

Review

Biopharmaceutics Classification System Class IV Drugs: Carriers and Barriers

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Abstract

Within the Biopharmaceutics Classification System (BCS), Class IV compounds exhibit both low aqueous solubility and low intestinal permeability, placing these compounds among the most formidable challenges in pharmaceutical development. These molecules are frequently subject to efflux–transporter interactions, most notably with P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and undergo extensive pre-systemic cytochrome P450 (CYP450) metabolism, collectively producing poor and erratic oral bioavailability (BA). This review provides a structured narrative synthesis of representative literature on formulation strategies for BCS IV drug delivery. Coverage spans solubility-enhancing and solid-state engineering technologies (cyclodextrins, amorphous solid dispersions, cocrystals, supersaturating systems), lipid-based and nanotechnology-based delivery platforms, transporter- and metabolism-targeted prodrug and permeation-enhancer strategies, alternative administration routes, and computational design tools. Notable marketed successes including Norvir® (ritonavir), Kaletra® (lopinavir), Neoral® (cyclosporine), Venclexta® (venetoclax), and Abraxane® (nab-paclitaxel) demonstrate that BCS IV classification need not preclude clinical and commercial success. This review consolidates and organises these strategies within a unified decision framework intended to serve as a comprehensive resource for pharmaceutical scientists formulating BCS IV compounds. Throughout, this review foregrounds an asymmetry too often left implicit: low solubility is mechanistically well-understood and reliably correctable, whereas the permeability barrier raises three harder questions: whether *in vitro* permeability predicts *in vivo* permeability, whether deliberately altering intestinal permeability carries a toxicological cost, and whether most strategies change permeability at all rather than raising exposure by other means.

Keywords: BCS Class IV; drug delivery; solubility enhancement; permeability enhancer; oral bioavailability; amorphous solid dispersion; lipid-based formulation; supersaturation; nanotechnology; PBPK modelling

1. Introduction

The Biopharmaceutics Classification System (BCS), introduced by Amidon et al. [1] in 1995, stratifies drugs according to two intrinsic properties: aqueous solubility and intestinal permeability [2]. Solubility is operationally defined as the ability of the highest immediate-release dose strength to dissolve in ≤250 mL of aqueous media over pH 1.0–7.5; permeability is assessed via *in vitro* intestinal epithelial models (typically Caco-2) or *in vivo* human absorption studies [2,3]. This classification is not merely descriptive but underpins regulatory biowaiver frameworks, including the U.S. Food and Drug Administration (FDA) biopharmaceutics classification system-based biowaiver guidance and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M9 guideline, both of which formally recognise the BCS as a basis for waiving *in vivo* bioequivalence testing for immediate-release oral products [4,5].

It is worth emphasising that the BCS was conceived primarily as a regulatory instrument for granting biowaivers rather than as a general-purpose formulation development tool, and its deliberately conservative solubility criterion,

based on the lowest solubility across gastric-to-intestinal pH within a 250 mL volume, can therefore overstate the practical solubility barrier relative to conditions in the fasted or fed human intestine (Fig. 1, Ref. [6]). Building on this observation, Butler and Dressman proposed the Developability Classification System (DCS) as a complementary, development-oriented framework: it substitutes an estimate of intestinal solubility (e.g., in fasted-state simulated intestinal fluid) for the BCS's gastric-referenced value, enlarges the reference dissolution volume to 500 mL to better reflect fluid available across the small intestine, and exploits the compensatory relationship between solubility and permeability to divide BCS Class II into a dissolution-rate-limited subclass (DCS IIa, amenable to particle-size control) and a solubility-limited subclass (DCS IIb, requiring an enabling solubilisation technology) [6]. Because a number of nominally BCS Class II and IV compounds prove more tractable once reassessed against DCS criteria, the DCS is introduced here as a companion lens for Class IV developability risk and is revisited in Section 9.4 alongside the related refined DCS. Given the compounded difficulty of correcting both solubility and permeability simultaneously, a considerable



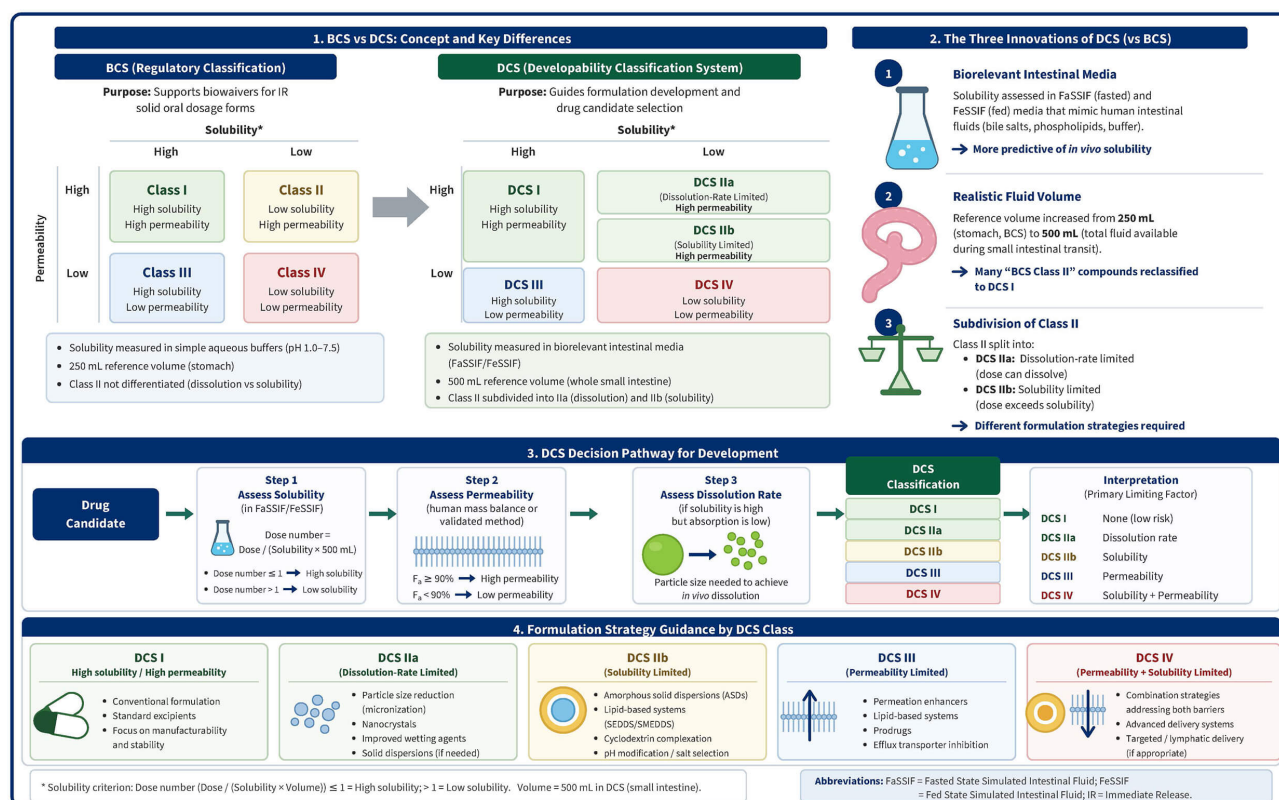


Fig. 1. Comparison of the biopharmaceutics classification system (BCS) and the developability classification system (DCS) for oral formulation strategy selection. (1) Concept and Key Differences: Whereas the regulatory BCS relies on aqueous media (pH 1.0–7.5) and a 250 mL volume (stomach) to support biowaivers, the DCS uses biorelevant intestinal media (FaSSiF/FeSSiF) and a 500 mL reference volume (small intestine) to better predict *in vivo* absorption. (2) Key Innovations: The DCS splits Class II into DCS IIa (dissolution-rate limited) and DCS IIb (solubility-limited), allowing tailored formulation approaches. (3) Decision Pathway: Drug candidates are classified sequentially via Dose Number (DN ≤ 1 for high solubility), fraction absorbed ($F_a \geq 90\%$ for high permeability), and dissolution rate. (4) Formulation Strategy Guidance: Recommended technical interventions by DCS class, ranging from conventional strategies (DCS I), particle size reduction/nanocrystals (DCS IIa), amorphous solid dispersions (ASDs) and lipid-based systems (DCS IIb/IV), to permeation enhancers and prodrugs (DCS III) (Author-created schematic based on the DCS framework proposed by [6]). Created with [Biorender.com](https://www.biorender.com).

number of pharmaceutical organisations deliberately deprioritise or discontinue BCS Class IV candidates during early discovery, since the attrition risk and extended formulation timelines this dual liability imposes frequently outweigh the anticipated return unless the molecule offers a compelling and otherwise unmet clinical benefit [2] (Fig. 2).

BCS Class IV drugs exhibit low solubility and low permeability simultaneously, a dual burden that renders traditional formulation approaches inadequate. Their biopharmaceutical liabilities include dissolution-rate-limited and solubility-limited absorption, P-glycoprotein (P-gp)/breast cancer resistance protein (BCRP) efflux at the enterocyte brush border, CYP3A4-mediated intestinal first-pass metabolism, and regionally variable intestinal permeability that can create narrow absorption windows [3,7]. A critical mechanistic distinction governs strategy selection: dissolution-rate-limited absorption (sink conditions prevail; particle size reduction increases absorption proportionally)

versus solubility-limited absorption (non-sink conditions; neither increasing dose nor reducing particle size reliably improves bioavailability), the latter requiring fundamentally different approaches [2].

Despite these obstacles, BCS IV molecules encompass numerous clinically indispensable compounds, antivirals, anticancer agents, immunosuppressants, diuretics, and bioactive nutraceuticals (Table 1, Ref. [7,8,9,10,11,12,13,14,15,16,17]). Poor aqueous solubility affects more than 40% of marketed drugs and new drug candidates, and an increasing proportion of pipeline candidates fall into BCS Class IV, driving continued innovation in formulation science [2,18]. Nutraceutical BCS IV compounds are included throughout this review because they frequently represent extreme examples of simultaneous solubility and permeability limitation and have served as valuable, well-characterised models for formulation development.

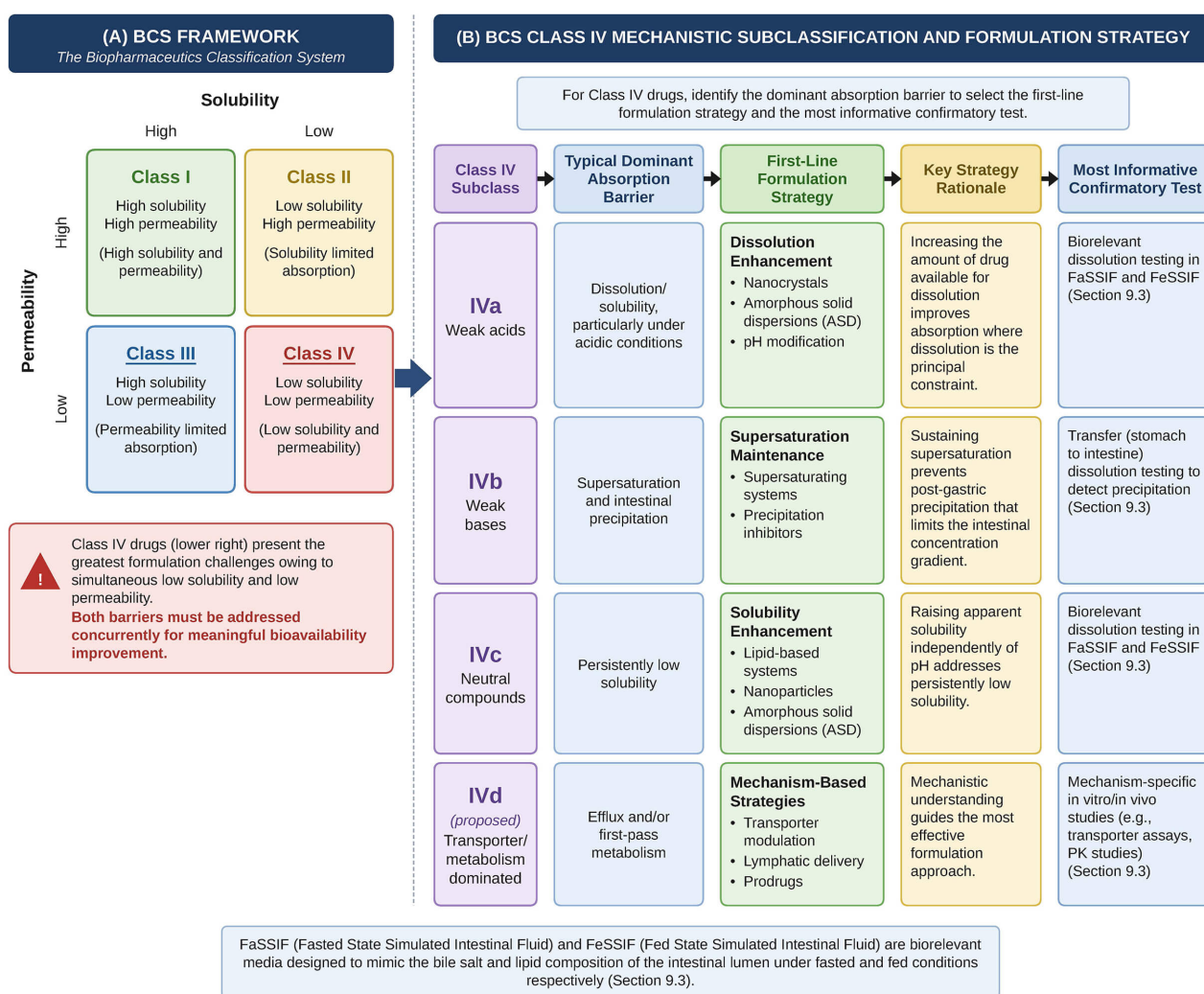


Fig. 2. The biopharmaceutics classification system (BCS) and a mechanistic subclassification of BCS Class IV. (A) Class IV drugs (lower right) present the greatest formulation challenges owing to simultaneous low solubility and low permeability. Both barriers must be addressed concurrently for meaningful bioavailability improvement. (B) Mechanistic subclassification of BCS Class IV drugs as defined in Section 1.1 and Table 2 (IVa, weak acids; IVb, weak bases; IVc, neutral compounds; IVd, efflux/metabolism dominated, proposed). The dominant absorption barrier differs by subclass, so the first-line strategy and the most informative confirmatory test differ accordingly. The confirmatory test proposed for the neutral (IVc) subclass is biorelevant dissolution testing in Fasted State Simulated Intestinal Fluid (FaSSIF) and Fed State Simulated Intestinal Fluid (FeSSIF), media designed to mimic the bile-salt and lipid composition of the intestinal lumen under fasted and fed conditions respectively (Section 9.3). Created with [Biorender.com](#).

This review provides a systematically organised, and comprehensive examination of all current and emerging drug delivery strategies for BCS IV compounds, unified by a rational decision framework (Fig. 1). Strategies are organised mechanistically rather than by formulation class alone, enabling selection based on the dominant absorption barrier for each molecule. Novel approaches reported in the past five to ten years receive particular emphasis.

This review is a narrative rather than a systematic review, and is written accordingly: it foregrounds mechanistic synthesis and a rational decision framework over exhaustive enumeration. The literature underlying it was identified through structured searches of PubMed, Web of

Science, and Scopus (January 2015 to mid-2026, with earlier foundational sources retained for classification frameworks such as the BCS and the DCS), using combinations of “BCS Class IV”, “biopharmaceutics classification”, “poorly soluble poorly permeable”, “solubility enhancement”, “permeability enhancer”, “lipid-based drug delivery”, “amorphous solid dispersion”, “nanocarrier oral bioavailability”, and the individual drug and technology names appearing throughout the text, supplemented by citation chaining from key reviews and by manufacturer and regulatory documentation for the marketed products discussed in Section 1.2. Preference was given to primary research reporting quantitative pharmacokinetic or perme-

Table 1. Representative BCS Class IV compounds (not exhaustive) encompassing pharmaceuticals, antivirals, antineoplastics, and nutraceuticals. Compiled from the literature.

Drug	Therapeutic class	Clinical application	Ref.
Furosemide	Diuretic	Loop diuretic for oedema and hypertension	[7]
Paclitaxel	Antineoplastic	Taxane chemotherapy for solid tumours	[8]
Ritonavir	Antiviral	HIV protease inhibitor; PK booster	[9]
Amphotericin B	Antifungal	Polyene for systemic mycoses	[10]
Lopinavir	Antiviral	HIV protease inhibitor (fixed dose with ritonavir)	[11]
Etravirine	Antiviral	NNRTI for HIV; BCS IV marketed product	[12]
Vorinostat	Antineoplastic	HDAC inhibitor for cutaneous T-cell lymphoma	[13]
Hydrochlorothiazide	Diuretic	Thiazide diuretic for hypertension	[14]
Abiraterone acetate	Antineoplastic	CYP17 inhibitor for prostate cancer; major food effect	[15]
Curcumin	Nutraceutical	Anti-inflammatory polyphenol from <i>Curcuma longa</i>	[16]
Etoposide	Antineoplastic	Topoisomerase II inhibitor	[17]

P-gp, P-glycoprotein; PK, pharmacokinetic; NNRTI, non-nucleoside reverse transcriptase inhibitor; HDAC, histone deacetylase; CYP17, cytochrome P450 17A1.

ability outcomes over abstracts or conference proceedings, and studies were included where they illustrated a mechanistically distinct strategy or a clinically or commercially validated example rather than on the basis of a fixed inclusion checklist, consistent with the narrative, mechanism-organised aim of the review.

1.1 Subclassification of BCS Class IV Compounds

Although the BCS treats Class IV as a single category, the compounds within it are mechanistically heterogeneous, and recognising sub-types helps match strategy to cause. Building on the acid, base, and neutral subclassification proposed for the BCS by Tsume and colleagues [19], BCS IV drugs can be usefully divided according to their ionisation behaviour and the principal reason their absorption fails (Table 2, Ref. [19], Fig. 1). Weak acids (IVa) dissolve poorly in the acidic stomach but more readily in the small intestine; weak bases (IVb) show the opposite, dissolving in the stomach and risking supersaturation-driven precipitation on gastric emptying; and neutral compounds (IVc) lack any pH window of high solubility. A fourth, transporter- and metabolism-dominated group (IVd) is proposed here to capture molecules whose low apparent permeability is driven less by passive membrane resistance than by P-glycoprotein and CYP3A-mediated first-pass loss [20,21]. The IVd subclass should be regarded as a heuristic framework intended to guide formulation strategy rather than as a formal regulatory extension of the BCS.

