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Comparative Assessment of Nanocrystal and Inclusion Complex Technologies for Solubility Enhancement of BCS Class II Drug Molecules

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Abstract: *A large proportion of new chemical entities entering pharmaceutical development pipelines exhibit poor aqueous solubility while retaining high intestinal permeability, placing them in Biopharmaceutics Classification System (BCS) Class II. For these molecules, dissolution rather than membrane permeation is the rate-limiting step governing oral absorption, making solubility- and dissolution-enhancing formulation strategies central to clinical success. Among the technologies available, drug nanocrystal engineering and cyclodextrin-based inclusion complexation represent two of the most extensively validated and commercially translated platforms. This review provides a comparative, evidence-based assessment of both technologies across mechanism of action, preparation methodology, physicochemical performance, regulatory track record, manufacturing scalability, and cost. Nanocrystals exploit the relationship between particle size and saturation solubility described by the Ostwald–Freundlich equation, achieving substantial dissolution-rate enhancement through increased surface area while preserving the crystalline, carrier-free nature of the drug; several products (Rapamune®, Emend®, Tricor®, Megace ES®) are commercially marketed using this approach. Inclusion complexation relies on host–guest molecular encapsulation within the cyclodextrin cavity, offering high reproducibility, well-characterized regulatory precedent, and ancillary benefits such as photostability and taste masking, although it is constrained by cavity-size selectivity and the comparatively larger excipient mass required per dose. Quantitative comparison of representative drug candidates drawn from the published literature indicates that nanocrystal technology generally affords larger absolute increases in saturation solubility and faster initial dissolution, whereas inclusion complexes offer superior batch-to-batch reproducibility, simpler analytical characterization, and a lower regulatory burden for line extensions. The review concludes that the optimal choice between the two platforms is compound- and context-specific, and that hybrid strategies combining both approaches represent an emerging direction in formulation science.*

Keywords: BCS Class II; nanocrystal; nanosuspension; cyclodextrin; inclusion complex; solubility enhancement; dissolution rate; oral bioavailability

I. INTRODUCTION

The Biopharmaceutics Classification System (BCS), introduced by Amidon and colleagues in 1995, classifies active pharmaceutical ingredients into four categories on the basis of their aqueous solubility and intestinal permeability [1]. BCS Class II compounds are characterized by low solubility and high permeability, meaning that drug dissolution in gastrointestinal fluid, rather than transport across the intestinal epithelium, is the principal barrier to systemic absorption [1,2]. Estimates suggest that 40–70% of new chemical entities identified through modern high-throughput

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screening campaigns fall into BCS Class II or the doubly compromised Class IV, making solubility-limited absorption one of the most pervasive challenges in contemporary drug development [3].

Poor aqueous solubility translates clinically into slow and incomplete dissolution, pronounced inter- and intra-subject variability in plasma exposure, a marked positive food effect on absorption, and, in many cases, attrition of otherwise pharmacologically promising candidates during preclinical and clinical development. Addressing this problem has become a central preoccupation of formulation science, and a wide spectrum of physical and chemical strategies has been developed, including particle size reduction (micronization and nanonization), salt formation, co-crystallization, solid dispersion and amorphization, self-emulsifying drug delivery systems, lipid-based carriers, and host–guest inclusion complexation with cyclodextrins [4,5].

Among these, drug nanocrystal technology and cyclodextrin-based inclusion complexation stand out for two reasons. First, both have an established, multi-decade record of laboratory investigation across hundreds of BCS Class II molecules. Second, both have achieved successful translation into commercially marketed products with full regulatory approval in major markets. Despite this shared maturity, the two technologies differ fundamentally in their underlying physicochemical mechanism, the nature of the resulting solid (carrier-free crystalline nanoparticle versus a discrete host–guest molecular complex), manufacturing infrastructure requirements, and the type of solubility gain that can realistically be expected for a given molecule.

This review provides formulation scientists, process engineers, and regulatory professionals with a structured, side-by-side comparison of nanocrystal and inclusion complex technologies, synthesizing mechanism of action, preparation methods, characterization approaches, comparative performance data drawn from the published literature, and the practical considerations that govern selection between the two platforms for a given BCS Class II drug candidate.

