nanocrystals improve oral bioavailability by reducing drug particle size and maintaining drug supersaturation. Int J Pharm. DOI: 10.1016/j.ijpharm.2024.124196.
45. Wang Y, Xuan J, Zhao G, Wang D, Ying N, Zhuang J. (2021). Improving stability and oral bioavailability of hydroxycamptothecin via nanocrystals in microparticles. Int J Pharm. DOI: 10.1016/j.ijpharm.2021.120729.
46. Banerjee A, Qi J, Gogoi R, Wong J, Mitragotri S. (2016). Role of nanoparticle size, shape and surface chemistry in oral drug delivery. J Control Release. DOI: 10.1016/j.jconrel.2016.07.051.
47. Arshad A, Arshad S, Alamgeer, et al. (2024). Zeta potential changing self-nanoemulsifying drug delivery systems: A newfangled approach for enhancing oral bioavailability of poorly soluble drugs. Int J Pharm. DOI: 10.1016/j.ijpharm.2024.123998.
48. Darwish MKM, Abu El-Enin ASM, Mohammed KHA. (2022). Optimized nanoparticles for enhanced oral bioavailability of a poorly soluble drug: solid lipid nanoparticles versus nanostructured lipid carriers. Pharm Nanotechnol. DOI: 10.2174/2211738510666220210110003.

49. Tan J, Liu J, Ran L. (2021). A Review of Pharmaceutical Nano-Cocrystals: A Novel Strategy to Improve the Chemical and Physical Properties for Poorly Soluble Drugs. Crystals. DOI: 10.3390/cryst11050463.
50. Hosszú Z, Pártos P, Mahdavi M, et al. (2026). The Role and Potential of Nanotechnology in Improving Solubility and Enhancing Bioavailability. Pharmaceutics. DOI: 10.3390/pharmaceutics18040478.
51. Sharma P, Katyal P, Magotra T, et al. (2026). Strategic Advances in Drug Delivery Systems for Overcoming Solubility and Permeability Barriers in Class II and IV Drugs. Curr Pharm Des. DOI: 10.2174/0113816128416755251028072444.
52. Noor AF, Alsaad AAA. (2026). Solid Lipid Nanoparticles as a Promising Strategy for Enhancing Oral Bioavailability of Poorly Absorbed Drugs. Tikrit J Pharm Sci. DOI: 10.25130/tjphs.2026.20.1.11.106.120.
53. Babu BV Shreyas, Prajapati MK. (2026). Advanced strategies for enhancing bioavailability using SNEDDS: Formulation design, mechanism, and applications. J Drug Deliv Sci Technol. DOI: 10.1016/j.jddst.2026.108364.
54. Wang Y, et al. (2022). Development of Fully Redispersible Dried Nanocrystals by Using Sucrose Laurate as Stabilizer. J Pharm Sci. DOI: 10.1016/j.xphs.2021.10.004.
55. Abuzar S, Hyun SM, Kim JH, et al. (2018). Enhancing the solubility and bioavailability of poorly water-soluble drugs using supercritical antisolvent process. Int J Pharm. DOI: 10.1016/j.ijpharm.2017.12.041.
56. Roberts AD, Zhang H. (2013). Poorly water-soluble drug nanoparticles via solvent evaporation in water-soluble porous polymers. Int J Pharm. DOI: 10.1016/j.ijpharm.2013.03.001.
57. Shegokar R, Müller RH. (2010). Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. Int J Pharm. DOI: 10.1016/j.ijpharm.2010.07.044.
58. Khan S, Baboota S, Ali J, Khan S, Narang RS, Narang JK. (2015). Nanostructured lipid carriers: An emerging platform for improving oral bioavailability of lipophilic drugs. Int J Pharm Investig. DOI: 10.4103/2230-973X.167661.
59. Beloqui A, del Pozo-Rodríguez A, Isla A, Rodríguez-Gascón A, Solinís MÁ. (2017). Nanostructured lipid carriers as oral delivery systems for poorly soluble drugs. J Drug Deliv Sci Technol. DOI: 10.1016/j.jddst.2017.06.013.
60. Poonia N, Kharb R, Lather V, Pandita D. (2016). Nanostructured lipid carriers: versatile oral delivery vehicle. Future Sci OA. DOI: 10.4155/fsoa-2016-0030.


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