Subclass assignment is practically useful because it predicts which interventions are likely to succeed. The rationale for each subclass's first-line strategy in Table 2 follows directly from its dominant rate-limiting mechanism: particle-size- and pH-based interventions are prioritised only where gastric or intestinal dissolution is rate-limiting, whereas enabling solubilisation and transporter-targeted approaches are reserved for subclasses in which raising the fraction of dissolved drug, or circumventing efflux and

first-pass loss, is the demonstrated bottleneck, rather than being offered as generic or interchangeable first-line options. For weak-acid IVa drugs, gastric solubility is the bottleneck, so particle-size reduction, amorphous solid dispersions (ASDs), and pH modification are preferred; for weak-base IVb drugs, the priority shifts to sustaining intestinal supersaturation with precipitation inhibitors and supersaturating systems; for neutral IVc drugs, lipid-based systems, nanoparticles, and amorphous dispersions that raise apparent solubility independently of pH are most effective; and for the proposed IVd group, transporter inhibition, lymphatic delivery, and metabolism-sparing prodrug approaches address the dominant efflux and first-pass barriers (Fig. 1).

Therapeutic peptides sit uneasily within this scheme, and the discomfort is itself instructive. The BCS was framed for passively absorbed, metabolically stable small molecules [2], whereas peptides breach those assumptions in three ways that make a Class IV assignment behave differently for them than for the small molecules that are this review's main concern. First, the limiting axis inverts: most peptides are reasonably water soluble, so the species that fall into IV rather than III are the hydrophobic, cyclic, or lipidated ones, for which low permeability rather than dissolution sets the ceiling, and the lead intervention becomes permeation enhancement combined with protease protection [22] rather than the solubility-oriented toolkit of Sections 2 to 5. Second, enzymatic instability, to which the permeability axis is blind, means that the apparent permeability of a peptide measured *in vivo* conflates true membrane resistance with luminal and brush-border peptidase loss, so its classification is in part a stability artefact. Third, both carrier-mediated transport and conformational adaptability subvert the passive-diffusion premise: di- and tripeptides are PEPT1 (SLC15A1) substrates whose active uptake the classification understates (Section 6.5), while macrocyclic peptides in the beyond-rule-of-5 space can shield their po-

Table 2. Proposed subclassification of BCS Class IV drugs by ionisation behaviour and dominant absorption barrier, with preferred formulation strategies.

Subclass	Typical property	Major limitation	Preferred strategies
IVa	Weak acids	Poor gastric solubility	Nanocrystals, ASD, pH modification
IVb	Weak bases	Intestinal precipitation	Supersaturating systems, precipitation inhibitors
IVc	Neutral compounds	Persistently low solubility	Lipid systems, nanoparticles, ASD
IVd (proposed)	Efflux/metabolism dominated	P-gp efflux and CYP3A first-pass	Transporter inhibition, lymphatic delivery, prodrugs

The IVd subclass is proposed in this review to capture transporter- and metabolism-limited compounds; the acid, base, and neutral framework follows Tsume et al. [19].

CYP3A, cytochrome P450 3A; ASD, amorphous solid dispersion.

lar surface area through reversible intramolecular hydrogen bonding and permeate far better than molecular weight and polar surface area predict [23]. Cyclosporine is the exemplar of this last behaviour and the one genuinely marketed Class IV peptide: a cyclic undecapeptide of low aqueous solubility and nominally prohibitive size whose oral viability rests on this chameleonic permeability, and whose erratic absorption was tamed by the self-microemulsifying Neoral® formulation (Section 1.2) [24,25]. Peptides are therefore best regarded not as a fifth subclass but as a boundary population that the same permeability-directed strategies, borrowed here in the reverse direction to Section 6.6, render tractable.

The molecular chameleonicity that rescues cyclosporine is not unique to peptides but defines a broader region of chemical space known as beyond the rule of 5 (bRo5), within which a growing number of orally administered drugs and clinical candidates violate one or more of Lipinski's limits on molecular weight, hydrogen-bond donor and acceptor counts, and calculated lipophilicity [26]. Many of these molecules are macrocycles, and their oral viability rests on conformational flexibility: by adopting expanded, polar-surface-exposed conformations in aqueous media and compact, intramolecularly hydrogen-bonded conformations within lipid membranes, so-called molecular chameleons reconcile the competing demands of aqueous solubility and passive permeability that would otherwise place large, polar compounds firmly in Class IV [27]. This behaviour blurs the deterministic link between physicochemical descriptors and absorption, on which the BCS implicitly depends, and indicates that some nominally Class IV scaffolds may be engineered toward acceptable oral exposure by controlling conformation rather than through formulation alone.

1.2 Marketed BCS Class IV Products and Enabling Technologies

The clearest evidence that BCS IV classification need not preclude success is the roster of marketed products built on these strategies (Table 3). Amorphous solid dispersion underpins the protease-inhibitor products Norvir® and Kaletra® and the BCL-2 inhibitor Venclexta®; self-

microemulsifying delivery transformed the erratic absorption of cyclosporine into the reproducible Neoral® formulation; albumin-bound nanoparticle technology produced the solvent-free taxane Abraxane®; and permeation enhancement by salcaprozate sodium enabled the first oral GLP-1 product, Rybelsus® [2,24,28,29]. Lipid-enabled reformulation of abiraterone further illustrates how a food-effect liability can be engineered out of an already-marketed BCS IV drug [15,30]. Amino-acid ester prodrugs provide a further validated route: valacyclovir and valganciclovir, the L-valyl prodrugs of the BCS IV antivirals acyclovir and ganciclovir, exploit intestinal PEPT1-mediated uptake to raise oral bioavailability several-fold over the parent drugs, and are marketed as Valtrex® and Valcyte® respectively. Collectively these products show that each major strategy class discussed in this review has translated to approved therapy.

A common thread runs through the clinical successes in Table 3: in every case the enabling technology was matched to the specific barrier that limited the parent molecule, dissolution-rate enhancement for the protease inhibitors, bile-salt-independent solubilisation for cyclosporine, and transient transcellular permeation enhancement for oral semaglutide, rather than a generic solubilisation step applied irrespective of mechanism. Regulatory acceptance followed the same pattern: each technology had an established safety and characterisation precedent (hot-melt extrusion and spray-dried dispersions for ASDs, decades of parenteral and oral lipid-excipient use for Self-microemulsifying drug delivery system (SMEDDS), and a defined excipient safety package for SNAC) before its BCS IV application, which is discussed further as a translational consideration in Section 11. What distinguishes these successes from the many BCS IV candidates that never reach the market is not the enabling technology alone but the combination of a compelling unmet clinical need with a formulation that met a regulatory-acceptable safety and manufacturability bar. Ritonavir, lopinavir, and venetoclax are used in HIV and oncology indications where the toxicity and complexity of an ASD were judged an acceptable trade-off against the alternative of an unformulatable, undosable drug. Cyclosporine's SMEDDS and abiraterone's lipid matrix tablet succeeded specifically because they eliminated a

Table 3. Representative marketed products employing enabling formulation technologies to overcome poor aqueous solubility and/or intestinal permeability.

Product	Drug	BCS class	Enabling technology	Rationale
Norvir®	Ritonavir	IV	Amorphous solid dispersion (hot-melt extrusion)	Low solubility/permeability antiretroviral; ASD improves dissolution vs. original capsule
Kaletra®	Lopinavir/ ritonavir	IV	Amorphous solid dispersion (hot-melt extrusion)	Both components BCS IV; ASD enables viable oral exposure
Neoral®	Cyclosporine	IV	Self-microemulsifying drug delivery system (SMEDDS)	Lipid/surfactant system reduces food effect, improves absorption
Venclexta®	Venetoclax	IV	Amorphous solid dispersion (hot-melt extrusions)	“Brick-dust” solubility; ASD required for therapeutic exposure
Abraxane®	Paclitaxel	IV	Albumin-bound nanoparticles	Solvent-free IV delivery, altered tissue distribution
Taxol®	Paclitaxel	IV	Cremophor EL/ethanol micellar solubilization	Classic surfactant-based solubilization of the same BCS IV molecule
AmBisome®/Abelcet®	Amphotericin B	IV	Liposomal/lipid-complex nanoparticles	Reduces toxicity, enables systemic delivery of a poorly soluble, poorly permeable polyene
Fortovase® (discontinued)	Saquinavir	IV	Soft gelatin capsule/lipid-based solubilization	Lipid vehicle improved oral exposure vs. earlier solid forms
Rybelsus®	Semaglutide + SNAC	Peptide (not BCS IV)	Permeation enhancer (SNAC, Eligen™)	Illustrates transcellular permeation enhancement for oral peptides
Mycapssa®	Octreotide + sodium caprylate	Peptide (not BCS IV)	Transient permeation enhancer (C8)	Second approved oral peptide using a fatty-acid permeation enhancer
Zytiga® (reformulated)	Abiraterone acetate	IV	Particle-size reduction: micronized crystalline API (Zytiga®); fine-particle/nano-amorphous reformulation (Yonsa®) permits a 500-mg dose with reduced food effect	BCS IV compound (EMA/FDA assessment reports); micronization and fine-particle reformulation improve dissolution rate and reduce food-effect variability
Kalydeco®/Orkambi®/Symdeko®	Ivacaftor (± lumacaftor/ tezacaftor)	II or IV (unresolved)—permeability data conflict in the literature	Amorphous solid dispersion (spray drying)	ASD enables oral dosing of CFTR modulator
Zelboraf®	Vemurafenib	IV	Co-precipitated amorphous dispersion (HPMCAS)	ASD-like solid-state form improves dissolution

Rybelsus® and Mycapssa® are peptides included to illustrate permeation-enhancer technology and are not themselves BCS Class IV drugs.

SNAC, salcaprozate sodium; API, active pharmaceutical ingredient; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; CFTR, cystic fibrosis transmembrane conductance regulator; HPMCAS, hydroxypropyl methylcellulose acetate succinate.

food-effect liability that made the earlier formulation clinically unworkable, converting a pharmacokinetic problem into a solved dosing problem. Regulatory acceptance of the enabling excipients was itself a precondition for these successes: hydroxypropyl methylcellulose acetate succinate, copovidone, and the medium-chain glyceride surfactants used in these products all carried prior regulatory history (or, as for SNAC in Rybelsus®, generated a new novel-excipient safety package specifically to support the application) before the finished product could be reviewed, illustrating that the excipient-qualification pathway, and not the underlying formulation science, is frequently the rate-limiting step for a novel BCS IV technology reaching patients.

1.3 An Asymmetry of Barriers: Why Permeability Is the Harder Half of the BCS IV Problem

The two defining liabilities of a Class IV compound are not equally tractable. Low solubility is the better-understood and more readily remedied barrier: its physical determinants are well-characterised, a mature toolkit reliably raises the quantity of drug in solution (Sections 2 to 5), and biorelevant dissolution testing now predicts *in vivo* behaviour closely enough to support formal *in vitro* to *in vivo* correlation. Low permeability is the harder, more uncertain problem, for three reasons addressed in turn below: whether *in vitro* permeability genuinely predicts permeability in the intact intestine; whether deliberately altering intestinal permeability carries a toxicological cost that solubilisation does not; and whether most BCS IV strategies change permeability at all, as opposed to raising systemic exposure by other means [3,18].

The contrast follows from the mechanics of passive absorption. Flux across the membrane is, to a first approximation, the product of the permeability coefficient, surface area, and the concentration gradient of free drug (Fick's first law); solubility-oriented strategies raise the gradient term without altering the coefficient itself, and because the resulting concentration is measurable *in vitro* under biorelevant, non-sink conditions with reasonable fidelity to *in vivo* dissolution, the solubility half of the problem is both diagnosable and correctable [3,18]. The permeability axis enjoys no comparable calibration: it rests on cell-based and artificial-membrane assays validated only for passively, transcellularly absorbed molecules. The Caco-2 monolayer, derived from a colonic adenocarcinoma, forms tighter junctions than the small intestine and systematically underpredicts paracellular permeability of small, hydrophilic, or ionised drugs, and its transporter complement and unstirred-layer properties vary markedly between laboratories, so absolute coefficients are rarely reproducible. For molecules whose absorption depends on carrier-mediated uptake or efflux, including the proposed IVd subclass of Section 1.1, an *in vitro* value may misrank the molecule qualitatively rather than merely misestimate

it, which is why regulatory permeability classification may instead rest on human pharmacokinetic data [3,18,20,21].

The second question follows from a fact the solubility framing obscures: intestinal permeability is a property of a barrier whose physiological purpose is selectivity, admitting nutrients while excluding pathogens, endotoxin, and macromolecular antigens. A formulation that genuinely increases epithelial permeability, particularly by opening the paracellular route, does so with limited molecular selectivity, raising the long-standing concern that permeation enhancers could promote co-absorption of luminal material and provoke inflammation, a risk mechanistically inseparable from their efficacy (Sections 6.4 and 11). For most BCS IV drugs the more prudent goal is therefore to move more drug across the existing barrier, by raising luminal concentration or recruiting an alternative route, rather than to breach it; deliberate permeability enhancement is best regarded as a strategy of last resort, justified only when permeability is demonstrably rate-limiting and the enhancer acts transiently, reversibly, and preferentially through the transcellular route, as for salcaprozate sodium [22,29]. No comparable toxicological liability attaches to raising solubility.

The third question is the most consequential: for most BCS IV strategies, intrinsic membrane permeability is never actually changed. A rise in fraction absorbed or systemic exposure can instead arise from the concentration term, from surface area or residence time, from a change of route, or from removal of an opposing active flux, so a rise in plasma exposure alone cannot establish a permeability change, since it convolves dose, dissolved concentration, absorption route, first-pass metabolism, and clearance. Lipid and bile-salt systems are especially prone to this confound, since an apparent gain may instead reflect lymphatic transport that bypasses first-pass metabolism (Section 4.5) or simply a larger dissolved fraction. Demonstrating a genuine rise in permeability requires effective permeability measured at controlled luminal concentration, such as intestinal perfusion, rather than inference from a systemic concentration-time profile; such measurements are seldom reported for the formulations catalogued here. Genuine modification of intrinsic permeability is in practice confined to two strategy classes, permeation enhancers and transporter-targeted prodrugs, so the toxicological liability of the second question applies specifically to these, while the larger part of the field improves absorption without touching the barrier at all.

Together, these questions recommend a discipline the remainder of this review adopts: separating raising exposure from raising permeability. The strategy sections that follow are framed by the barrier each approach genuinely addresses, Section 11 distinguishes permeability demonstrated *in vitro* from exposure demonstrated *in vivo*, and Section 9.3 returns to the unequal maturity of dissolution and permeability prediction. The solubility problem is, in

large measure, solved; the permeability problem is where the genuine difficulty, and opportunity, of Class IV development now lies.

Calling the solubility problem largely solved is a statement about mechanistic understanding and predictive testing, not about the absence of practical failure modes: ASDs remain prone to recrystallisation on storage, lipid-based systems remain vulnerable to oxidative degradation and digestion-dependent precipitation, and both are treated as such throughout (Sections 3.1, 4.1, and 11) rather than presented as risk-free. The sections that follow are organised to track the barrier each strategy principally addresses rather than by formulation technology alone: Sections 2 and 3 target the dissolution and solid-state axis of the solubility barrier; Section 4 addresses solubility and, via lymphatic transport and digestion-dependent effects, the boundary between solubility and permeability; Sections 5 and 6 address permeability directly, through nanocarrier-mediated transport and transporter- or metabolism-limited absorption respectively; Sections 7 and 8 address special formulation technologies and alternative administration routes that can bypass either barrier; and Section 9 addresses the computational and biorelevant testing tools used to predict performance across both axes. Section 10 then draws these strands together into the decision framework.

2. Solubility-Oriented Strategies

Sections 2 to 6 present formulation strategies in a weighted sequence reflecting their industrial maturity and typical order of consideration in development: solubility-oriented excipient strategies and solid-state engineering, including ASDs and particle-size (micronization/nanocrystal) approaches (Sections 2–3), are industrially established first-line options and are considered before committing to lipid-based delivery systems (Section 4), which are likewise well validated but demand more specialised manufacturing. Nanocarrier platforms beyond simple nanocrystals (Section 5) are, with a few marketed exceptions, comparatively exploratory for small-molecule BCS IV drugs and are positioned after the established options. Transporter-targeted prodrugs and permeability enhancers (Section 6) are reserved as second-line, more specialised strategies for the subset of compounds in which permeability, rather than solubility, is demonstrably rate-limiting.

Dissolving a BCS IV drug is necessary but not sufficient for absorption; the concentration gradient at the mucosal surface must be maintained long enough for permeation to proceed. Each strategy below raises the amount of drug in solution, but must be chosen with awareness of the solubility–permeability trade-off: many solubilising excipients can reduce the thermodynamic activity (free-drug fraction) available for membrane crossing, potentially negating the solubility gain [18,31]. It bears emphasis, as Section 1.3 argues, that the strategies in Sections 2 to 5 raise the quantity of dissolved drug and hence the concentration

gradient driving absorption: they increase flux without rendering the membrane intrinsically more permeable, which is precisely why their *in vitro* to *in vivo* behaviour is comparatively predictable.

2.1 Cyclodextrins, Nanoclays, and Hybrid Systems

Cyclodextrins (CDs) are cyclic oligosaccharides whose hydrophobic cavities form non-covalent inclusion complexes with lipophilic drugs, raising apparent aqueous solubility while presenting a hydrophilic exterior to the dissolution medium [32]. Per-6-thiolated α -CD (all primary hydroxyl groups replaced with –SH) delivered furosemide with a 6.87-fold improvement in Caco-2 apparent permeability coefficient (Papp), a 6.55-fold improvement across rat intestinal mucosa, and a 4.9-fold increase in oral bioavailability. The thiol groups form reversible disulfide bonds with mucosal cysteine residues, prolonging formulation residence at the absorption site [33].