II. BCS CLASS II DRUGS: BIOPHARMACEUTICAL RATIONALE

2.1 Definition and absorption-limiting behavior

Within the BCS framework, a drug is designated as having 'high solubility' if the highest single therapeutic dose dissolves completely in 250 mL or less of aqueous medium across the physiological pH range of 1.0–7.5, and as having 'high permeability' if at least 85% of an administered oral dose is absorbed in humans, typically inferred from mass-balance or intestinal-perfusion data [1,2]. BCS Class II drugs satisfy the permeability criterion but fail the solubility criterion, so that despite efficient transcellular or paracellular transport once dissolved, the rate and extent of dissolution in the gut lumen controls overall systemic absorption.

This dissolution-rate-limited behavior has several practical consequences: absorption is frequently incomplete and dose-disproportionate, since increasing the dose does not proportionally increase the dissolved drug mass; co-administration with food, particularly a high-fat meal, can substantially alter exposure by changing luminal solubilization capacity; and bioavailability is highly sensitive to the physical form of the drug substance particle size, crystal habit, and polymorphic form making formulation strategy a decisive determinant of clinical performance [3,6].

Table 1. The Biopharmaceutics Classification System (BCS) and the corresponding absorption-limiting step.

BCS Class	Solubility	Permeability	Absorption-limiting step
I	High	High	Gastric emptying; generally well absorbed
II	Low	High	Dissolution rate in GI fluid (focus of this review)
III	High	Low	Permeability across intestinal membrane
IV	Low	Low	Both dissolution and permeability

Source: compiled from Amidon et al. [1] and subsequent BCS guidance literature [2,3].

2.2 Representative BCS Class II molecules

BCS Class II encompasses a structurally diverse set of drugs spanning multiple therapeutic categories, including fenofibrate and atorvastatin (lipid-lowering agents), carvedilol and felodipine (cardiovascular agents), itraconazole and griseofulvin (antifungals), aprepitant and domperidone (antiemetic/prokinetic agents), rivaroxaban (anticoagulant),

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irbesartan (antihypertensive), and curcumin (a widely studied nutraceutical), among many others [7,8]. The diversity of this list illustrates why no single solubilization technology is universally optimal; molecular weight, melting point, log P, the presence of ionizable groups, and crystal lattice energy all influence which enhancement strategy will perform best for a particular compound.

III. NANOCRYSTAL TECHNOLOGY

3.1 Mechanism of action

Drug nanocrystals are carrier-free, sub-micron crystalline particles of the parent drug (generally below 1000 nm, and frequently in the 100–400 nm range), stabilized in suspension by surfactants or polymeric stabilizers rather than encapsulated within a matrix [9,10]. The technology improves apparent solubility and dissolution rate through three interrelated effects described qualitatively by the Noyes–Whitney and Ostwald–Freundlich relationships: (i) particle size reduction dramatically increases the specific surface area available for solvation, directly accelerating the dissolution rate; (ii) below approximately 1 μm, the increased surface curvature raises the surface free energy of the particle, which the Ostwald–Freundlich equation predicts will elevate the equilibrium saturation solubility itself, not merely the dissolution rate; and (iii) nanocrystals can adhere more closely to the mucosal surface, increasing the effective concentration gradient driving passive diffusion across the gut wall [9,11].

Because nanocrystals contain close to 100% drug substance with only a thin stabilizer coating, they avoid the dose-volume penalties associated with carrier-based systems such as inclusion complexes or lipid nanoparticles, which is particularly advantageous for high-dose drugs.

3.2 Preparation methods

Nanocrystal manufacturing methods are conventionally grouped into top-down approaches (which reduce the size of larger crystals through mechanical energy input), bottom-up approaches (which build nanocrystals from molecularly dissolved drug through controlled nucleation and growth), and combinative or hybrid technologies that sequence both approaches to improve efficiency and reduce the energy or time required [9,12]. Table 2 summarizes the principal methods within each category.

Table 2. Classification of nanocrystal preparation technologies.

Approach	Representative methods	Key process characteristics
Top-down	Media (wet) milling; high-pressure homogenization; combinative precipitation–homogenization	Mechanical attrition of coarse crystals; widely used industrially; risk of media/metal contamination in milling
Bottom-up	Antisolvent (solvent–antisolvent) precipitation; controlled crystallization; supercritical fluid methods	Nucleation and crystal growth from solution; fine control over polymorphic form; risk of crystal growth/Ostwald ripening on storage
Combinative	Precipitation followed by homogenization; precipitation–lyophilization–homogenization (PLH)	Pre-treatment (precipitation) reduces particle size before mechanical milling, improving efficiency and reducing energy input

Source: synthesized from reviews of nanocrystal preparation technology [9,10,12].

3.3 Characterization

Nanocrystal suspensions are routinely characterized for particle size and polydispersity index by dynamic light scattering, zeta potential (as an indicator of physical stability against aggregation), crystallinity and polymorphic form by powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC), surface morphology by scanning or transmission electron microscopy, and saturation solubility and dissolution rate under sink and non-sink conditions [13]. A representative study on kojic acid nanocrystals, for example, reported particle sizes in the 110–150 nm range

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with negative zeta potential and acceptable polydispersity across three optimized formulations, alongside confirmatory DSC, PXRD, and FTIR characterization [13].

3.4 Commercial translation

Nanocrystal technology has the strongest record of commercial translation among nanoscale solubilization platforms, with several FDA-approved oral and parenteral products on the market since 2000 (Table 3). The relatively short historical gap between initial patenting and regulatory approval for these products in some cases under ten years reflects both the technological simplicity of the carrier-free nanocrystal concept and the regulatory familiarity with milling-derived particle size reduction as a formulation strategy [14,15].

Table 3. Selected FDA-approved nanocrystal-based pharmaceutical products.

Product (brand)	Drug substance	Manufacturer	Approval (indication)	Preparation method
Rapamune®	Sirolimus	Wyeth/Pfizer	2000 (immunosuppressant)	Wet/pearl milling
Emend®	Aprepitant	Merck	2003 (antiemetic)	Wet/pearl milling
Tricor®	Fenofibrate	Abbott/AbbVie	2004 (dyslipidemia)	Wet/pearl milling
Megace ES®	Megestrol acetate	Par Pharmaceutical	2005 (anorexia/cachexia)	Pearl milling
Triglide®	Fenofibrate	SkyePharma/Sciele	2005 (dyslipidemia)	High-pressure homogenization
Invega Sustenna®	Paliperidone palmitate	Janssen	2009 (antipsychotic, depot injection)	Wet milling

Source: compiled from nanocrystal translational research reviews [14,15,16].

IV. CYCLODEXTRIN INCLUSION COMPLEX TECHNOLOGY

4.1 Mechanism of action

Cyclodextrins (CDs) are cyclic oligosaccharides composed of six, seven, or eight α-1,4-linked glucopyranose units (α-, β-, and γ-cyclodextrin, respectively), forming a truncated cone with a hydrophilic outer surface and a relatively hydrophobic internal cavity [17,18]. A poorly soluble drug molecule of appropriate size and lipophilicity can partially or fully insert into this cavity, forming a non-covalent host–guest inclusion complex stabilized by van der Waals forces, hydrophobic interactions, and hydrogen bonding. Because the hydrophobic guest is shielded from the aqueous environment by the hydrophilic exterior of the cyclodextrin, the apparent aqueous solubility of the drug–cyclodextrin complex is substantially higher than that of the free drug, and dissolution and membrane permeation kinetics are correspondingly improved [17,19].

Beyond solubility enhancement, inclusion complexation frequently confers secondary benefits relevant to BCS Class II formulation, including protection of labile drugs from hydrolysis, oxidation, or photodegradation; reduction of unpleasant taste or odor; and, in some cases, reduced local irritation upon parenteral or ophthalmic administration [18,20].

4.2 Cyclodextrin types and selection

Native α-, β-, and γ-cyclodextrins differ in cavity diameter and intrinsic aqueous solubility, with β-cyclodextrin historically the most widely used owing to its favorable cavity size for many drug-like molecules but limited by comparatively low intrinsic water solubility. Chemically modified derivatives, notably 2-hydroxypropyl-β-cyclodextrin (HPβCD) and sulfobutylether-β-cyclodextrin (SBEβCD, marketed as Captisol®), dramatically improve aqueous solubility and reduce nephrotoxic potential relative to native β-cyclodextrin, and are now preferred for parenteral

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applications and for many oral BCS Class II formulations [17,21]. Table 4 summarizes the principal cyclodextrins used in pharmaceutical inclusion complexation.

Table 4. Principal cyclodextrins used for pharmaceutical inclusion complexation.