Baicalin, a BCS IV flavone glycoside, achieved approximately 5-fold solubility enhancement via γ -CD complexation [34]. Combining CDs with nanoclays (RAMEB–sepiolite ternary systems) produced a synergistic ~12-fold solubility increase relative to free drug, with compressed tablets showing superior dissolution versus commercial references. Rifaximin β -CD complexation via malaxation and wet milling also produced more soluble forms with retained full antimicrobial potency [35]. Lopinavir microspheres prepared with thiolated xyloglucan, a natural tamarind-seed polysaccharide, enhanced permeation 3.15-fold *ex vivo* and improved relative bioavailability 3.22-fold over commercial lopinavir–ritonavir in rats [11].

2.2 Hydrotropes

Hydrotropes solubilise hydrophobic compounds in water by mechanisms distinct from micellisation. Piperazine (natural) and sodium benzoate (synthetic) were incorporated into solid dispersions of hydrochlorothiazide. Both hydrotropes dose-dependently increased solubility and *in vitro* drug release, with response surface methodology optimising the formulation. Hydrotropes offer low toxicity and regulatory simplicity, making them attractive for ionisable BCS IV molecules [14].

2.3 Amino Acid Salt Formation

L-lysine forms 1:1 molar complexes with BCS IV flavonoids (quercetin, rutin) via co-precipitation and co-grinding. Solubility enhancement factors of 68- to 433-fold and up to 6-fold faster dissolution were observed; quercetin–lysine Papp increased 4-fold. Chemical stability was confirmed by antioxidant capacity assays [36]. The ionisation state of lysine facilitates electrostatic and hydrogen-bonding interactions that disrupt crystal packing and improve hydration, offering a sustainable, low-cost platform particularly suited to nutraceutical BCS IV molecules.

2.4 Polymeric Solubilisers, Copolymers, and the Solubility–Permeability Trade-Off

Soluplus® (polyvinyl caprolactam–polyvinyl acetate–PEG graft copolymer) and TPGS form polymeric micelles that encapsulate lipophilic drugs in their hydrophobic cores [37,38]. TPGS additionally inhibits P-gp efflux at formulation-achievable concentrations, a rare dual functionality that simultaneously addresses both BCS IV barriers [38].

A critical cautionary example: Eudragit EPO (dimethylaminoethyl methacrylate copolymer) produced a profound 940-fold solubility increase for mefenamic acid, yet simultaneously reduced membrane permeability *in vitro* and *in vivo*. The unstirred water layer (UWL) adjacent to the GI membrane was identified as the mechanistic bottleneck: the polymer retains the drug in micellar form, reducing the free-drug concentration available for passive diffusion. Formulation scientists are advised to use the minimum EPO concentration required to dissolve the dose throughout the GIT; excess EPO provides no further solubility gain but compounds permeability loss [31].

2.5 Supersaturating Drug Delivery Systems

Supersaturating drug delivery systems (SDDS) generate and transiently maintain drug concentrations above equilibrium solubility, creating an elevated thermodynamic driving force for membrane permeation. The ‘spring-and-parachute’ model captures this: the formulation rapidly generates supersaturation (spring) while a precipitation-inhibiting polymer sustains it (parachute) [39,40].

For rifaximin, a BCS IV P-gp substrate with slow crystallisation in acid, a copovidone/HPC-SL ASD maintained supersaturation at 200× the crystalline equilibrium solubility for 20 h. Crucially, at this level P-gp efflux was saturated, simultaneously improving permeability: a rare demonstration that a solubility-focused strategy can also overcome the permeability barrier when the efflux mechanism is saturable [41].

2.6 Solubility–Permeability Trade-Off

Raising drug concentration via solubilising excipients can paradoxically reduce the free-drug fraction (thermodynamic activity) available for passive diffusion. For every BCS IV formulation strategy, the net impact on both dissolved drug concentration and membrane permeability must be evaluated, ideally using biphasic *in vitro* models that simultaneously measure dissolution and permeation [18,31,39]. The Eudragit EPO and mefenamic acid example detailed in Section 2.4 is the archetypal case: a 940-fold solubility increase that reduced permeability both *in vitro* and *in vivo*. It is treated as a central cautionary lesson in Section 11.

2.7 Ionic Liquids and Deep Eutectic Solvents

Ionic liquids and deep eutectic solvents are an emerging solubilisation strategy that reframes the active ingredient itself rather than the dosage form around it. By pairing an ionisable drug with a counter-ion to form a low-melting salt, the active pharmaceutical ingredient ionic liquid concept can deliver controlled, often dramatically higher, solubility while eliminating the polymorphism and crystallinity problems that limit conventional solid forms [42]. Deep eutectic solvents, formed by hydrogen-bonding mixtures such as choline-based systems, achieve comparable solubilisation through a different physical mechanism and can render an otherwise intractable solid into a stable liquid API.

For BCS IV compounds the appeal is that these liquids can act on both barriers at once. The choline and geranate system, variously described as an ionic liquid or a deep eutectic solvent, not only solubilises its payload but also enhances paracellular transport and transiently thins the mucus layer, enabling meaningful oral absorption of insulin *in vivo* [43]. The same dual solubility and permeability action makes ionic liquids and deep eutectic solvents an attractive, if still early-stage, option for poorly soluble and poorly permeable small molecules; the principal hurdles to clinical translation remain large-scale manufacture, long-term stability, and a still-maturing regulatory pathway for liquid APIs.

3. Solid State Engineering: Amorphous, Co-Amorphous, and Cocrystal Systems

3.1 Amorphous Solid Dispersions (ASDs)

ASDs convert crystalline drug into its higher-energy amorphous form molecularly dispersed within a hydrophilic polymer matrix, raising apparent solubility and dissolution rate [28]. The amorphous form may be 10- to 1600-fold more soluble than the crystalline form; stabilisation against recrystallisation during storage is the primary engineering challenge. Ternary ASDs (drug + polymer + surfactant/second polymer) extend the ASD concept by improving physical stability and wettability [44].

3.1.1 Manufacturing Technologies

Hot melt extrusion (HME): Continuous, solvent-free, scalable. Oleanolic acid in PVP VA64 produced dramatically higher AUC and C_{max} vs. physical mixture and commercial tablet [45]. Etravirine HME ASDs (systematic 5-stage screening approach) achieved >2× dissolution improvement with confirmed physical and chemical stability [46].

Spray drying: Third-generation pH-modulated daidzein dispersions achieved ~20-fold C_{max} increase with earlier T_{max} [47]. Curcumin in amorphous chitosan oligosaccharide matrix (surfactant-free) produced 1.55–3.01× AUC vs. pure drug [48]. Chlorthalidone in Soluplus–SLS polymer–surfactant complex achieved

>80% release in 15 min and maintained 6× supersaturation over equilibrium solubility for 6 h in biorelevant medium [49].

Hybrid/nanoamorphous approaches: Ritonavir nanoamorphous micellar dispersion in Soluplus® prepared by QbD-DM3 rational design integrates amorphous conversion, micellar solubilisation, and nanosizing in a single system [50].

3.1.2 Polymer Carrier Selection Principles

Polymer choice critically governs supersaturation duration. Drug–polymer miscibility (Flory–Huggins interaction parameters) and hydrogen-bonding capacity are primary selection criteria [51]. Bergenin phospholipid complex ASD (BNPC-SD) co-administered with the P-gp inhibitor verapamil achieved 202.46% relative oral bioavailability vs. free drug, demonstrating that combining ASD with efflux inhibition synergistically addresses both BCS IV barriers [52]. Naftopidil–chitosan–fumaric acid solid dispersions (polymer-free approach) showed that hydrogen bonding between drug and fumaric acid was the dominant driver of dissolution enhancement [53].

Physical instability remains the principal barrier to ASD translation: the amorphous state is thermodynamically metastable and can recrystallise during storage, especially above roughly 80% of the glass transition temperature (T_g) or under humid conditions that plasticise the matrix, so accelerated stability testing (40 °C/75% RH) with polarised light microscopy, XRPD, and modulated DSC is essential rather than optional. Manufacturing route imposes its own constraints: HME requires the drug to be thermally stable at processing temperatures typically 20–40 °C above T_g or melting point, restricting its use for thermolabile biologics-adjacent small molecules, and screw design/residence time must be re-optimised at each scale-up step because shear and thermal history affect the extent of amorphous conversion. Spray drying avoids thermal stress but introduces residual organic solvent limits (ICH Q3C), generally poor bulk density requiring downstream densification, and batch-to-batch variability in particle morphology that can alter tabletability. Drug loading is also constrained in practice, typically 10–30% w/w before miscibility limits or dissolution-medium supersaturation collapse are reached, so high-dose BCS IV compounds may require impractically large tablet or capsule sizes even when the ASD approach is chemically sound. Representative ASD formulations for BCS IV drugs are summarised in Table 4 (Ref. [28,41,44,45,46,47,48,49,50,51,52,53]).

3.2 Co-Amorphous Systems

Co-amorphous systems are single-phase amorphous binary or ternary mixtures of a drug with a low-molecular-weight co-former (amino acid, flavonoid, second drug). Unlike polymer-based ASDs, co-formers can themselves be pharmacologically active enabling dual-mechanism formu-

lations that simultaneously improve dissolution and inhibit efflux or metabolism [54].

Furosemide–Arginine: Co-amorphous salt mixtures prepared by spray drying simultaneously enhanced both dissolution AND permeation of furosemide. Formulations with P-gp inhibitor co-formers (piperine, verapamil, quercetin) improved dissolution but not permeation, highlighting arginine's unique ability to address both barriers through salt formation [54].

Docetaxel–Myricetin: Coamorphous 1:1 molar ratio with the natural P-gp inhibitor myricetin produced persistent supersaturated dissolution and 3.9-fold higher C_{max} and 3.1-fold higher AUC vs. crystalline docetaxel in rats compared to only 2.6-fold C_{max} and 1.3-fold AUC for amorphous docetaxel alone [55].

Ursolic Acid–Piperine: Co-amorphous system (5.3–7× solubility; 7–8× dissolution; 5.8× AUC improvement vs. crystalline form). Piperine in this system both inhibited CYP3A4 and increased Caco-2 permeability, but its synchronised dissolution meant ~60% less free piperine was released than from pure piperine, a critical pharmacokinetic insight for co-amorphous design [56].

Hydrochlorothiazide–L/D-Arginine: Cryomilling in 1:1 molar ratio produced co-amorphous salts with single T_g, evidence of salt formation, improved stability at elevated temperature and humidity, and enhanced dissolution and permeation potential [57].

3.3 Cocrystal Engineering and Salt Formation

Pharmaceutical cocrystals combine the drug with a pharmaceutically acceptable co-former via non-covalent interactions, modifying physicochemical properties without chemical alteration. Cocrystals often offer superior thermodynamic stability over amorphous forms while still providing enhanced solubility [58].

Furosemide: Cocrystals with imidazole and 5-fluorocytosine produced up to 118-fold solubility improvement, 1.3–2.6× intrinsic dissolution, and 2.1–2.8× permeability enhancement vs. pure drug [59]. Spray Flash Evaporation (SFE) nanocrystals gave a 4.5-fold dissolution rate increase [60].

Curcumin–Trimesic Acid: New cocrystal phase with enhanced dissolution and confirmed anti-invasion activity in 3D tumour models [61].

Etravirine–L-Tartaric Acid: Co-crystals at 1:1, 1:2, and 2:1 molar ratios synthesised to exploit solubility increase in the solid form for this HIV NNRTI [62].

Sulfamethoxazole: Cocrystal forms prepared by ball milling and solution crystallisation demonstrated improved aqueous solubility [63].

Translating a cocrystal from screening hit to registered product carries distinct regulatory and manufacturing considerations relative to ASDs or salts. Because cocrystals are neither a salt nor a polymorph of the parent drug, most regulatory agencies require the co-former

Table 4. Amorphous solid dispersion formulations for BCS IV drugs, including marketed products and investigational systems [28,41,44,45,46,47,48,49,50,51,52,53].

Drug	Carrier polymer	Method	Key finding
Ritonavir (Norvir®)	PVPVA/Soluplus®	HME	A widely cited commercial example of an amorphous solid dispersion.
Lopinavir (Kaletra®)	PVPVA	HME	Fixed-dose combination; landmark commercial success
Venetoclax (Venclexta®)	Copovidone	HME	Marketed oncology ASD; dose-reduced formulation
Oleanolic acid	PVP VA64	HME	Enhanced AUC and C _{max} vs. PM and commercial tablet
Etravirine	PVP	HME	>2× dissolution rate; stable ASD; 5-stage systematic screening
Ritonavir (hybrid)	Soluplus®	QbD-DM3	Nanoamorphous micellar dispersion; combined mechanisms
Daidzein	Multi-polymer	Spray drying	~20× C _{max} with 3rd-generation pH-modulated SDDS
Curcumin	Chitosan oligosaccharide	Spray drying	1.55–3.01× AUC; surfactant-free saccharide matrix
Chlorthalidone	Soluplus–SLS complex	Spray drying	6× supersaturation for 6 h; >80% release in 15 min
Rifaximin	Copovidone/HPC-SL	Spray drying	200× crystalline solubility maintained 20 h; saturates P-gp
Bergenin	Phospholipid complex	Co-precipitation	202.46% relative BA with verapamil (P-gp inhibitor)
Naftopidil	Chitosan-fumaric acid	Solvent evaporation	H-bond with fumaric acid as dissolution driver; stable

PVPVA, polyvinylpyrrolidone-vinyl acetate copolymer; SLS, sodium lauryl sulfate; HPC-SL, hydroxypropyl cellulose (SL, low-viscosity grade); QbD-DM3, Quality by Design–DM3 strategy; AUC, area under the curve; PM, physical mixture; HME, hot melt extrusion; SDDS, supersaturating drug delivery systems.

to be classified as an excipient with its own safety qualification (generally-recognised-as-safe status or equivalent) and the cocrystal to be shown, via slurry and thermodynamic stability studies, not to dissociate back to the parent drug and free co-former under storage or in the GI tract before absorption, since dissociation would forfeit the intended solubility benefit. Scale-up from screening (typically solvent evaporation or slurry conversion on a milligram scale) to manufacturing throughput is most reliably achieved by hot-melt or twin-screw reactive extrusion or by continuous cooling crystallisation, both of which require re-verification of cocrystal stoichiometry and polymorphic form, as some cocrystal systems exhibit their own polymorphism with different dissolution profiles. These solid-state engineering strategies are summarised in Table 5 (Ref. [36,54,55,56,57,59,61,62,63]).

3.4 Nanocrystals and Micronization

Nanocrystals (nanosuspensions) are pure-drug particles reduced to 100–1000 nm, stabilised by surfactants or polymers. They increase both dissolution rate (Noyes-Whitney: increased surface area) and potentially saturation solubility (Ostwald-Freundlich effect) without excipient-induced thermodynamic activity reduction [64,65].

TPGS/PVA ticagrelor nanosuspension: 2.8-fold improved GI permeation and 2.2-fold enhanced oral bioavailability vs. commercial product [66]. QbD-designed furosemide nanosuspensions revealed that two-way interactions between stabiliser type, drug concentration, and antisolvent:solvent ratio were the critical quality attributes governing particle size distribution [67]. Abraxane® (nab-paclitaxel) an albumin-bound paclitaxel nanoparticle remains the most prominent commercially successful BCS IV nanotechnology product [68]. Spray Flash Evaporation (SFE) produced furosemide nanocrystals with 4.5-fold dissolution rate increase [60].

Nanocrystal manufacture by wet media milling or high-pressure homogenisation is well established at commercial scale, but the resulting suspension is thermodynamically driven to coarsen over time via Ostwald ripening (smaller particles dissolving and redepositing onto larger ones), so long-term physical stability depends critically on stabiliser selection and concentration and must be confirmed over the intended shelf life rather than inferred from short-term data. Converting the aqueous nanosuspension into a solid oral dosage form, typically by spray drying or layering onto pellets/tablets, risks irreversible particle aggregation on drying, which can erase the dissolution-rate

Table 5. Solid-state engineering strategies (co-amorphous, cocrystal, amino acid salt) for BCS IV drugs [36,54,55,56,57,59,61,62,63].

Drug	Co-former/System	Type	Key outcome	Ref.
Furosemide	Arginine + P-gp inhibitors	Co-amorphous salt	Enhanced dissolution and permeation simultaneously	[54]
Docetaxel	Myricetin (P-gp inhibitor)	Co-amorphous	3.9× C _{max} ; 3.1× AUC vs. crystalline DTX	[55]
Ursolic acid	Piperine (CYP3A4 inhibitor)	Co-amorphous	5.8× AUC; 5.3–7× solubility; CYP inhibition	[56]
HCT	L/D-Arginine	Co-amorphous salt	Single T _g ; enhanced dissolution + permeation	[57]
Furosemide	Imidazole/5-FC	Cocrystal/salt	Up to 118× solubility; 2.8× permeability	[59]
Curcumin	Trimesic acid	Cocrystal	Enhanced dissolution; anti-invasion activity confirmed	[61]
Etravirine	L-Tartaric acid	Cocrystal	Increased solubility in solid form for HIV NNRTI	[62]
Sulfamethoxazole	Various co-formers	Cocrystal	Improved aqueous solubility	[63]
Quercetin/Rutin	L-Lysine	Amino acid salt	68–433× solubility; up to 4× Papp	[36]

HCT, hydrochlorothiazide; CYP3A4, cytochrome P450 3A4; 5-FC, 5-fluorocytosine; DTX, docetaxel.

advantage the nanosizing was meant to provide, so a cryo- or lyoprotectant and redispersibility testing after reconstitution are standard requirements rather than optional refinements.

4. Lipid-Based Drug Delivery Systems (LBDDS)

LBDDS exploit the body's endogenous lipid digestion and absorption pathways to overcome BCS IV dual barriers. Oral lipid formulations can enhance GI solubilisation, stimulate secretion of endogenous biliary lipids, promote chylomicron formation, and facilitate lymphatic absorption by-passing hepatic first-pass metabolism entirely [24,69]. The Lipid Formulation Classification System (LFCS) stratifies LBDDS from Type I (pure oils) through Type IV (surfactant/cosolvent without lipid), providing a rational selection framework [24].