Cyclodextrin	Glucose units	Cavity diameter (Å)	Aqueous solubility	Typical regulatory status
α-Cyclodextrin	6	4.7–5.3	Moderate	Approved excipient
β-Cyclodextrin	7	6.0–6.5	Low (~1.85 g/100 mL)	Approved; renal caution parenterally
γ-Cyclodextrin	8	7.5–8.3	High	Approved excipient
HP-β-Cyclodextrin	7 (derivatized)	~6.0–6.5	Very high (>50 g/100 mL)	USP-NF/EP listed; widely used parenterally
Sulfobutylether-β-CD	7 (derivatized)	~6.0–6.5	Very high	FDA-approved (e.g., Captisol®)

Source: compiled from cyclodextrin pharmaceutical application reviews [17,18,21].

4.3 Preparation methods

Inclusion complexes are most commonly prepared by kneading (mixing drug and cyclodextrin with a small volume of solvent to form a paste, followed by drying), the co-evaporation/solvent evaporation method (co-dissolution in a common solvent followed by solvent removal), freeze-drying (lyophilization) of an aqueous drug–cyclodextrin solution, spray-drying, and co-precipitation [19,22]. Ternary complexes incorporating a third auxiliary component, such as an amino acid (e.g., arginine) or a hydrophilic polymer (e.g., polyvinylpyrrolidone, poloxamer 188, or soluplus), are increasingly used to further increase complexation efficiency and stability constant beyond what is achievable with the binary drug–cyclodextrin system alone [22,23]. For instance, ternary complexation of repaglinide and nateglinide with HPβCD and arginine increased the stability constant roughly 10-fold relative to the binary HPβCD complex for repaglinide [22].

4.4 Characterization

Confirmation of true inclusion complex formation (rather than simple physical mixing) requires a combination of analytical techniques: phase solubility analysis to determine the stoichiometry and stability constant of complexation, differential scanning calorimetry and powder X-ray diffraction to demonstrate loss of the drug's characteristic crystalline melting endotherm and diffraction pattern, Fourier-transform infrared spectroscopy to detect shifts in characteristic guest functional-group vibrations, and nuclear magnetic resonance (particularly 2D ROESY) to directly demonstrate spatial proximity between guest protons and the cyclodextrin cavity protons [19,20].

4.5 Cyclodextrin-based nanosponges and polymeric extensions

Beyond simple binary inclusion complexes, cyclodextrins can be cross-linked into porous, three-dimensional nanosponge networks that combine the host–guest complexation chemistry of the cyclodextrin with the additional drug-loading capacity and controlled-release behavior of a porous polymeric matrix. A recent study using a microwave-assisted, greener synthesis approach produced domperidone-loaded β-cyclodextrin nanosponges with a particle size of approximately 196 nm, drug entrapment efficiency of 84%, and significantly enhanced dissolution relative to the free drug, illustrating convergence between the nanocrystal and inclusion-complex paradigms [24].

V. COMPARATIVE ANALYSIS

Direct comparison of nanocrystal and inclusion complex technologies requires evaluation across multiple, partially independent axes: mechanism of solubilization, the physical state of the resulting drug product, manufacturing and scale-up considerations, regulatory standing, and the magnitude of solubility or bioavailability improvement that can be

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expected. Table 5 synthesizes this multi-axis comparison; Table 6 then presents representative quantitative outcomes drawn from the BCS Class II drug literature for each platform.

Table 5. Multi-parameter comparison of nanocrystal and inclusion complex technologies for BCS Class II drug solubilization.

Parameter	Nanocrystal technology	Inclusion complex technology
Mechanism	Increased surface area and surface free energy of carrier-free crystalline particles (Ostwald–Freundlich effect)	Host–guest molecular encapsulation within hydrophilic cyclodextrin cavity
Final drug state	Crystalline (or partially amorphous at the particle surface); carrier-free	Discrete molecular complex; drug effectively molecularly dispersed
Drug loading / dose efficiency	Very high (~100% drug, thin stabilizer coat); favorable for high-dose drugs	Lower; CD is typically present at 1:1–1:4 molar ratio, substantially increasing dosage form bulk
Typical particle/complex size	100–1000 nm (top-down); can be smaller via bottom-up routes	Molecular scale (sub-nanometer complexation); aggregates/nanosponges 150–300 nm
Manufacturing complexity	Moderate–high; specialized milling/homogenization equipment, long processing times for milling	Low–moderate; conventional kneading, evaporation, spray-drying or freeze-drying equipment
Scale-up & reproducibility	Sensitive to milling time, media, and stabilizer concentration; risk of Ostwald ripening/aggregation on storage	Generally high reproducibility; well-defined stoichiometry; phase-solubility methods support quality control
Stabilizer/excipient burden	Surfactants/polymeric stabilizers (e.g., TPGS, poloxamer, HPMC) at low concentration (0.1–2%)	Cyclodextrin itself constitutes the major excipient mass; ternary agents (polymers, amino acids) optional
Regulatory precedent	Multiple FDA-approved products since 2000 (Rapamune®, Emend®, Tricor®, Megace ES®, Invega Sustenna®)	Multiple FDA/EMA-approved products using HPβCD/SBEβCD; cyclodextrins are USP-NF/EP-listed excipients
Ancillary benefits	Mucoadhesion may enhance absorption; suitable for oral, parenteral, ocular, and dermal routes	Taste/odor masking; photostabilization; chemical protection from oxidation/hydrolysis
Principal limitation	Physical instability (crystal growth, aggregation) during storage; energy-intensive processing	Cavity-size selectivity restricts applicability; high CD mass per dose; possible nephrotoxicity of native βCD parenterally

Source: synthesized by the authors from refs. [9–26].

A central practical distinction concerns drug loading efficiency. Because nanocrystals are essentially pure drug substance with only a thin (often sub-1% w/w) stabilizer coating, they are particularly well suited to drugs administered at relatively high doses, where the bulk excipient load of a competing technology would be prohibitive. Inclusion complexes, by contrast, typically require cyclodextrin at molar ratios of 1:1 to 1:4 (drug:CD), and because cyclodextrins have molecular weights several-fold greater than most small-molecule drugs, the resulting dosage form can become bulky for high-dose actives a consideration that has historically restricted cyclodextrin complexation to lower-dose, higher-potency BCS Class II drugs [17,19].

Conversely, inclusion complexation benefits from a more mechanistically transparent and analytically verifiable process. Phase-solubility analysis directly yields a stability constant (K) and complexation efficiency that can be used for rational formulation optimization, and the chemistry of host–guest complexation is largely independent of batch-to-

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batch milling variability a recurring concern with nanocrystal manufacture, where milling time, media composition, and stabilizer concentration must be tightly controlled to avoid both under-processing and excessive Ostwald ripening during storage [9,12,19].

Table 6. Representative solubility, dissolution, and bioavailability outcomes for selected BCS Class II drugs formulated as nanocrystals or inclusion complexes.

Drug (BCS II)	Technology	Particle size / complex feature	Solubility / dissolution gain	Reported bioavailability gain
Kojic acid	Nanocrystal (top-down, HPH)	110–150 nm	Markedly enhanced dissolution vs. pure drug [13]	Not reported (in vitro study)
Rivaroxaban	βCD inclusion complex (1:1–1:4)	Molecular complex; polymer-assisted	Increased saturation solubility and dissolution with βCD plus hydrophilic polymer [25]	~2.1× (analogous CD systems) [26]
Domperidone	βCD-based nanosponge	~196 nm; 84% entrapment	Significantly faster dissolution vs. free drug [24]	~2.3× (representative CD-nanosponge systems)
Irbesartan	HPβCD complex; HPβCD–SLN hybrid	Molecular complex ± lipid nanoparticle	Improved saturation solubility (91.3 µg/mL baseline) [26]	2.1× (HPβCD alone); 9.9× (HPβCD–SLN hybrid) [26]
Fenofibrate	Nanocrystal (wet milling / HPH)	~100–400 nm (commercial)	Markedly increased dissolution; food-effect-independent absorption	Reduced fed/fasted variability; ~3× improved relative exposure vs. micronized form (literature range) [14,15]
Aprepitant	Nanocrystal (wet milling)	~100–200 nm (commercial)	Saturation solubility scales inversely with particle size below 1 µm [11]	Substantially improved oral bioavailability enabling clinical dosing [14]

Source: compiled from refs. [13,14,15,24,25,26]. Values are illustrative of reported trends; exact magnitudes vary with formulation conditions, stabilizer/CD selection, and species/study design.