A mechanistic insight from saquinavir studies: lipid digestion changes the thermodynamic activity of dissolved drug by altering colloidal structures present in the intestinal lumen, directly modifying apparent permeability independent of solubilisation effects. Simple *in vitro* permeation experiments run sequentially after *in vitro* digestion provided IVIVC for both free-drug concentration and k_{app}, total [70].

4.1 Self-Emulsifying Systems (SEDDS/SMEDDS/SNEDDS)

These isotropic oil/surfactant/cosolvent mixtures spontaneously form fine emulsions or nanoemulsions upon aqueous dilution in the GIT, providing rapid drug solubilisation. Neoral® (cyclosporine SMEDDS) remains the landmark commercial example [24].

Ticagrelor SMEDDS: a Capmul MCM/Cremophor EL/Transcutol P system optimised by mixture design improved Caco-2 permeability and antiplatelet activity, giving 5.7-fold higher AUC than a raw ticagrelor suspension in rats [71].

Docetaxel/Cyclosporin A Co-loaded SNEDDS: Sequential release of CsA (P-gp inhibitor) before DTX from ~30 nm droplets achieved 9.2-fold greater BA than DTX solution and 3.4-fold greater than DTX SNEDDS alone demonstrating the power of sequential P-gp inhibitor release [25].

Etoposide (VP-16) SNEDDS: 6.4-fold higher AUC than drug suspension and 2.4-fold higher than VePesid® (commercial product), with good IVIVC [72].

Canagliflozin Solid SS-SMEDDS: Neusilin US2 adsorbent with Poloxamer 188 PPI; molecularly dispersed state confirmed; enhanced jejunal *ex vivo* permeability; reduced hepatic metabolism and P-gp efflux vs. pure drug [73].

Abiraterone Acetate Lipid Matrix Tablet: Medium-chain triglycerides/castor oil PEG40 SMEDDS spray-dried onto mesoporous silica and compressed into tablets achieved 704.80% relative bioavailability vs. reference potentially enabling dose reduction and elimination of the mandatory fasting requirement that severely burdens prostate cancer patients [15,30].

Rebamipide Counter-Ion SNEDDS: Counter-ion complex with tetrabutylphosphonium hydroxide (TBPOH) overcame poor lipid solubility; Eudragit EPO maintained high luminal concentrations in gastric environment and improved oral absorption [74].

Conversion of liquid SEDDS to solid SEDDS (S-SEDDS) via adsorption onto porous carriers or spray drying

addresses physical/chemical stability, dosing accuracy, and dosage form limitations of liquid systems [75].

Manufacturing and stability limitations temper these gains in practice. Long-chain and medium-chain triglycerides are susceptible to lipid peroxidation, so formulations require antioxidant inclusion (tocopherol, BHT) and nitrogen headspace during filling; oxidation products can also degrade co-formulated drug or generate off-flavours that affect patient acceptability. Soft- and hard-gelatin capsule shells are incompatible with formulations containing free aldehydes or low-molecular-weight polyethylene glycols, which cross-link gelatin and cause pellicle formation and delayed dissolution on storage; HPMC shells largely avoid this but are less compatible with highly hygroscopic fills. Dilution of a SEDDS/SMEDDS in GI fluid is not always benign: surfactant partitioning into bile-salt micelles or dilution below the critical micellar concentration can trigger drug precipitation before absorption, so *in vitro* lipolysis testing (simulated intestinal fluid with pancreatic lipase, monitoring free drug versus precipitated drug through the digestion cascade) is now considered essential for de-risking formulations rather than dissolution testing alone, which does not capture digestion-mediated supersaturation or precipitation. Drug loading is again capacity-limited by the compound's oil/surfactant solubility, and self-emulsification time and resultant droplet size can drift with excipient lot-to-lot variability, so tight excipient specifications and robust design-space definition are needed for reproducible manufacture at scale.

4.2 Lipid Nanoparticles: SLNs, NLCs, and Surface Engineering

Solid Lipid Nanoparticles (SLNs): Docetaxel palmitate SLNs demonstrated *in silico* (molecular docking) evidence of lower P-gp binding affinity vs. paclitaxel and unmodified docetaxel, offering reduced efflux susceptibility alongside improved pharmacokinetics and pharmacodynamics [76].

Nanostructured Lipid Carriers (NLCs): Ticagrelor-NLC achieved a relative oral bioavailability of 254.99% (a 2.5-fold increase) and superior antiplatelet activity vs. raw TGL [77]. Curcumin-NAPG-NLC (surface-modified with N-acetyl-L-cysteine-PEG(100)-monostearate) showed AUC 499.45-fold vs. curcumin solution and 116.89-fold vs. unmodified NLC, attributed to combined mucoadhesion and mucus penetration enhancement by the NAPG conjugate [78].

4.3 Vesicular Systems: Liposomes, Chitosomes, and Niosomes

Chitosomes (Chitosan-coated Liposomes): Furosemide chitosomes demonstrated improved solubility and dissolution vs. crystalline drug, with chitosan coating providing mucoadhesive properties extending intestinal residence [79].

Niosomes: Non-ionic surfactant vesicles offering greater chemical stability than liposomes at lower cost.

Lipid Nanocapsules: FRET and NTA analysis confirmed intact transcellular crossing of a human intestinal epithelium model, providing direct evidence for the transcellular transport pathway of intact nanocapsules [80].

4.4 Colloidal Carriers

pH-responsive nanocolloids self-assembled from β -lactoglobulin (BLG) cross-linked with epsilon poly-L-lysine (BCP/BCEP) demonstrated high curcumin loading, pH-triggered release, and improved solubility, dissolution, permeability, and biological activity confirming the utility of nutraceutical-derived hybrid self-assembled colloidal systems for protecting hydrophobic drugs from harsh GI conditions [81].

Nanoemulsions and their variants (SNEDDS, SMEDDS) provide enhanced drug loading, protection from environmental degradation, and site/time-specific release [82]. Rebamipide microemulsion (Capmul MCM/-Solutol HS15/ethanol) significantly enhanced dissolution and oral bioavailability with no discernible intestinal toxicity [83].

4.5 Lymphatic Delivery

Formulations promoting chylomicron-associated transport through intestinal lymphatics deliver drug via mesenteric lymph to the thoracic duct, bypassing hepatic first-pass metabolism entirely. Long-chain triglycerides, phospholipids, and selected surfactants promote lymphatic uptake; drug log P is the primary molecular predictor of lymphatic transport extent [84]. The distinction drawn in Section 1.3 matters here: lymphatic transport raises systemic exposure by circumventing hepatic first-pass metabolism, not by increasing the permeability of the intestinal membrane, so an exposure gain achieved by a lymphatic strategy should not be reported as a permeability enhancement, and is in fact one of the likeliest confounders when a lipid-based formulation is said to have improved permeability. Representative lipid-based drug delivery systems for BCS Class IV drugs are summarised in Table 6 (Ref. [15,24,25,30,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85]).

SPNMS-TPGS mangiferin micelles (Section 5.3) also confirmed higher lymphatic uptake in *ex vivo* intestinal perfusion studies, illustrating that lipid-mimicking nanocarriers can achieve lymphatic access without formulating a classical LBDDS [86].

4.6 Formulation Strategies to Mitigate Food Effects

A defining clinical liability of many BCS IV drugs is a large positive food effect, in which co-administration with a meal increases exposure several-fold, producing unpredictable dosing and restrictive label instructions. The mech-

Table 6. Lipid-based drug delivery systems for BCS Class IV drugs
[15,24,25,30,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85].

System	Drug	Enhancement	Key mechanism
SMEDDS	Ticagrelor	5.7× AUC vs raw	Capmul MCM/Cremophor EL/Transcutol P; improved permeability
Co-loaded SNEDDS (DTX/CsA)	Docetaxel	9.2× vs. DTX solution	Sequential P-gp inhibitor (CsA) then drug release
SNEDDS (VP-16)	Etoposide	6.4× vs. suspension	2.4× vs. VePesid®; good IVIVC
Solid SS-SMEDDS	Canagliflozin	Reduced hepatic metabolism	Poloxamer 188 PPI; P-gp bypass; molecularly dispersed
Lipid matrix tablet	Abiraterone acetate	704.80% relative BA	Molecular dispersion in lipid; dose/food-effect reduction
Counter-ion SNEDDS	Rebamipide	Improved oral absorption	TBPOH complex overcomes poor lipid solubility
NLC	Ticagrelor	254.99% relative BA vs. raw drug	Solid lipid matrix; enhanced antiplatelet PD
NAPG-NLC	Curcumin	499.45× AUC vs. solution	Mucoadhesion + mucus penetration by NAPG conjugate
SLN (palmitate conjugate)	Docetaxel	Lower P-gp affinity (<i>in silico</i>)	Lipid conjugation reduces efflux susceptibility
Lipid nanocapsules	Various BCS IV	Intact transcellular transport	FRET/NTA confirmed nanocarrier integrity
BLG-polyLysine nanocolloids	Curcumin	Improved GI protection + BA	pH-responsive; nutraceutical-based self-assembly

NLC, nanostructured lipid carrier; SLN, solid lipid nanoparticle; BLG, β -lactoglobulin; TBPOH, tetrabutylphosphonium hydroxide; SNEDDS, self-nanoemulsifying drug delivery system; SS, supersaturable; SMEDDS, self-microemulsifying drug delivery system; CsA, cyclosporine A; NAPG-NLC, N-acetyl-L-cysteine-PEG(100)-monostearate-modified nanostructured lipid carrier; GI, gastrointestinal; IVIVC, *in vitro*–*in vivo* correlation; PPI, polymeric precipitation inhibitor; PD, pharmacodynamic; FRET, Förster resonance energy transfer; NTA, nanoparticle tracking analysis.

anism is physicochemical: a fatty meal slows gastric emptying, raises intestinal pH, and, most importantly, triggers secretion of bile salts and biliary lipids that solubilise poorly soluble drug, while lipid digestion products generate an absorptive colloidal phase [87]. Abiraterone acetate shows a roughly ten-fold food effect, and posaconazole, lurasidone, and venetoclax show similarly large, clinically troublesome increases that force patients to coordinate dosing with food.

The rational solution is to build the solubilising environment into the formulation so that performance no longer depends on the fed state. Lipid-based and self-emulsifying systems present the drug in a pre-solubilised, pre-dispersed form that mimics the postprandial milieu, while amorphous dispersions and mesoporous silica raise apparent solubility independently of bile-salt availability. The lipid matrix tablet of abiraterone discussed in Section 4.1 exemplifies the approach, achieving high relative bioavailability while eliminating the mandatory fasting requirement that burdens prostate cancer patients [15,30]. Designing explicitly for food-effect robustness, and confirming it with fed and fasted biorelevant dissolution, is becoming a standard expectation for BCS IV development.

5. Nanotechnology-Based Approaches

Nanotechnology dramatically increases the surface area-to-volume ratio of BCS IV drugs, accelerating dis-

solution kinetics while enabling novel permeation pathways (transcellular, lymphatic, receptor-mediated endocytosis). Multiple distinct platforms have been validated, each with characteristic advantages and limitations (Table 7, Ref. [10,13,60,64,86,88,89,90,91,92,93,94,95,96,97]). Relative to the industrially established, first-line approaches above (ASDs, lipid-based systems, and particle-size engineering), most of the nanocarrier platforms surveyed here remain second-line or exploratory for small-molecule BCS IV drugs, reserved for cases in which solubilisation alone is insufficient or a genuinely novel absorption route is required [64,88]. Recent appraisals of physical-modification strategies for poorly water-soluble drug substances reach a similar conclusion, placing drug nanoparticles, solid dispersions, and lipid-based formulations ahead of more elaborate nanocarriers for routine development of such candidates [98].

5.1 Mesoporous Silica Nanoparticles (MSNs)

MSNs offer high surface area ($>800 \text{ m}^2/\text{g}$), tunable pore architecture (2–50 nm), and readily modifiable surface chemistry. Vorinostat encapsulated in amino-modified MSNs (MCM-41-NH₂) achieved 3.9-fold solubility, ~4-fold Caco-2 permeability, and robust induction of histone hyperacetylation and apoptosis in HCT116 colon and HH cutaneous T-cell lymphoma cells [13]. MSN inkjet

Table 7. Nanotechnology platforms for BCS Class IV drug delivery with representative outcomes
[10,13,60,64,86,88,89,90,91,92,93,94,95,96,97].

Platform	Drug example	Key outcome	Mechanism/Advantage
Nanocrystals (TPGS/PVA)	Ticagrelor	2.2× BA; 2.8× GI permeation	Surface area increase; Ostwald-Freundlich; no excipient dilution of activity
Abraxane® (nab-PTX)	Paclitaxel	~3.5× vs. Taxol®	Albumin binding; clinical-grade nanotechnology
MSN (amino-modified)	Vorinostat	3.9× solubility; ~4× permeability	Tunable pore/surface; anticancer activity confirmed <i>in vitro</i>
MSN Inkjet Printing	Various BCS IV	Flexible deposition platform	Personalised/digital manufacturing of nano formulations
Carbon Nanotubes	Docetaxel	pH-dependent release; enhanced BA	Tumour microenvironment targeting; reduced clearance
Fullerenol Conjugates	Docetaxel	5.8× BA; 4.3× IC50	Erythrocyte compatible; low protein binding
Titanate Nanotubes	HCT	Enhanced loading/release	Novel inorganic carrier; unique surface bonding
Boric acid-coated Nanocomposite	Camptothecin	Superior anticancer vs. free CPT	Glycocalyx diol targeting; rapid transmembrane translocation
OA-CMCS Micelles	Docetaxel	6.57× Papp; 2.62× AUC	Chitosan mucoadhesion; reduced P-gp susceptibility
Soluplus® Micelles	Amphotericin B	6× Caco-2 uptake; 3.5× Papp	Microfluidics preparation; micellar stabilisation
PLGA-Piperine Micelles	Docetaxel	6.5× BA; 3.3× brain BA	Pre-released piperine inhibits CYP3A4 + P-gp sequentially
SPNMS + TPGS	Mangiferin	6.6× permeability; 3.0× BA	Lymphatic uptake; dual P-gp + CYP450 inhibition via TPGS
PLGA NPs	Apremilast	2.25× BA; sustained release	Biodegradable polymer; once-daily potential

TPGS, D- α -tocopheryl polyethylene glycol succinate; SPNMS, self-assembled phospholipidic nano-mixed micelles; CPT, camptothecin. ↓, Decrease / Reduction.

printing using PEI-surface-functionalised particles demonstrated feasibility as a flexible deposition platform for pharmaceutical drug screening and potentially personalised dosage form manufacturing [89].

5.2 Carbon Nanotubes, Fullerenes, and Inorganic Nanosystems

Carbon nanotubes and fullerenes are included below for mechanistic completeness, but neither has an approved pharmaceutical product or an active clinical program, and both carry unresolved concerns regarding incomplete biodegradability, long-term pulmonary and hepatic accumulation, and batch-to-batch variability in surface functionalisation that have so far kept them at a purely pre-clinical, proof-of-concept stage. Readers seeking clinically translatable nanocarrier platforms for BCS IV compounds should instead prioritise the lipid nanoparticle, polymeric micelle, and nanocrystal systems described in Sections 4.2, 5.3, and 3.4, which have regulatory precedent (e.g., Abraxane®) or are in active clinical development.

Hydroxylated carbon nanotubols (CNTnols) conjugated with aspartic acid enabled controlled, pH-dependent docetaxel release in the acidic tumour microenvironment, with pharmacokinetic studies confirming enhanced bioavailable fractions, reduced clearance, and prolonged bioresidence [90]. Aspartic acid–fullerenol conjugates loaded with docetaxel achieved 5.8-fold bioavailability en-

hancement and 4.3-fold IC50 reduction with favourable erythrocyte compatibility [91].

Titanate nanotubes (TNTs) explored for hydrochlorothiazide demonstrated feasibility of spiral cross-sectioned inorganic nanotubes as drug carriers with unique bonding mechanisms distinguishable from organic polymer systems [92]. Boric acid-coated camptothecin nanocomposites combined nanoscale size with amorphous solid state; boric acid groups reacted specifically with diol moieties in the cell glycocalyx, facilitating rapid transmembrane translocation and superior anticancer activity vs. free CPT and crystalline nanoparticles [93].

5.3 Polymeric Nanocarriers and Micelles

Polymer nanocarriers improve bioavailability through multiple synergistic mechanisms: increased solubilisation, mucoadhesion (positively charged nanocarrier + negatively charged mucin), tight junction modulation, receptor-mediated endocytosis and transcytosis, and M-cell phagocytosis via Peyer's patches [94]. Preclinical evidence across these mechanisms has since been appraised systematically, confirming consistent solubilisation and absorption gains for polymeric micelles while identifying micelle stability in gastrointestinal fluid, manufacturing scale-up, and regulatory precedent as the barriers that still separate the platform from clinical use [99].

OA-CMCS Micelles (Docetaxel): Oleic acid grafted carboxymethyl chitosan micelles achieved $6.57\times$ Caco-2 Papp vs. free DTX, $1.97\times$ Cmax, $2.62\times$ AUC in rats attributable to increased paracellular absorption and reduced P-gp susceptibility [95].

Soluplus® Micelles (Amphotericin B): Microfluidics-prepared AmB polymeric micelles showed 6-fold greater Caco-2 uptake and 3.5-fold greater permeability than free drug [10].

PLGA-Piperine Micelles (Docetaxel): 6.5-fold bioavailability, 3.5-fold longer retention, 3.3-fold single-point brain bioavailability; piperine released before DTX to pre-inhibit CYP3A4 and P-gp [96].

SPNMS-TPGS (Mangiferin): Self-assembled phospholipidic nano-mixed micelles with TPGS achieved 6.6-fold intestinal permeability augmentation and 3.0-fold bioavailability improvement in rats; higher lymphatic uptake confirmed *ex vivo* [86].

Apremilast PLGA NPs: Sustained release; 2.25-fold greater bioavailability vs. suspension in rats [97].

5.4 Intestinal Mucus as a Barrier to Nanocarrier Delivery

Beyond aqueous solubility and the epithelial membrane, the adherent mucus layer is a third barrier that disproportionately affects the nanoscale carriers increasingly used for BCS IV drugs. Mucus is a continuously secreted, cross-linked mesh of mucin glycoproteins that traps foreign particles by steric and adhesive interactions and clears them within minutes to hours, sharply limiting the residence time available for drug release and absorption [100]. Conventional mucoadhesive carriers, long assumed to be advantageous, are in fact immobilised in the outer, rapidly shed mucus and may never reach the epithelium.