VI. GRAPHICAL COMPARISON OF PERFORMANCE TRENDS

Figure 1 illustrates the general relationship between particle size and relative saturation solubility predicted by the Ostwald–Freundlich equation, which underlies the performance gains observed for nanocrystal formulations. The relationship is markedly nonlinear: solubility enhancement remains modest until particle size falls below approximately

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1 µm, after which further size reduction yields disproportionately large gains, providing the theoretical rationale for the typical 100–400 nm target range used in commercial nanocrystal products.

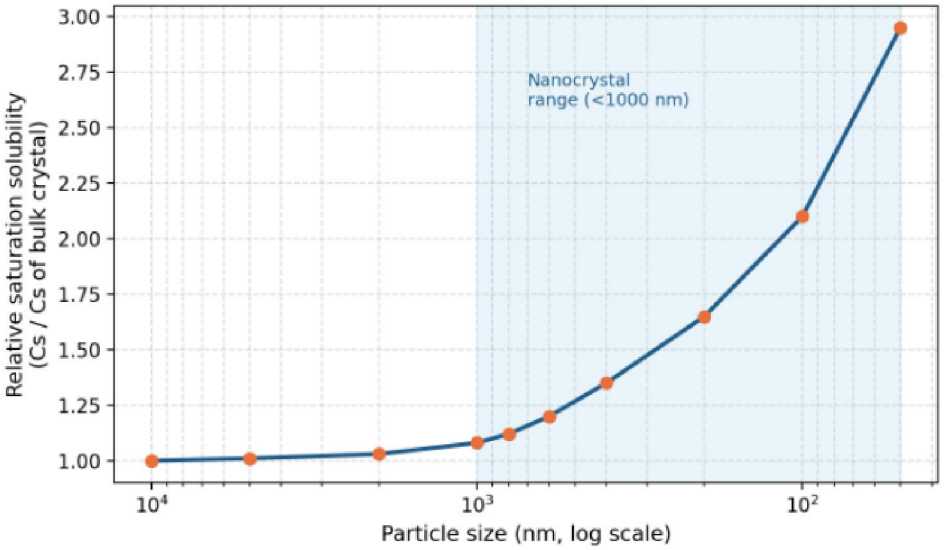

Figure 1. Illustrative relationship between drug particle size and relative saturation solubility (Cs relative to the bulk crystalline drug), based on the qualitative trend described by the Ostwald–Freundlich equation [9,11]. Values are representative of reported trends rather than measurements for a single specific compound.

Figure 2 compares representative fold-increases in relative oral bioavailability reported in the literature for nanocrystal, inclusion-complex, and hybrid formulations of selected BCS Class II drugs. While direct cross-study comparison must be interpreted cautiously given differing study designs, species, and dosing conditions, the data illustrate that both platforms are capable of multi-fold bioavailability improvement, and that hybrid approaches combining inclusion complexation with a secondary nanocarrier (e.g., HPβCD–solid lipid nanoparticle systems) can outperform either technology used alone.

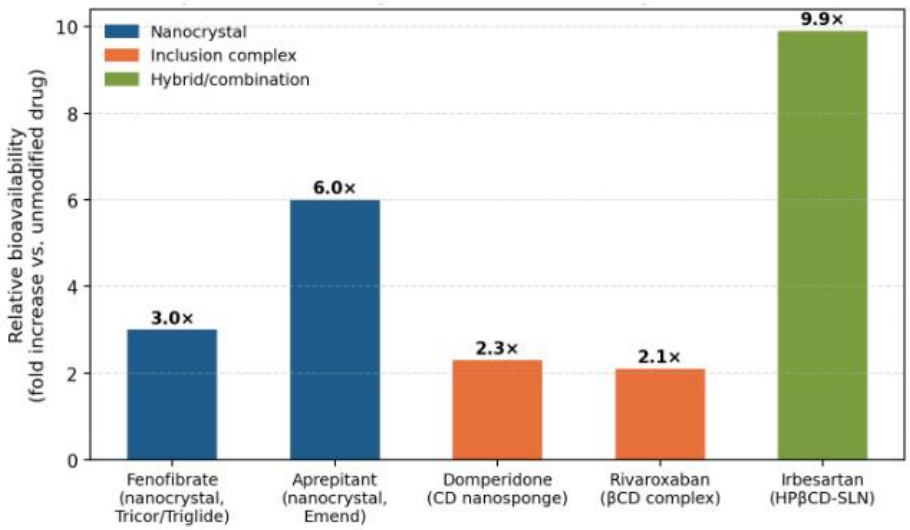

Figure 2. Representative relative bioavailability (fold increase versus the unmodified drug) reported for nanocrystal and inclusion-complex formulations of selected BCS Class II drugs [14,15,25,26].