Newer carriers are therefore engineered around the mucus layer rather than against it, using four complementary tactics: mucus penetration, controlled mucoadhesion, rapid mucus diffusion, and prolonged mucosal retention. Dense, low-molecular-weight poly(ethylene glycol) coatings shield surface charge and hydrophobic patches to create mucus-penetrating particles that diffuse through the mesh almost as freely as in water, with the density and length of the PEG layer governing the outcome [100,101]. Zwitterionic coatings achieve a similar muco-inert surface, while N-acetylcysteine-modified systems and thiomers act on the mucus itself, the former loosening the mucin network and the latter forming reversible disulfide bridges with mucin to anchor the carrier for sustained, localised release [102]. Surface-engineered lipid nanocarriers that combine mucus penetration with mucoadhesion, such as the curcumin system discussed in Section 4.2, illustrate how these tactics translate into order-of-magnitude exposure gains for BCS IV payloads [78].

A complementary design strategy treats mucoadhesion and mucus penetration as combinable rather than mutually exclusive. Reported approaches include decorating

a single carrier with both mucoadhesive and mucopenetrating ligands, pairing mucoadhesive ligands with mucolytic enzymes, and nesting a mucus-penetrating carrier within a mucoadhesive formulation that releases it at the mucosal surface so that retention and epithelial access are achieved in sequence rather than traded against one another [103].

6. Transporter-Mediated Strategies and Prodrug Design

6.1 P-Glycoprotein Inhibition

P-gp actively effluxes absorbed BCS IV substrates back into the intestinal lumen, an absorption barrier orthogonal to low passive permeability. Excipients such as TPGS, Pluronic block copolymers, and Cremophor EL inhibit P-gp at formulation-achievable concentrations and, incorporated into SEDDS or polymeric micelle systems, simultaneously address solubility, dissolution, and efflux without the drug-drug interaction liability of pharmacological inhibitors [38,104]. Plant-derived co-formers such as myricetin (co-amorphous systems, Section 3.2) and piperine (PLGA micelles, Section 5.3) achieve the same effect without a separate excipient [55,96].

6.2 Influx Transporter Targeting: ASBT

ASBT Prodrug (Paclitaxel-CPP): Cholic acid-functionalised PEGylated paclitaxel (CPP), linked via redox-responsive disulfide bond, self-assembled into nanoparticles with $>30,000$ -fold solubility improvement. Caco-2 permeability was 4-fold higher via apical sodium-dependent bile acid transporter (ASBT)-mediated endocytosis. Rat pharmacokinetics showed 10-fold higher oral bioavailability than Taxol® [105].

ASBT-targeted delivery is mechanistically attractive but constrained by the transporter's normal physiological role: ASBT mediates enterohepatic recirculation of a finite bile-acid pool concentrated in the terminal ileum, so uptake capacity is limited and saturable, and high-affinity conjugates risk interfering with endogenous bile-acid and lipid-soluble-vitamin absorption if dosed chronically at high levels. Because the ileal ASBT-expressing region is anatomically restricted, formulations must also survive transit through the proximal small intestine without premature release, which typically requires an enteric or delayed-release component layered onto the conjugate itself, adding a further manufacturing and stability variable beyond the bioconjugation chemistry.

6.3 Amino Acid and Valyl Prodrug Strategies

Two design considerations govern whether an amino acid or valyl prodrug reaches the clinic. First, activation depends on intestinal or hepatic esterase/peptidase activity that varies between individuals and, for some enzymes, across ethnic groups and disease states (e.g., reduced hepatic esterase activity in cirrhosis) [106], so first-in-human and population pharmacokinetic studies must ex-

plicitly characterise activation-rate variability rather than assuming it mirrors preclinical species. Second, a prodrug is regulated as a distinct new chemical entity requiring its own toxicology, genotoxicity, and CMC package for the prodrug itself and, where relevant, the released moiety, rather than being treated as a minor formulation variant of the parent drug; this materially lengthens the regulatory pathway relative to formulation-only approaches (Sections 2–5) and is only justified when those approaches have been shown insufficient to overcome the permeability barrier.

Prodrug design masks unfavourable physicochemical properties, converting a drug into a more soluble or permeable derivative that is reconverted *in vivo*. Amino acid prodrugs introduce recognition motifs for intestinal peptide (PepT1/PepT2) or amino acid transporters, converting passively poorly absorbed drugs into actively transported substrates, as exemplified clinically by the oseltamivir ethyl ester and by valyl prodrugs of nucleoside analogues [107]. For BCS IV drugs this strategy can improve solubility and permeability simultaneously, though variable esterase or protease activation across patients requires careful pharmacokinetic characterisation [105].

6.4 Permeability Enhancers: SNAC, Sodium Caprate, and Emerging Agents

Permeability enhancers (PEs) act on the epithelial membrane or its junctional architecture to transiently increase transcellular or paracellular flux, without structural modification of the API. Because they are, together with transporter-targeted prodrugs, among the few strategies that genuinely alter intestinal barrier permeability rather than raise exposure through concentration or route (Section 1.3), their use is justified only once biorelevant testing confirms permeability, not dissolved concentration, is rate-limiting [22,29]. The mechanisms of action of these agents are illustrated in Fig. 3.

6.4.1 Salcaprozate Sodium (SNAC): Mechanism and Clinical Validation

Salcaprozate sodium (SNAC) is the most clinically consequential PE to date, serving as the enabling excipient in Rybelsus® (oral semaglutide, Novo Nordisk, 2019), the first orally bioavailable GLP-1 receptor agonist. Its approval demonstrated, at regulatory scale, that a peptide of near-zero passive permeability could achieve adequate systemic exposure through a PE-enabled tablet [29,108]. SNAC acts through a localised gastric high-pH microenvironment that protects co-formulated drug from degradation, transcellular membrane fluidisation, and luminal protease inhibition; because absorption is predominantly gastric, strict fasting and low-volume water administration are required [29,109]. Applicability to BCS IV small molecules remains less established than for macromolecules: the mechanism favours gastric rather than jejunal absorption windows, and the high SNAC:drug ratio needed (20:1 to

100:1 w/w) may be impractical outside potent, low-dose compounds [108,109].

The transcellular mechanism has since been resolved at molecular resolution. Constant-pH molecular dynamics simulation, supported by NMR and light-scattering measurements, indicates that SNAC aggregates within the lipid bilayer to create transient, enhancer-filled fluid defects: semaglutide anchors by its fatty-acid tail while its polar body sinks through these SNAC-rich pockets, in a process the authors liken to quicksand. The mechanism rationalises both the reversibility of the effect and the high enhancer-to-drug ratios required [110].

6.4.2 Sodium Caprate (C10) and Medium-Chain Fatty Acid Derivatives

Sodium caprate (C10) is a medium-chain fatty acid PE that acts paracellularly, activating phospholipase C at the enterocyte apical membrane to trigger calcium-dependent contraction of the peri-junctional actomyosin ring and transiently widen tight junctions. Because this route admits luminal macromolecules, including endotoxins and food antigens, with limited selectivity, it carries greater theoretical safety concern than SNAC's transcellular mechanism and has required extensive long-term characterisation in clinical programmes [22,111]. C10 has been applied as an intestinal permeation enhancer in oral solid dosage formulations, where it has been formulated with low-molecular-weight heparin and has entered clinical trials for oral insulin delivery [22], with clinical evaluation also reported for bisphosphonates and antisense oligonucleotides [111]. Its permeation-enhancing action is concentration-dependent and coincides with transient, rapidly reversible epithelial perturbation at the concentrations required for efficacy [22,111].

6.4.3 Chitosan and Thiolated Cyclodextrin Derivatives

Chitosan, a cationic polysaccharide, interacts electrostatically with anionic claudin and occludin tight junction proteins below its pKa (~6.5) to open the paracellular route; N-trimethyl chitosan (TMC) retains positive charge across the full intestinal pH range, extending this mechanism to the jejunum and ileum. Beyond permeability enhancement, chitosan's mucoadhesive properties extend epithelial residence time, an advantage for BCS IV compounds with narrow absorption windows, and chitosan-coated liposomes and solid dispersions have improved oral bioavailability of furosemide and other BCS IV compounds preclinically [79,112]. Per-6-thiolated cyclodextrins combine cyclodextrin solubilisation with disulfide-mediated paracellular opening, achieving up to 6.87-fold permeability enhancement concurrent with solubilisation *in vitro*, directly addressing both barriers with a single excipient [33].

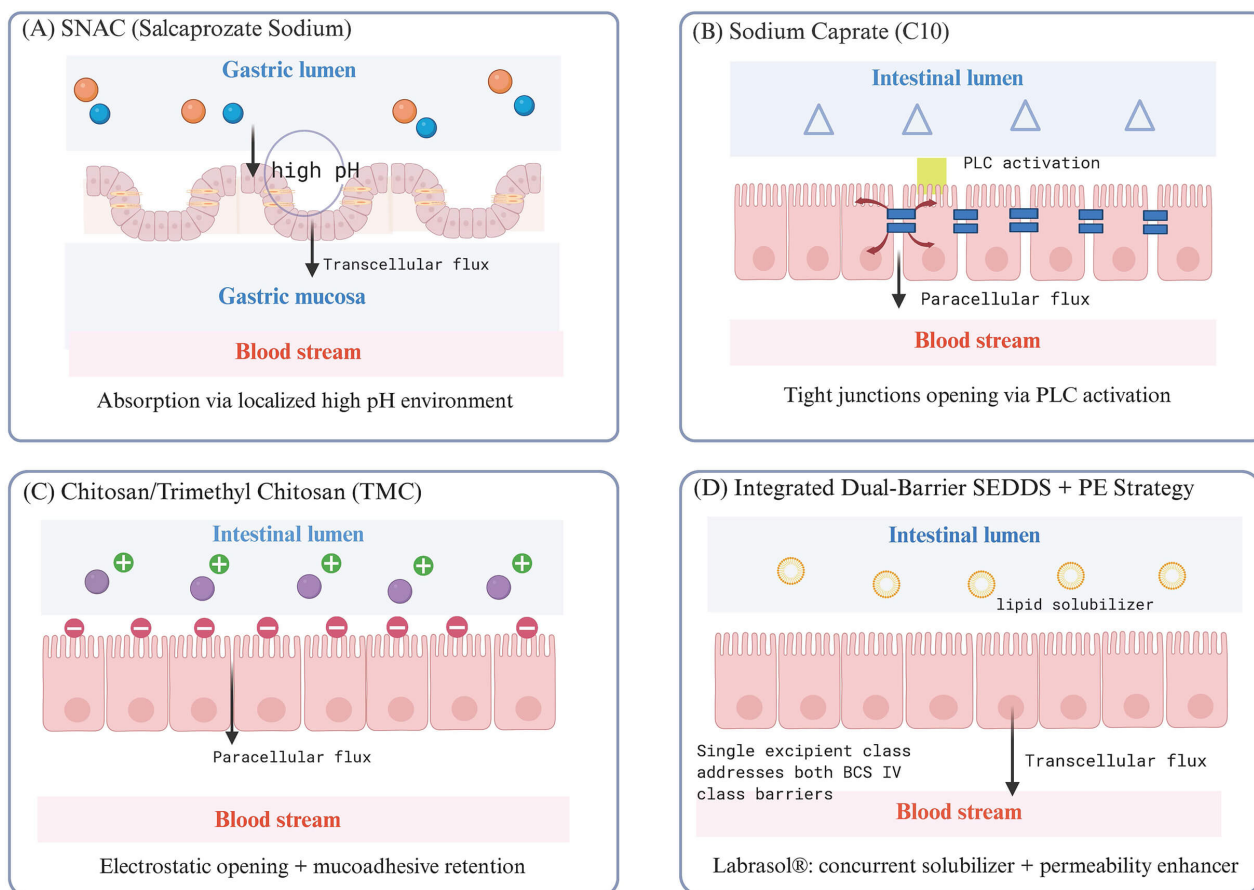


Fig. 3. Mechanisms of action of gastrointestinal permeability enhancers in BCS Class IV drug formulation. (A) SNAC (salcaprozate sodium) creates a localised high-pH microenvironment at the gastric mucosa and facilitates transcellular flux via membrane fluidisation; absorption is predominantly gastric. (B) Sodium caprate (C10) transiently widens tight junctions via phospholipase C activation and peri-junctional actomyosin ring contraction. (C) Chitosan/trimethyl chitosan (TMC) opens the paracellular route via electrostatic interaction with claudin and occludin tight junction proteins while simultaneously providing mucoadhesive retention at the absorptive epithelium. (D) Integrated dual-barrier SEDDS + PE strategy combining Labrasol® (caprylocaproyl polyoxyl-8 glycerides, a mixture of PEG-8 esters and glycerides with caprylic (C8) and capric (C10) acids) as a concurrent solubiliser and permeability enhancer within a self-emulsifying system, addressing both BCS IV barriers with a single excipient class. Created with [Biorender.com](https://www.biorender.com/).

6.4.4 Comparative Advantages, Limitations, and BCS IV-Specific Considerations

PEs address permeability alone and offer no solubilisation benefit, so deployment is warranted only once biorelevant testing establishes permeability, rather than luminal drug concentration, as rate-limiting [18,22]. Their principal advantage is that no API modification is required; effects are transient and reversible, and PEs can be combined with solubilising systems to address both barriers at once, with Rybelsus® providing regulatory precedent [29,108,111]. Key limitations, summarised below, are why few PEs beyond SNAC have reached commercialisation [22,29,113]:

SNAC—gastric, transcellular route; requires fasting and a high SNAC:drug ratio (2C10 to 0:1–100:1 w/w), limiting use to potent, low-dose compounds.

Sodium caprate (C10)—intestinal, paracellular route; non-selective tight-junction opening requires extensive long-term safety data on co-absorption of luminal antigens.

Chitosan/TMC—intestinal, paracellular route with added mucoadhesion; pH-dependent charge limits chitosan to the proximal intestine (TMC extends the range).

Thiolated cyclodextrins—intestinal, paracellular route combined with solubilisation; dual-barrier benefit from a single excipient.

All agents—pharmacokinetic variability driven by gastrointestinal pH, mucus, motility, and fed/fasted state, and novel agents face full excipient-qualification requirements in regulatory submissions.

The enhancer landscape has broadened well beyond SNAC and C10, to paracellular agents such as tight-junction-modulating peptides, novel transcellular surfac-

tants such as sucrose laurate, ionic liquids such as choline geranate (Section 2.7), and micro- and nanoparticulate carriers. The verdict is nonetheless sobering: none of the transcellular agents to emerge in recent years has proved superior to C10, and the limiting factor is argued to be not cost or intellectual property but the absence of enhancers that substantially outperform those already established, together with a lack of reliable, physiologically relevant *in vitro* and *ex vivo* models with which to screen for efficacy [114].

Placed on a common scale, the magnitude of enhancement is agent- and molecule-dependent rather than uniform: SNAC increased oral semaglutide bioavailability from an essentially non-oral peptide baseline to a clinically viable ~1% at the approved dose, sufficient because the peptide's potency tolerates low absolute bioavailability; sodium caprate has produced 2- to 10-fold increases in the intestinal permeability of co-administered small and mid-sized molecules in preclinical models, with more modest (2- to 3-fold) increases typical in confirmatory human studies; and thiolated cyclodextrins have achieved the largest reported single-excipient effect for a BCS IV small molecule to date, at up to 6.87-fold permeability enhancement, though this figure derives from *in vitro* Caco-2 data and has not yet been confirmed clinically [33]. These figures are not directly comparable across studies given differing test molecules, species, and assay conditions, but they illustrate that PE selection should be matched to how large an enhancement the specific molecule's potency and dose actually require, rather than defaulting to the most potent agent available.

6.5 The Intestinal Transporter Landscape: Efflux and Uptake Systems

P-glycoprotein dominates discussion of efflux, but it is one of several transporters that jointly determine the fate of a BCS IV drug at the enterocyte, and a complete account must consider both efflux and uptake systems (Table 8, Ref. [20,21]). On the apical, efflux side, P-glycoprotein (*ABCB1*) is joined by breast cancer resistance protein (BCRP, *ABCG2*) and multidrug resistance-associated protein 2 (MRP2, *ABCC2*), which share overlapping substrate ranges and can compensate for one another, so that inhibiting P-gp alone may not relieve efflux of a drug that is also a BCRP or MRP2 substrate [20,21].

Uptake transporters offer the opposite: an opportunity rather than an obstacle. The peptide transporter PEPT1 (SLC15A1), the organic anion-transporting polypeptides (OATPs), the apical sodium-dependent bile acid transporter (ASBT), the monocarboxylate transporter MCT1, and the organic cation transporters (OCTs) can each be exploited by prodrug or ligand design to actively import a drug that would otherwise permeate poorly, as discussed for the ASBT strategy in Section 6.2 [20]. Many BCS IV failures reflect the combination of these transporter limitations with low solubility, so that neither a solubility nor a permeabil-

ity intervention alone suffices; mapping a candidate against the full transporter landscape early in development clarifies which combined strategy is required [21].

6.6 Lessons From Oral Biologics for Small-Molecule BCS IV Delivery

Much of the recent momentum in overcoming the permeability barrier originates in the oral peptide field. SNAC and sodium caprate, developed to carry peptides across the epithelium, act on the same pathways that limit small molecules (Section 6.4) [108]. Ionic liquids developed for oral insulin, which simultaneously protect the payload and open the paracellular route, point the same way (Section 2.7) [43]. Device-based approaches, including intestinal patches, microneedle-bearing capsules, and self-orienting ingestible injectors, demonstrate that the permeability barrier can also be solved mechanically, offering a template for the most difficult, transporter- and metabolism-limited BCS IV molecules (Section 12.4) [115]. A complementary, receptor-based route exploits the neonatal Fc receptor (FcRn), which mediates pH-dependent transcytosis of Fc- and albumin-binding constructs across the intestinal epithelium; Fc-decorated nanoparticles have been absorbed via this pathway *in vivo*, though payload capacity and competition with endogenous ligands remain unresolved [116,117].

7. Special Formulation Technologies

7.1 Liqui-Solid Technology

Liqui-solid technology converts drug solutions or dispersions in non-volatile solvents into dry, free-flowing powders by adsorption onto a carrier (e.g., microcrystalline cellulose) and a coating agent (e.g., Aerosil). This improves drug wettability and increases dissolution surface area while maintaining solid dosage form manufacturability [118].

A three-pronged colon delivery system for sulfasalazine integrated pH-controlled release (Eudragit S-100, preventing gastric release), microbially triggered release (pectin and guar gum, metabolised by colonic microbiota), and liquisolid technology (burst release upon polysaccharide digestion in the colon). This approach is particularly rational for BCS IV drugs requiring site-specific colonic delivery [118].

7.2 Gastroretentive Dosage Forms (GRDFs)

Gastroretentive dosage forms extend gastric residence time through floating, bioadhesive, swelling, or magnetic mechanisms. GRDFs are strategically indicated for BCS IV drugs with: (i) absorption windows restricted to the proximal small intestine (upper GI), (ii) pH-dependent solubility favouring gastric dissolution, or (iii) instability in the intestinal environment. By prolonging the period during which the formulation resides at the optimal absorption region, GRDFs can meaningfully improve bioavailability for these 'situational' BCS IV molecules [119,120].

Table 8. The intestinal transporter landscape relevant to BCS Class IV absorption [20,21].

Direction	Transporter	Gene	Role for BCS IV drugs
Efflux (drug out)	P-glycoprotein	<i>ABCB1</i>	Major brush-border efflux; broad substrate range
Efflux (drug out)	BCRP	<i>ABCG2</i>	Co-effluxes many P-gp substrates; compensates for P-gp
Efflux (drug out)	MRP2	<i>ABCC2</i>	Effluxes conjugated and anionic drugs
Uptake (drug in)	PEPT1	<i>SLC15A1</i>	Imports peptidomimetic and valyl prodrugs
Uptake (drug in)	OATPs	<i>SLCO</i> family	Import anionic and amphipathic drugs
Uptake (drug in)	ASBT	<i>SLC10A2</i>	Bile-acid transporter; target for bile-acid prodrugs
Uptake (drug in)	MCT1	<i>SLC16A1</i>	Imports carboxylate drugs and prodrugs
Uptake (drug in)	OCTs	<i>SLC22A</i> family	Import organic cations

Apical efflux transporters (ABC family) oppose absorption and frequently act in concert, whereas solute-carrier uptake transporters can be harnessed by prodrug and ligand strategies to drive active import. Effective design considers the full set rather than P-glycoprotein alone.

BCRP, breast cancer resistance protein; MRP2, multidrug resistance-associated protein 2; OATPs, organic anion-transporting polypeptides; ASBT, apical sodium-dependent bile acid transporter; OCTs, organic cation transporters; PEPT1, peptide transporter 1; MCT1, monocarboxylate transporter 1.

Furosemide provides a well-studied example: its absorption window in the proximal small intestine combined with low permeability makes it a natural candidate for GRDF strategies that maintain therapeutic concentrations at the absorption site for longer. Floating matrix tablets and bioadhesive polymer systems have been reported [7,119]. GRDF approaches are most powerful when pharmacokinetic modelling confirms the absorption window and regional permeability variation for the specific drug; PBPK modelling is therefore integral to GRDF design for BCS IV molecules [121].

7.3 3D Printing Technologies

Fused Deposition Modelling (FDM) 3D printing enables precise morphological control of tablets, with structural characteristics directly governing dissolution behaviour.

MSN inkjet printing (Section 5.1) extends additive manufacturing to nanoparticulate systems, enabling defined-volume deposition of pharmaceutical nanoparticle suspensions on diverse substrates for drug screening and personalised dosage form applications [89].

8. Alternative Routes of Administration

8.1 Pulmonary Delivery

The pulmonary route provides direct systemic access through the highly vascularised alveolar surface (surface area $\sim 100\text{ m}^2$), bypassing GI degradation and hepatic first-pass metabolism. Ursolic acid (UA), a BCS IV pentacyclic triterpene, showed ~ 80 -fold bioavailability increase and 114-fold pulmonary $\text{AUC}_{0-t}/\text{dose}$ increase after intratracheal instillation vs. oral dosing in rats. Incubation experiments confirmed substantially reduced metabolism of UA in rat lung microsomes vs. liver microsomes, directly attributable to low lung CYP/UGT expression [122,123].

Dry powder inhaler formulations of BCS IV drugs incorporating nanoparticle technologies optimise aerody-

namic particle size for deep lung deposition while maintaining nano-enhanced dissolution characteristics. Inhaled amphotericin B for pulmonary aspergillosis and inhaled paclitaxel for primary lung tumours represent clinically relevant applications of this route for BCS IV compounds [123].

8.2 Transdermal Delivery

Transdermal delivery eliminates GI absorption barriers and hepatic first-pass metabolism while providing sustained, controlled drug release. The stratum corneum imposes a significant additional permeation barrier, particularly for larger, less lipophilic BCS IV molecules; nano-enabled systems substantially improve penetration. Curcumin ethosomal gel (ethanol-enriched phospholipid vesicles) demonstrated improved *ex vivo* skin permeation [16]. The combination of nanocarrier encapsulation and elastic lipid vesicles (transfersomes) represents the most advanced transdermal strategy for BCS IV compounds requiring systemic delivery. Apremilast-loaded PLGA nanoparticles for psoriasis (primarily oral) could benefit from transdermal approaches via nanovesicular systems for local dermatological indications [124].

9. Computational Modelling and Dissolution Testing

9.1 Physiologically Based Pharmacokinetic (PBPK) Modelling

PBPK models integrate drug-specific parameters (solubility, permeability, particle size, pKa, log P, P-gp/CYP substrate status) with physiological variables (GI pH, transit times, fluid volumes, transporter expression, regional permeability gradients) to mechanistically simulate oral absorption [121,125].

Global sensitivity analysis (GSA) of PBPK models for BCS IV compounds revealed that parameters governing both dissolution AND absorption remain simultaneously important across all dose levels unlike Classes I–III

where fewer parameters dominate because both solubility and permeability can act as the rate-limiting step at any given dose [121]. For bioavailability prediction, GI wall and hepatic clearance parameters additionally contribute. A semi-physiological Monte Carlo simulation framework for bioequivalence design confirmed that the parent drug is the most sensitive analyte for detecting differences in pharmaceutical quality across all BCS IV scenarios studied [126].

Species-specific *in vitro* biorelevant tools integrated with PBPK modelling more accurately predicted *in vivo* food effects and formulation performance at preclinical stages vs. non-species-specific approaches, as demonstrated in a venetoclax case study [127].

9.2 AI and Machine Learning in BCS IV Formulation Design

Artificial intelligence (AI) and machine learning (ML) are increasingly applied to pharmaceutical formulation development, enabling high-throughput virtual screening of excipient libraries, prediction of drug–polymer miscibility and ASD physical stability, optimisation of lipid formulation composition, and prediction of nanosuspension physical stability [128].

For BCS IV drugs, ML models trained on large datasets of polymer–drug interaction parameters can predict the most promising ASD polymer candidates without exhaustive experimental screening a critical advantage given the large combinatorial space of potential formulations. Integration with PBPK modelling creates a quantitative systems pharmacology (QSP) workflow where ML-optimised formulations are virtually tested for *in vivo* performance before any material synthesis [128]. In a recent proof of concept, micro-quantity high-throughput screening was combined with machine learning to predict the formation of both binary and ternary ASDs; from 1272 experimentally prepared dispersions, the models learned to distinguish the 188 systems that formed amorphous dispersions from the 1084 that crystallised, substantially reducing the material and time required for early formulation selection [129].

The same composition-to-outcome modelling paradigm is extending beyond amorphous dispersions to particulate and lipid-based BCS IV carriers more broadly. A comprehensive synthesis of machine learning applications across polymeric nanoparticles, lipid nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, nanosuspensions, self-emulsifying systems, niosomes and nanocrystals shows that models can now predict critical quality attributes, including particle size, encapsulation efficiency, drug loading and release behaviour, directly from formulation composition across the nanocarrier platforms discussed in Section 5 [130]. The most mature instance of this approach is lipid nanoparticle design for nucleic-acid delivery, where models trained on curated ionisable-lipid and formulation datasets predict transfection efficiency and guide lipid

selection; although developed for mRNA cargoes, the same feature-based prediction strategy, mapping composition and process parameters to a measurable delivery outcome, is directly transferable to the lipid-based small-molecule carriers of Section 4 [131].

A parallel application, complementary to the polymer- and lipid-selection models above, is the direct prediction of solid oral dosage form critical quality attributes from formulation composition and process parameters. A newly curated database integrating physicochemical, compositional and digitised dissolution data from nearly 700 marketed oral products now supports machine learning models that predict disintegration time, hardness and full dissolution profiles ahead of any physical trial batch, illustrating both the promise of this approach for BCS IV tablet development and its current dependence on the availability of standardised, structured formulation data [132]. The same data-driven logic is beginning to reach the compression step itself: in-line process analytical technology coupling real-time compression- and ejection-force data to machine learning and deep learning models has been used to sort defective tablets during manufacture at over 99% accuracy, extending AI-based formulation prediction from the design bench to real-time quality control on the production floor, a manufacturing consideration developed further in Section 11 [133].

These gains are bounded by the quality and scope of the training data available. Published ASD and nanosuspension datasets are dominated by a relatively narrow set of well-studied polymers and stabilisers, so model predictions for chemically novel excipients or unusual drug substructures should be treated as hypothesis-generating rather than definitive, and prospective experimental confirmation remains necessary before a computationally selected formulation advances to clinical material. Regulatory agencies have not yet published finalised, formulation-specific guidance on how AI/ML-derived process or formulation decisions should be documented and justified in a marketing application, so sponsors currently rely on general model-validation and computational-tool qualification frameworks, and this regulatory ambiguity, more than the technology itself, is currently the rate-limiting step for routine adoption.

The broader shift underway is from empirical trial-and-error formulation development to rational, mechanism-based design informed by computation. AI/ML-guided development can substantially reduce both the number of formulation candidates requiring physical preparation and the number of animal pharmacokinetic studies needed to advance a BCS IV compound to clinical formulation [128].

9.3 Biorelevant Dissolution Testing

Biorelevant media (FaSSiF, FeSSiF, FaSSGF, FeSSGF) capture the pH, bile salt concentration, phospholipid composition, and osmolality of fasted and fed intestinal flu-

ids more accurately than compendial aqueous media, providing substantially better predictive power for BCS IV drug dissolution *in vivo* [134]. This unequal maturity is the practical counterpart of the asymmetry set out in Section 1.3: dissolution supports formal *in vitro* to *in vivo* correlation, whereas no comparably robust quantitative correlation exists for permeability. A permeability change is established *in vivo* only by measuring effective permeability at a controlled luminal concentration, as in single-pass or regional intestinal perfusion, not by inference from a plasma concentration-time profile, so permeability inputs to the models below carry greater uncertainty than the solubility and dissolution inputs.

BCS subclassification guides dissolution test design: IVa (acids) may have high solubility at physiological intestinal pH; IVb (bases) risk of precipitation in the small intestine; IVc (neutral) require bile acids and lipids in dissolution medium to capture micellar solubilisation. Stomach-intestine transfer models simulate the pH transition from gastric to intestinal environment, identifying precipitation risks during transit [135].

For BCS IV drugs formulated for lymphatic absorption, biphasic dissolution systems incorporating an organic (octanol or MCT oil) absorption sink layer better capture the driving force for lymphatic uptake than single-phase aqueous methods, which can significantly overestimate supersaturation duration. PAMPA combined with single-pass rat intestinal perfusion (SPIP) modelling provides simultaneous dissolution–permeation data closely predicting *in vivo* outcomes [41,134].

Closely related to these biphasic methods is a family of small-scale dissolution–permeation (D/P) apparatuses that place a dissolution compartment and a permeation barrier in series so that the two processes are measured concurrently rather than sequentially. Side-by-side diffusion systems such as the μ FLUX and MacroFLUX cells, and the PermeaLoop device, pair a biorelevant donor compartment with an artificial membrane or cell monolayer and resolve the true thermodynamic driving force for absorption from supersaturating formulations, which sequential dissolution-then-permeation testing tends to overstate [136,137]. For BCS IV and supersaturating systems this distinction matters, because the benefit of a solubility-enhancing formulation is realised only if the generated supersaturation persists long enough to drive flux across the membrane before precipitation intervenes. Coupling D/P readouts to physiologically based biopharmaceutics models (PBBM) allows the interplay of dissolution, supersaturation, precipitation, and permeation to be propagated into predicted plasma exposure, strengthening the mechanistic dissolution-to-pharmacokinetic linkage exploited in the transfer and precipitation modelling described above [135].

Folic acid biowaiver analysis confirmed that none of the evaluated immediate-release folic acid products showed rapid dissolution at pH 1.2 or 4.5, precluding

biowaiver by current BCS criteria underscoring that BCS IV classification carries significant regulatory implications for bioequivalence strategy [138]. Table 9 (Ref. [41,121,125,126,127,128,134,135,138]) summarises these computational modelling and biorelevant dissolution testing approaches.

9.4 Developability Assessment and the Developability Classification System (DCS)

Before a formulation platform is selected, a structured developability assessment characterises the molecular liabilities that determine which strategies can succeed. The most informative descriptors extend well beyond equilibrium aqueous solubility to include kinetic solubility, supersaturation propensity and crystallisation tendency, glass-forming ability (GFA classes I to III), lipophilicity (log P and log D), ionisation behaviour (pKa), human intestinal effective permeability (Peff), efflux ratio, and dose number [139,140]. Read together, these parameters define whether a candidate is dissolution-rate-limited, solubility-limited, supersaturation-limited, or transporter- and metabolism-limited, and therefore which of the strategies in Sections 2 to 8 is rational rather than merely available (Table 10). A poor glass former, for example, signals that an amorphous solid dispersion will be difficult to stabilise and that a lipid-based or co-amorphous route may be preferable, whereas a high efflux ratio with otherwise adequate solubility points to transporter-directed and lymphatic strategies over further solubilisation.

The BCS defines high solubility against the full dose strength dissolving in 250 mL across pH 1.0 to 7.5, a deliberately conservative boundary that consigns many compounds to Class IV even when their solubility in the small intestine is adequate. The Developability Classification System (DCS) proposed by Butler and Dressman refines this by using intestinal rather than gastric solubility, by recognising the compensatory interplay of solubility and permeability in the small intestine, and by distinguishing dissolution-rate-limited from solubility-limited absorption through the solubility-limited absorbable dose concept [6]. The refined DCS (rDCS) extends this further by incorporating an estimate of the particle size needed to overcome dissolution-rate limitation [141]. Because the DCS classifies on biopharmaceutically relevant rather than regulatory criteria, many nominal BCS IV compounds prove to be dissolution-limited only under particular physiological conditions and therefore more tractable than their BCS assignment implies. Used alongside mechanistic PBPK simulation (Section 9.1), which resolves the same questions dynamically and candidate-specifically, the BCS, DCS, and PBPK progression moves from a regulatory screen, to a developability screen, to a quantitative prediction; the three are complementary and are best applied together when triaging a BCS IV candidate.

Table 9. Computational modelling and biorelevant dissolution testing tools for BCS Class IV formulation development [41,121,125,126,127,128,134,135,138].

Method/Tool	Application	Key advantage for BCS IV
PBPK modelling	Oral absorption prediction	Integrates solubility, permeability, transit, regional absorption windows, transporter expression
Global sensitivity analysis	Identifying rate-limiting parameters	Both dissolution AND permeability parameters critical in BCS IV across all dose levels
Monte Carlo BE simulation	Bioequivalence study design	Parent drug most sensitive analyte; reduces failed trials; metabolite selection guidance
Species-specific <i>in vitro</i> + <i>in silico</i>	Preclinical food effect prediction	More accurate vs. generic biorelevant media; venetoclax case study demonstrated
AI/ML formulation screening	ASD polymer selection; nanoscale optimisation	Virtual high-throughput screening; drug–polymer miscibility prediction; reduces animal use
FaSSiF/FeSSiF media	Biorelevant dissolution	Captures bile salt/phospholipid/pH of intestinal fluid; far better IVIVC than water
BCS subclassification (IVa/b/c)	Dissolution specification strategy	IVa (acid) vs. IVb (base) vs. IVc (neutral) guides medium selection and supersaturation approach
Biphasic dissolution (organic sink)	LBDDS/lymphatic formulations	Prevents overestimation of supersaturation; better predicts lymphatic absorption driving force
PAMPA + SPIP (combined)	Permeability assessment	Simultaneous dissolution–permeation; strong correlation with <i>in vivo</i> outcomes for BCS IV
Stomach–intestine transfer model	Precipitation risk on transit	Simulates gastric-to-intestinal pH shift; identifies precipitation risk before animal studies

PBPK, physiologically based pharmacokinetic; AI, artificial intelligence; ML, machine learning; SPIP, single-pass rat intestinal perfusion; LBDDS, lipid-based drug delivery systems; BE, bioequivalence; PAMPA, parallel artificial membrane permeability assay.

Table 10. Developability descriptors that should be characterised before formulation selection, the absorption liability each one signals, and the strategy class most likely to resolve it.

Parameter	Why it matters	Preferred strategy
High efflux ratio	Transporter-limited absorption	TPGS or inhibitor-co-loaded systems; lymphatic delivery
Poor glass-forming ability (GFA I)	Amorphous solid dispersion prone to recrystallisation	Lipid-based systems; co-amorphous stabilisation
High log P (>5)	Intestinal lymphatic transport potential	SMEDDS/SNEDDS; nanostructured lipid carriers
High precipitation tendency	Supersaturation lost on gastric emptying	Supersaturating systems with precipitation inhibitors
High dose number	Solubility-limited absorption	Salt or cocrystal formation; nanocrystals
Low Peff with low efflux	Passive-permeability-limited absorption	Permeation enhancers (SNAC, C10); prodrug strategies

The descriptors are diagnostic rather than prescriptive, and most BCS Class IV candidates present more than one simultaneously.