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Figure 3 presents generalized in vitro dissolution profiles contrasting an unmodified crystalline BCS Class II drug with cyclodextrin inclusion complex and nanocrystal formulations of the same hypothetical compound. The curves are constructed to reflect the qualitative shape and relative ordering of dissolution profiles consistently reported across the nanocrystal and inclusion-complex literature: nanocrystals typically achieve the most rapid initial dissolution due to their very high specific surface area, while inclusion complexes show a substantial but somewhat slower approach to complete dissolution, both clearly outperforming the unmodified crystalline drug.

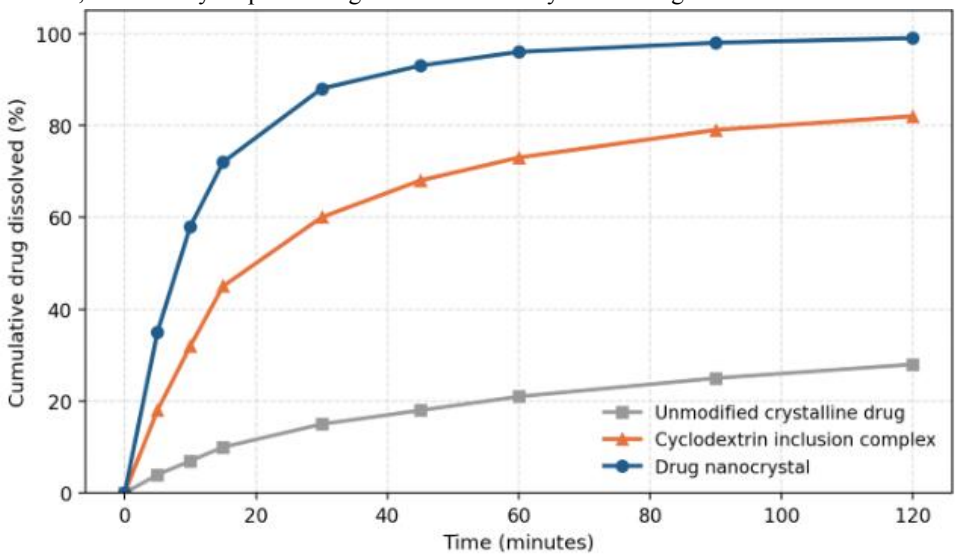

Figure 3. Generalized, illustrative in vitro cumulative dissolution profiles for a model BCS Class II drug as an unmodified crystalline solid, a cyclodextrin inclusion complex, and a nanocrystal formulation, constructed to reflect qualitative trends reported in the literature [9,13,19,24,25].

VII. FACTORS GOVERNING TECHNOLOGY SELECTION

7.1 Molecular suitability

Cyclodextrin complexation is fundamentally constrained by geometric fit: the guest molecule (or a relevant lipophilic fragment of it) must approximate the dimensions of the host cavity for efficient, high-stability-constant complexation to occur. Drugs that are too large, too polar, or structurally mismatched to available native or modified cyclodextrins may show only marginal solubility improvement regardless of optimization effort [17,19]. Nanocrystal technology imposes no comparable size-matching requirement and is, in principle, applicable to essentially any poorly soluble crystalline drug, although very low melting point or markedly amorphous-prone compounds may be more prone to recrystallization or particle growth during processing and storage [9,12].

7.2 Dose considerations

For high-dose BCS Class II drugs (several hundred milligrams or more per dose), nanocrystal technology is generally preferred because of its near-100% drug loading, whereas the substantial cyclodextrin mass required for an equivalent inclusion complex formulation would result in an impractically large dosage form. For low-dose, high-potency compounds, the dosage-form bulk penalty of cyclodextrin complexation is far less consequential, and the additional analytical and regulatory familiarity of cyclodextrin excipients can make inclusion complexation the more attractive default choice [17,19].

7.3 Manufacturing infrastructure and cost

Wet milling and high-pressure homogenization equipment represent a significant capital investment and require careful process validation to control milling time, temperature, and media wear; in addition, downstream processing of the

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resulting nanosuspension into a solid oral dosage form (e.g., via granulation onto a carrier or spray-drying) adds further process steps [9,12]. Inclusion complex preparation by kneading, co-evaporation, or spray-drying generally uses more conventional pharmaceutical processing equipment already present in most manufacturing facilities, which can lower the barrier to adoption, particularly for smaller manufacturers or for early-phase clinical formulation work [19,22].