10. Rational Decision Framework for BCS IV Formulation Selection

No single formulation platform is universally optimal for BCS IV drugs. The rational approach begins with mechanistic characterisation to identify the dominant absorption barrier, followed by selection and combination of strategies targeting that barrier, with biorelevant dissolution and PBPK modelling as the final validation gates. Fig. 4 (Ref. [2,3,7,18,24,31,39,121,125,128,134,135,142]) provides the comprehensive decision framework. Table 11 (Ref. [10,11,13,14,15,16,22,25,28,29,30,31,32,33,34,35,36,47,

48,49,50,54,55,58,59,60,61,62,63,64,71,72,73,74,76,77,78,84,86,89,90,91,95,96,97,105,107,108,109,111,112,113,118,119,120,121,122,123,124,125,127,128,134,143]) provides a comprehensive master summary of all formulation strategies discussed in this review.

The strategies reviewed in the preceding sections can be condensed into a single problem-to-solution matrix that maps the dominant limitation of a candidate to the technologies most likely to resolve it (Table 12). The matrix is a starting point for rational selection rather than a substitute for candidate-specific assessment, and it is most powerful when combined with the subclass assignment of Section

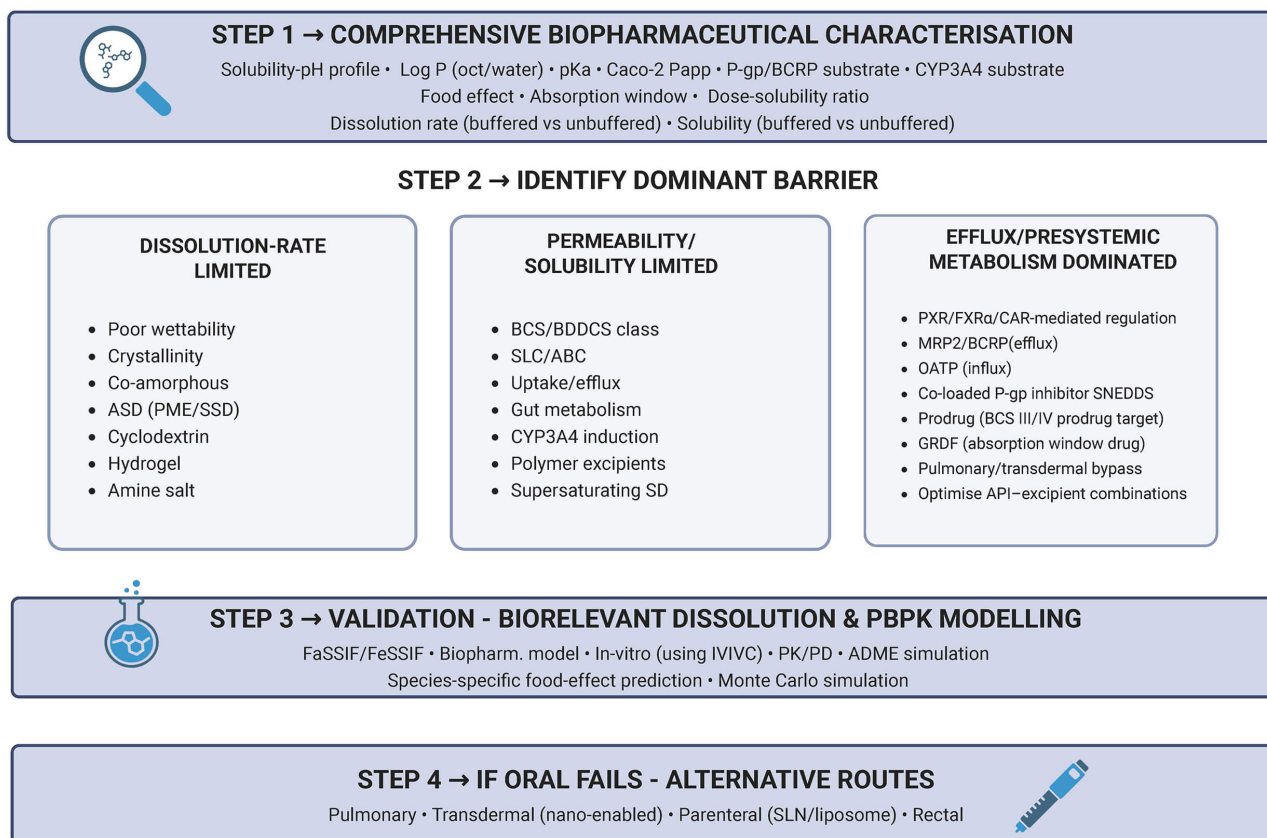


Fig. 4. Rational decision framework for BCS Class IV formulation strategy selection. Step 1 characterises the drug biopharmaceutically; Step 2 identifies the dominant absorption barrier(s) and maps appropriate strategies; Step 3 validates with biorelevant dissolution and PBPK modelling; Step 4 explores alternative administration routes when oral development cannot succeed [2,3,7,18,24,31,39,121,125,128,134,135,142]. Created with [Biorender.com](https://biorender.com).

1.1 and the transporter mapping of Section 6.5, since many BCS IV drugs present more than one limitation simultaneously and therefore call for combined strategies.

As a capstone to this framework, Fig. 5 consolidates the decision logic into a single diagnostic map that links the question a formulator asks of a candidate, through the strategy class that answers it, to a marketed product that exemplifies the solution. Whereas Fig. 4 sets out the sequential workflow and Table 12 maps limitations to technologies, Fig. 5 closes the loop by anchoring each diagnostic route to a clinically validated exemplar.

11. Manufacturing Scale-Up, Stability, and Regulatory Considerations

Despite strong scientific progress, three persistent challenges constrain the translation of BCS IV formulation innovations from laboratory to market [75,144]:

Scale-up reproducibility: Nano and lipid platforms that perform well at small scale frequently exhibit particle size drift, encapsulation efficiency loss, and altered release profiles at manufacturing scale, particularly with respect to mixing energy input, temperature control, and shear history. Hot melt extrusion and spray drying have the most

established scale-up precedents for ASDs; emulsion-based systems are more sensitive to process variables [144].

Physical stability during storage: Amorphous forms whether in ASDs, co-amorphous systems, or nanoamorphous systems are thermodynamically metastable and can recrystallise over time, erasing dissolution advantages. Polymer selection (based on Flory–Huggins interaction parameters and T_g elevation), moisture control, and antiplasticiser strategies are critical. Accelerated stability studies under ICH Q1 conditions and solid-state characterisation (XRPD, DSC, FTIR) must be integral to ASD development [51,145,146].

Regulatory pathway: Complex formulations (nanoparticles, lipid systems, cocrystals) may require more extensive characterisation data and safety toxicology for novel excipients. PBPK model-informed regulatory submissions increasingly support biowaiver applications and formulation bridging studies, offering a pathway to reduce the burden of clinical bioequivalence studies for certain BCS IV modifications [125,138].

Regulatory acceptance of the excipient itself, rather than of the finished dosage form, is frequently the binding constraint for a chemically novel BCS IV technol-

Table 11. Comprehensive master summary of all formulation strategies for BCS Class IV drugs, organised by primary target and mechanism.

Strategy	Primary target	Mechanism	Success example	Key Refs.
Cyclodextrin + Nanoclay	Solubility	Inclusion complex + synergistic clay	Furosemide 4.9× BA; Baicalin 5× solubility; RAMEB-sepiolite 12× solubility	[11,32,33,34,35,143]
Hydrotropes	Solubility	Non-micellar aqueous solubilisation	HCT SDs (piperazine + sodium benzoate)	[14]
Amino Acid Salts	Solubility + Permeability	Crystal packing disruption; salt formation	Quercetin/Rutin: 68–433× solubility; 4× Papp	[36]
Eudragit EPO (low dose)	Solubility (selective)	Cationic polymer solubilisation	Mefenamic acid 940×; MUST minimise dose to avoid Papp loss	[31]
ASD (HME)	Solubility + Dissolution	Amorphous form; polymer matrix	Norvir®, Kaletra®, Venclexta® (all marketed products)	[28]
ASD (Spray Drying)	Solubility + Dissolution	Amorphous; pH-modulated SD	Daidzein 20× Cmax; Curcumin 3× AUC; Chlorthalidone 6× supersaturation	[47,48,49]
Hybrid Nanoamorphous	Solubility + Dissolution	ASD + micelle + nanosizing	Ritonavir QbD-DM3 nanoamorphous micellar dispersion	[50]
Co-amorphous (Arginine)	Solubility + Permeability	Salt formation; dual barrier address	Furosemide-ARG: enhanced dissolution AND permeation simultaneously	[54]
Co-amorphous (P-gp inhibitor)	Solubility + Efflux	Amorphous + P-gp inhibition	DTX-Myricetin: 3.9× Cmax, 3.1× AUC vs. crystalline DTX	[55]
Cocrystals	Solubility + Stability	Non-covalent crystal engineering	Furosemide-IMI: 118× solubility; 2.8× permeability	[58,59,61,62,63]
Nanocrystals/SFE	Dissolution Rate	Surface area; Ostwald-Freundlich	SFE furosemide 4.5× dissolution	[60,64]
MSN	Solubility + Permeability	Mesoporous encapsulation	Vorinostat: 3.9× solubility, 4× permeability; confirmed anticancer activity	[13,89]
Carbon Nanotubes/ Fullerenes	Permeability + Targeting	pH-dependent release; tumour targeting	DTX-CNT: tumour microenvironment release; 5.8× BA	[90,91]
Polymeric Micelles	Solubility + Permeability + Efflux	Core-shell; mucoadhesion; P-gp inhibition	SPNMS-TPGS: 6.6× permeability + lymphatic uptake	[10,86,95,96,97]
SEDDS/SMEDDS (co-loaded)	Solubility + Efflux	Self-emulsification; P-gp inhibitor co-load	DTX/CsA SNEDDS: 9.2× vs. DTX solution	[25,71,72,73,74]
Lipid Matrix Tablet	Solubility + Food Effect	Molecular dispersion in solid lipid	Abiraterone: 704.80% relative BA; food effect reduction	[15,30]
SLN/NLC	Solubility + Lymphatic	Solid lipid matrix; mucosal interaction	Cur-NAPG-NLC: 499.45× AUC vs. solution	[76,77,78]
Lymphatic Delivery	Bypass first-pass	Chylomicron association	Long-chain TG formulations; SPNMS-mangiferin	[84,86]
ASBT Prodrug	Permeability (active transport)	Influx transporter targeting	CPP: 10× vs. Taxol®	[105]
Amino Acid/Valyl Prodrug	Permeability	PepT1/2 or transporter targeting	Oseltamivir prodrug paradigm; improved permeation	[107]
Liquisolid + pH/ Microbial Trigger	Solubility + Site-specific	Wettability + colonic microbiome delivery	Sulfasalazine 3-pronged colon delivery system	[118]
Gastroretentive (GRDF)	Absorption window drugs	Extended gastric residence	Furosemide GRDF; narrow-window BCS IV drugs	[119,120]
Pulmonary	Bypass GI + first-pass	Alveolar absorption; low lung CYP	Ursolic acid: ~80× BA vs. oral; amphotericin B inhalation	[122,123]

Table 11. Continued.

Strategy	Primary target	Mechanism	Success example	Key Refs.
Transdermal (nano-enabled)	Bypass GI + first-pass	Stratum corneum permeation	Curcumin ethosomes; apremilast nanocarriers	[16,124]
PBPK + Biorelevant Dissolution	Prediction + Optimisation	Mechanistic simulation	Venetoclax food effect; rifaximin ASD; furosemide windows	[121,125,127,134]
AI/ML Formulation Design	Optimisation + Screening	Virtual high-throughput; drug-polymer prediction	ASD polymer selection; nano optimisation; animal use reduction	[128]
Permeability Enhancers (SNAC, C10, Chitosan)	Permeability	Excipient co-formulation; no API modification	Rybelsus® (oral semaglutide + SNAC); Labrasol® in SEDDS; chitosan-coated liposomes	[22,29,108,109,111,112, 113]

EPO, Eudragit EPO; SFE, spray flash evaporation; MSN, mesoporous silica nanoparticle; SEDDS, self-emulsifying drug delivery system; GRDF, gastroretentive dosage form; IMI, imidazole.

Table 12. Formulation selection matrix mapping the dominant biopharmaceutical limitation of a BCS Class IV candidate to the technologies most likely to resolve it. Candidates with several concurrent limitations require combined strategies.

Dominant problem	Preferred technologies
Low solubility only	Amorphous solid dispersion; nanocrystals
Low permeability only	SNAC and other permeation enhancers; prodrugs
P-glycoprotein substrate	TPGS and inhibitor-loaded systems; lymphatic delivery
CYP3A4 metabolism	Lipid-based systems; piperine and other inhibitor co-formulations
Large food effect	SNEDDS; lipid matrix systems
Narrow absorption window	Gastroretentive dosage forms
Extensive first-pass metabolism	Lymphatic delivery
Poor solid-state stability	Cocrystals and salt formation

ogy. In the United States, an excipient with no prior use in an approved product at the intended route, dose, and duration lacks a regulatory presumption of safety, so the sponsor must generate a stand-alone toxicology package, often through the FDA's Novel Excipient Review Pilot Program, before or alongside the drug product application; the European Medicines Agency applies an analogous case-by-case justification requirement rather than a positive excipient list. This burden falls disproportionately on the newer technologies surveyed here, permeation enhancers, cocrystal co-formers, and functionalised nanocarrier surface chemistries, for which no prior human exposure database exists, and explains why formulations built on well-precedented excipients (PVP, HPMCAS, medium-chain glycerides) have historically reached approval faster than mechanistically superior but regulatorily untested alternatives. SNAC's qualification to support Rybelsus® is the clearest recent precedent that a genuinely novel excipient can be qualified *de novo*, but the multi-year safety package this required illustrates why sponsors continue to default to precedented excipients wherever the formulation science permits.

The OPTI-OX powder-in-capsule dry-granulation platform, developed for BCS IV drugs, illustrates the convergence of manufacturability and performance: by dry granulating a binary blend of API and polymeric carrier directly into capsules, it achieves ASD-like dissolution en-

hancement without the thermal stress of HME or solvent use of spray drying [147].

Failures and Lessons Learned

Balanced appraisal of BCS IV strategies requires attention to their characteristic failure modes, which recur across the literature and temper the successes catalogued above. The most instructive is the solubility and permeability trade-off: aggressive solubilisation with surfactants, cyclodextrins, or cosolvents can lower the free, thermodynamically active fraction of drug and thereby reduce flux across the membrane, so that apparent solubility rises while absorption does not (Section 2.6). Supersaturating systems fail in the converse way when the generated supersaturation is not stabilised, precipitating before absorption is complete, and ASDs can recrystallise on storage or on contact with gastrointestinal fluid, erasing the solubility advantage they were designed to provide.

Other failures are translational rather than mechanistic. Nanocrystal and nanoparticle formulations that perform well in the laboratory frequently encounter scale-up, physical-stability, and cost barriers that prevent commercialisation, and some permeation enhancers improve absorption only at concentrations that also injure the epithelium, placing a safety ceiling on their use [22]. Finally, poor *in vitro* to *in vivo* correlation has repeatedly misdirected development, because non-biorelevant dissolution testing

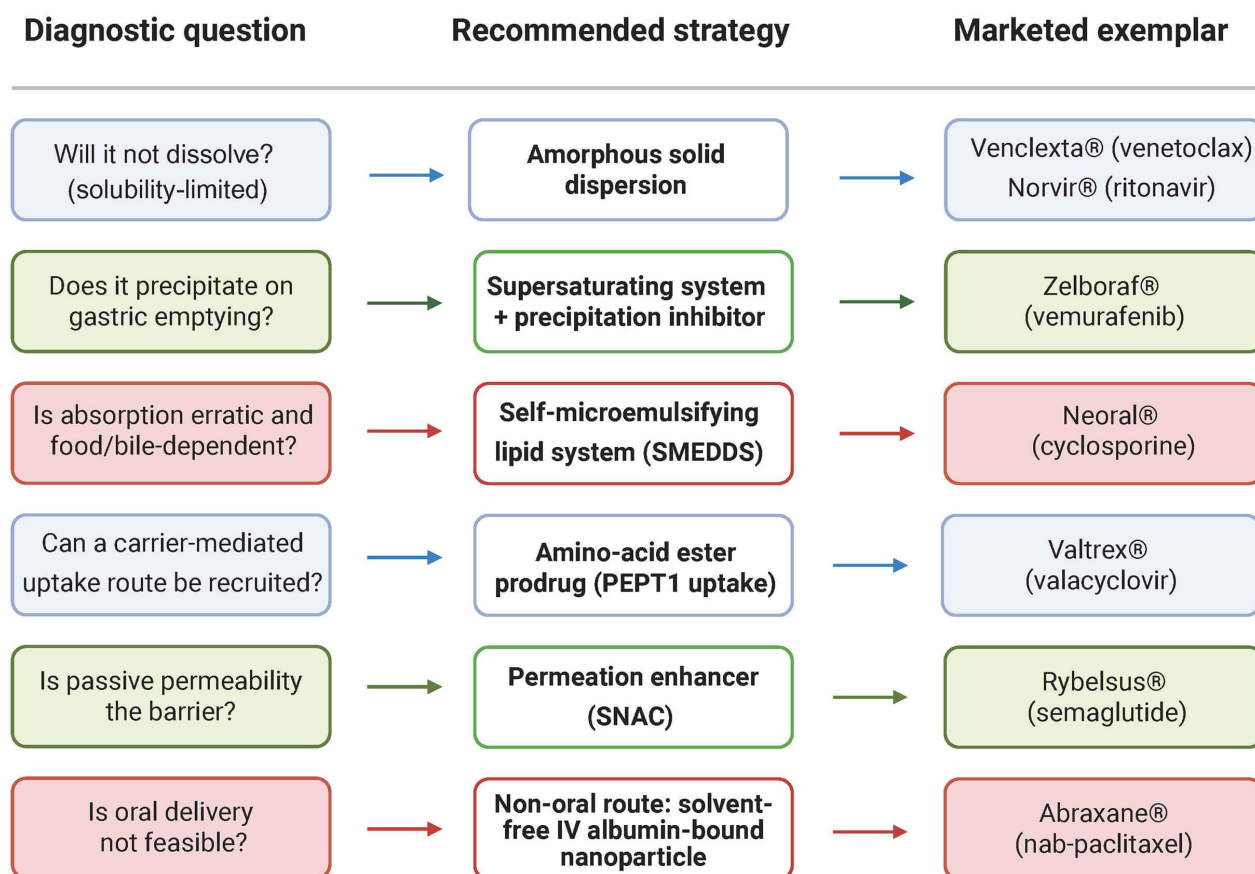


Fig. 5. Integrated strategy map for BCS Class IV drugs. Each diagnostic question identifies the dominant absorption barrier, the recommended strategy names the mechanism-matched formulation class, and the marketed exemplar shows the approach realised in an approved product. Many candidates trigger more than one route and are best addressed by combined strategies. Created with [Biorender.com](https://biorender.com).

under sink conditions flatters formulations whose real behaviour is governed by non-sink supersaturation and precipitation. The unifying lesson is that BCS IV development must be guided by mechanism-matched, biorelevant evaluation from the outset, and that a strategy which addresses one barrier must be checked for unintended effects on the other.

A caveat applies to the strength of evidence behind the permeability gains catalogued above, which span a spectrum. A minority are confirmed by improved oral pharmacokinetics *in vivo*, including the thiolated cyclodextrin furosemide system (6.55-fold higher flux across rat intestinal mucosa and 4.9-fold higher oral bioavailability), the SPNMS-TPGS mangiferin micelle (6.6-fold permeability and 3-fold bioavailability gains with supporting lymphatic-uptake evidence), and the ASBT-targeted paclitaxel prodrug (10-fold higher oral bioavailability than Taxol®). A larger group rests on *in vitro* or *ex vivo* permeability alone, such as the quercetin and rutin lysine salts (up to 4-fold higher Papp with no *in vivo* exposure data presented). Presenting these as separate evidence tiers, namely

permeability demonstrated *in vitro*, permeability linked to improved *in vivo* exposure, and clinically validated approaches, would convey the maturity of each strategy more accurately than a single undifferentiated list.

Much of the *in vitro* evidence derives from Caco-2 monolayers, which overexpress some transporters and underrepresent the mucus layer, intestinal fluid dynamics, immune cells, and microbiota. Many permeability-enhancing technologies therefore remain validated primarily in Caco-2 systems, and their translation to human absorption remains incompletely established. The organ-on-chip and microphysiological models noted in Section 12.4 are beginning to narrow this gap, but a gain measured in a static monolayer should not be equated with improved absorption in the dynamic intestinal environment. This is the empirical counterpart of the argument made at the outset in Section 1.3: a permeability gain measured in a static monolayer is not yet evidence of a permeability gain in the intact intestine, and an increase in systemic exposure, which may be lymphatic or solubility-driven, is not in itself evidence of any permeability change at all.

Table 13. Why promising BCS IV formulations fail: recurrent failure modes and their consequences.

Failure mode	Consequence
Solubility–permeability trade-off	More drug dissolved but a smaller free-drug fraction available for absorption
Supersaturation collapse	Precipitation before absorption is complete
Efflux compensation	P-glycoprotein inhibition offset by BCRP or MRP2
Permeation enhancer toxicity	Epithelial safety ceiling reached before adequate enhancement
Poor <i>in vitro</i> to <i>in vivo</i> correlation	Strong Caco-2 results but weak <i>in vivo</i> pharmacokinetics
Scale-up instability	Aggregation, irreproducibility, and cost cause commercial failure
Food-effect dependence	Variable clinical exposure between fed and fasted states

Improved systemic exposure is also not synonymous with enhanced permeability. Self-emulsifying systems, micelles, lipid nanoparticles, and lymphatic carriers typically modify solubilisation, dissolution, presystemic metabolism, lymphatic transport, and gastric emptying at the same time, so an increase in AUC cannot be attributed to permeability alone. Where causality has not been isolated, the defensible interpretation is that improved exposure was consistent with enhanced permeability, while concurrent effects on solubilisation, lymphatic transport, and presystemic metabolism cannot be excluded.

The Eudragit EPO and mefenamic acid system of Section 2.4, a 940-fold solubility gain that nonetheless reduced permeability both *in vitro* and *in vivo*, remains the clearest single illustration of these competing effects. The principal recurrent failure modes are summarised in Table 13, offered as a deliberate counterpoint to the success-oriented examples elsewhere in this review.

12. Recent Advances in Formulation Development

Formulation science for BCS Class IV compounds has advanced markedly over the past five years, with the most consequential progress arising not from any single technology but from the deliberate combination of complementary mechanisms within one dosage form. Three themes dominate the recent literature: the convergence of solubilisation and permeation enhancement into integrated multi-mechanism platforms, the clinical and regulatory maturation of permeation enhancers for oral delivery, and the displacement of empirical screening by computation-guided and additively manufactured design. Each is presented below as an extension of the strategy-specific discussion in Sections 2 to 11.

12.1 Convergence Toward Multi-Mechanism Platforms

The clearest recent trend is the shift from formulations that address a single barrier to systems that act on solubility, dissolution, and efflux simultaneously. Co-loaded self-nanoemulsifying systems that release a P-glycoprotein inhibitor ahead of the active drug have produced order-of-magnitude bioavailability gains for taxanes, exploiting temporal control of excipient release rather than higher

inhibitor doses [25]. Surface-engineered lipid nanocarriers extend this logic to the mucus barrier, with mucus-penetrating conjugate coatings raising curcumin exposure by two orders of magnitude over uncoated carriers [78]. At the molecular level, co-amorphous and cocrystal engineering increasingly employ co-formers that are themselves pharmacologically active or efflux-inhibitory, removing the need for a separate excipient and improving physical stability in a single step (Section 3.2). The unifying principle is that BCS IV bioavailability is seldom limited by one factor alone, so durable solutions engineer for several barriers at once. The same convergence is evident at the level of conventional solid dosage forms: a recent amorphous solid-dispersion formulation of the BCS IV antiplatelet agent ticagrelor combined copovidone (PVP VA 64) with vitamin E TPGS, improving polymorphic stability and dissolution performance while incorporating an excipient reported to inhibit P-glycoprotein-mediated efflux. In a small dose-adjusted preclinical study in Wistar rats, a 70 mg dose of the solid-dispersion tablet was found to give exposure equivalent to 90 mg of a conventional immediate-release comparator formulated in line with the reference product Brilinta® [148].

12.2 Permeation Enhancement Reaches the Clinic

For molecules whose absorption is permeability-limited rather than dissolution-limited, chemical permeation enhancers have moved from concept to approved product. The regulatory acceptance of salcaprozate sodium (SNAC) in oral semaglutide established that a transient, reversible, and well-tolerated enhancer can carry a macromolecule across the gastrointestinal epithelium at commercially viable, if modest, bioavailability [108,113]. Comparative work on SNAC and sodium caprate has clarified that these agents act through overlapping membrane-perturbation and transcellular mechanisms rather than wholly distinct pathways, which informs rational enhancer selection for poorly permeable small molecules as well as peptides [108]. Parallel advances in site-specific delivery, including accurate colonic-targeting technologies, allow enhancers and payloads to be released where epithelial permeability and residence time are most favourable [147]. Permeation enhancement has thus become a cred-

ible primary strategy for the permeability axis of the BCS IV problem, complementing the solubility-oriented methods that have historically dominated the field.

12.3 Computation-Guided and Additively Manufactured Design

Recent formulation development is increasingly model-led. Mechanistic physiologically based biopharmaceutics modelling now links *in vitro* dissolution and permeability inputs to predicted *in vivo* performance, supporting *in vitro* to *in vivo* prediction rather than retrospective correlation alone and reducing the experimental burden of screening [135]. Coupled with machine-learning methods (Section 9.2) and biorelevant, non-sink dissolution testing (Section 9.3), these tools allow the dominant absorption barrier to be identified and the formulation matched to it before significant laboratory investment. The supersaturation phenomenon that transiently saturates intestinal efflux transporters, demonstrated for rifaximin, shows how mechanistic insight gained from modelling can be translated into a practical supersaturating dosage form [41]. Additive manufacturing and other flexible deposition platforms (Section 7.3) extend this rational, data-driven approach toward individualised dosing of BCS IV compounds, completing a clear trajectory from empirical trial and error toward predictive, mechanism-matched design.

12.4 Future Directions: AI, Digital Twins, and Microphysiological Models

The forward edge of BCS IV formulation is increasingly computational and biomimetic. Machine learning and generative artificial intelligence are being applied to excipient selection and formulation optimisation, learning from accumulated formulation data to propose carrier and process combinations that would be slow to find empirically, while physiologically based biopharmaceutics models supply the mechanistic backbone that keeps such predictions interpretable (Section 9) [135]. The natural extension is the formulation digital twin, a continuously updated *in silico* replica of a product and its *in vivo* behaviour that lets formulators test changes virtually before committing them to the bench, and, ultimately, autonomous formulation laboratories in which model-driven design, robotic execution, and high-throughput microfluidic screening close the loop with minimal human intervention. For BCS IV compounds in particular, digital-twin applications already under exploration include virtual bioequivalence assessment, virtual food-effect prediction, virtual formulation screening across competing solubilisation and permeation strategies, and individualised dose selection for populations in which transporter or metabolic capacity differs, each of which can reduce the number of clinical and animal studies needed to reach a robust formulation decision [128].

In parallel, microphysiological systems are narrowing the gap between *in vitro* screening and human out-

comes. Gut-on-a-chip and broader organ-on-chip devices reconstruct intestinal architecture, peristalsis-like mechanics, fluid flow, mucus secretion, and even the resident microbiota within a controlled microfluidic environment, offering a more predictive absorption model than static cell monolayers and a potential partial replacement for animal studies [149]. A related and rapidly maturing toolkit includes patient-derived human intestinal organoids, organoid-derived intestine-on-a-chip systems that recreate region-specific epithelium and transporter expression, and dynamic mucus models that capture the diffusion barrier poorly represented by Caco-2 monolayers [150]. For BCS IV compounds these platforms are increasingly used to predict effective permeability, to assess food effects and the behaviour of supersaturating or precipitating formulations under near-physiological conditions, and to interrogate transporter-mediated efflux and drug-transporter interactions in a human-relevant context. Coupling these human-relevant absorption models with AI-guided design and digital-twin simulation points toward a future in which the dominant barrier of a BCS IV candidate is identified, and a mechanism-matched formulation designed and de-risked, largely *in silico* and on chip before significant laboratory or animal investment. Realising this vision will require standardised, shareable data and validated model performance, but the direction of travel is clear.

Three specific classes of emerging platform merit closer attention as direct responses to the limitations of Caco-2 monolayers noted throughout this review. Human intestinal organoids and related 3D tissue constructs, derived from adult intestinal stem cells or induced pluripotent stem cells, differentiate into enterocytes, goblet cells, enteroendocrine cells, and Paneth cells and thereby recapitulate the multicellular architecture, transporter expression, and CYP3A4-mediated metabolic capacity that immortalised, single-cell-type Caco-2 lines lack, giving more physiologically grounded predictions of carrier-mediated transport, drug metabolism, and mucin-barrier interaction [151,152]. Microfluidic gut-on-a-chip systems address the complementary limitation of the static, unstirred Transwell® format by imposing fluid flow and cyclic mechanical strain that mimic intestinal peristalsis and luminal shear stress; these dynamic cues drive spontaneous villus-like morphogenesis, tighten the epithelial barrier as measured by transepithelial electrical resistance (TEER), restore phase I/II drug-metabolising capacity, and permit co-culture with human gut microbiota under anaerobic conditions, opening a route to modelling microbiome-mediated drug degradation and permeation that Caco-2 monocultures cannot capture [149,153,154]. Finally, *ex vivo* human intestinal tissue, mounted in Ussing chambers or evaluated in regional systems such as InTESTine™, remains the closest surrogate to first-in-human behaviour: because these preparations retain the native extracellular matrix, lamina propria, resident immune cell populations, and region-specific

cytoarchitecture from duodenum to colon, they offer the most direct read on regional permeability and pre-systemic metabolism for compounds whose Caco-2 performance is difficult to interpret, and are increasingly used as a bridging step before clinical testing of complex or poorly permeable BCS IV candidates [155,156]. Newer gut microphysiological systems built from induced pluripotent stem cell-derived intestinal epithelium extend this capability further, demonstrating functional drug transporter and CYP3A4 activity and yielding absorption predictions that approach clinical observations for compounds that Caco-2 monolayers handle poorly [157].

13. Limitations and Translational Barriers

The strategies surveyed in this review show impressive preclinical performance, but several limitations temper their translational promise and merit explicit acknowledgement. First, the fold-increases in solubility and bioavailability cited throughout derive from heterogeneous studies that differ in species, dose, reference formulation, and analytical method, so absolute magnitudes are not directly comparable; a large relative gain measured against a poorly absorbed free-drug control can also overstate the clinical benefit for a molecule whose baseline exposure is already very low. Second, most of the enabling technologies discussed remain at the laboratory or early preclinical stage, and the scale-up of nanocrystals, ASDs, and self-emulsifying systems frequently encounters particle-size drift, loss of encapsulation efficiency, and altered release on transition to manufacturing scale (Section 11) [144]. Third, the physical instability of amorphous and supersaturating systems, including recrystallisation on storage, phase separation, and gradual loss of the kinetic solubility advantage, continues to limit shelf life and is among the most common reasons a promising formulation fails to reach the clinic [139,145]. Fourth, several of the most effective platforms carry a substantial cost and regulatory burden, since novel permeation enhancers require full excipient qualification and lipid and nanoparticle systems add manufacturing complexity, while the regulatory pathway for many of these excipients is still maturing. Finally, the recurrent failure modes summarised in Table 13, including batch-to-batch variability, food effects, and weak *in vitro* to *in vivo* correlation, show that preclinical success does not guarantee clinical translation, and that biorelevant dissolution and physiologically based modelling, although increasingly powerful, cannot yet fully replace human pharmacokinetic confirmation. These limitations do not diminish the genuine progress described above, but they underline that rational strategy selection must be paired with realistic expectations regarding manufacturability, stability, cost, and the gap between preclinical metrics and clinical outcome.

14. Conclusions and Future Perspectives

BCS Class IV compounds defined by dual low solubility and low permeability have historically represented some of the most challenging drug development programmes. Yet the past decade has produced a remarkable diversity of formulation tools that, when selected rationally based on the dominant absorption barrier for each molecule, enable clinical and commercial success. Marketed products including Norvir®, Kaletra®, Neoral®, Venclexta®, and Abraxane® unambiguously demonstrate that BCS IV classification is not a development dead-end [2,24,28]. For a formulator approaching a new BCS IV candidate, the practical starting point is the subclass assignment of Section 1.1 and the corresponding formulation selection matrix of Section 10, which condense the strategies reviewed here into a stepwise decision tool keyed to the dominant absorption barrier; the synthesis below summarises the principles behind that tool rather than restating it.

The most conceptually important insights emerging from recent literature are: (i) the solubility and permeability trade-off is real and must be explicitly modelled, not assumed away; (ii) co-amorphous and cocrystal strategies can simultaneously address both barriers at the molecular level; (iii) the supersaturation-efflux transporter saturation phenomenon (demonstrated for rifaximin) reveals a new mechanism by which SDDS can overcome the permeability barrier for P-gp substrates; (iv) AI/ML integration with PBPK modelling is transforming formulation design from empirical to rational at a systems level; and (v) the shift from single-function to multi-mechanism formulations exemplified by co-loaded P-gp inhibitor SNEDDS, piperine-tagged polymeric micelles, and co-amorphous P-gp inhibitor systems represents the dominant future direction; and (vi) permeability enhancers, most prominently SNAC (salcaprozate sodium), have achieved regulatory validation with Rybelsus® (oral semaglutide, 2019) and represent a structurally non-invasive route to overcome the permeability barrier of BCS IV compounds where dissolution is not the rate-limiting step [22,29,31,41,55,96,108,109,111,112,113,128].

Emerging future directions include: precision nanotechnology with stimulus-responsive (pH, redox, enzyme) drug release; neonatal Fc receptor (FcRn)-mediated transcytosis as an underexplored permeability pathway; patient-specific and paediatric formulations via 3D/4D printing; digital twin modelling of individual patient GI physiology for personalised dosage form design; expansion of green chemistry and biopolymer-derived carriers (natural polysaccharides, plant-derived excipients); integration of microbiome science to inform colonic formulation design for BCS IV drugs requiring distal GI delivery; and further translation of permeability enhancer technology building on the SNAC/Rybelsus® precedent to small-molecule BCS IV drugs in low-dose, high-potency pipelines.

Underlying several of these directions is a growing appreciation that the intestinal microbiota are not a passive backdrop but an active determinant of absorption: resident bacteria deconjugate and transform bile acids and thereby reshape the micellar solubilisation on which BCS IV dissolution depends, modulate the expression of intestinal transporters and the properties of the mucus barrier, and directly metabolise some xenobiotics before they reach the systemic circulation, so that interindividual and formulation-dependent differences in microbial composition can alter the *in vivo* performance of an otherwise well-characterised BCS IV product [158].

The field is undergoing a fundamental shift from ‘make it soluble’ to ‘solve the entire absorption problem rationally’. BCS IV molecules increasingly benefit from this evolution. The convergence of computational science, advanced materials innovation, mechanistic pharmacokinetics, and regulatory-validated permeability enhancement technologies positions the pharmaceutical sciences community to meaningfully improve the clinical development success rate for this challenging but commercially significant drug class. Above all, the field is learning to separate raising exposure from raising permeability: the solubility barrier is, in large measure, solved, whereas the permeability barrier, once the questions of *in vitro* to *in vivo* predictivity, toxicological cost, and genuine mechanism are taken seriously, remains the defining challenge and the principal opportunity of Class IV development.

Author Contributions

RL, ND conceived the review, conducted the literature analysis, and initially wrote the manuscript; YA and NS prepared all figures, critically revised the manuscript and further refined it for important intellectual content, and verified and approved the final version. All figures (Figs. 1,2,3,4,5) are original schematics created for this review and have not been published elsewhere; no third-party copyright permissions are required. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Given his role as the Editorial Board member, Neal M. Davies had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Hirofumi Takeuchi.

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AI tool, ChatGPT, was used for grammatical editing and formatting assistance. The authors reviewed and edited all output and take full responsibility for the content of the manuscript.

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