7.4 Physical and chemical stability

Nanocrystal suspensions are thermodynamically metastable with respect to particle size; without adequate stabilizer selection and concentration, Ostwald ripening (the preferential growth of larger particles at the expense of smaller ones, driven by the same surface-energy effect that gives nanocrystals their solubility advantage) can occur during storage, eroding the achieved benefit over shelf life [9,11]. Inclusion complexes, once formed, are generally more thermodynamically stable as discrete molecular species, although they remain susceptible to drug expulsion from the cavity under conditions that disrupt the host–guest interaction (e.g., extreme pH, competing endogenous molecules in vivo, or dilution below the critical complexation concentration) [19,20].

7.5 Regulatory and intellectual property considerations

Both technologies benefit from extensive regulatory precedent; cyclodextrins (particularly HPβCD and SBEβCD) are listed in the USP-NF and European Pharmacopoeia as approved excipients with well-characterized safety profiles, while milling-based nanocrystal manufacture has a comparably long history of FDA approvals dating to 2000 [14,17,21]. From an intellectual property perspective, nanocrystal and inclusion-complex reformulation of an off-patent or near-patent-expiry BCS Class II drug have both been used as strategies to generate new, patentable formulation intellectual property and corresponding regulatory exclusivity, a commercially significant consideration in lifecycle management strategies for the originator company [8,14].

VIII. EMERGING HYBRID AND COMBINATION APPROACHES

An increasingly active area of formulation research blurs the boundary between nanocrystal and inclusion-complex technologies, combining the two mechanisms within a single delivery system. Cyclodextrin-based nanosponges, in which cyclodextrin molecules are cross-linked into a porous, nanostructured network, retain the host–guest complexation chemistry of conventional cyclodextrins while adding a nanoscale particulate architecture more reminiscent of a nanocrystal or nanoparticle carrier; such systems have demonstrated significantly enhanced solubility and dissolution for domperidone and other BCS Class II actives, while also offering the possibility of more sustained or controlled drug release [24,27].

A second hybrid strategy combines cyclodextrin inclusion complexation with a secondary lipid- or polymer-based nanocarrier. In one representative example, irbesartan formulated as an HPβCD inclusion complex achieved a 2.1-fold improvement in relative oral bioavailability over a plain suspension, while solid lipid nanoparticles (SLNs) of the same drug achieved a 6.6-fold improvement; combining both strategies into an HPβCD-complexed SLN formulation achieved a 9.9-fold improvement, substantially exceeding either platform alone and also producing a more favorable, sustained pharmacodynamic profile in an animal hypertension model [26]. Such results suggest that the mechanisms underlying nanocrystal/nanoparticle-based and inclusion-complex-based solubilization are at least partially additive rather than purely redundant, supporting continued investigation of combination strategies for particularly challenging BCS Class II (and Class IV) candidates.

Green and more sustainable variants of both technologies are also emerging, including microwave-assisted and solvent-minimized synthesis routes for cyclodextrin nanosponges, and supercritical fluid or other low-solvent bottom-up nanocrystal production methods, reflecting the broader pharmaceutical industry trend toward more environmentally sustainable manufacturing [24,27].

IX. DISCUSSION

The comparative evidence assembled in this review supports several general conclusions, while also highlighting the danger of over-generalizing across a chemically and clinically diverse drug class. First, both nanocrystal and inclusion-

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complex technologies are capable of producing clinically meaningful improvements in solubility, dissolution rate, and oral bioavailability for BCS Class II drugs, and both have an established record of successful regulatory approval and commercial marketing. Neither technology should therefore be regarded as categorically superior; rather, the appropriate choice depends on the specific physicochemical and clinical-dose profile of the candidate molecule.

Second, the magnitude of bioavailability improvement reported in the literature appears, on average, to favor nanocrystal technology for compounds where the dissolution-rate-limiting step is dominant and where dose size permits a carrier-free formulation, consistent with the very large surface-area increase achievable through nanonization. However, the data in Table 6 also indicate that inclusion complexation, particularly when used in combination with auxiliary polymers (ternary complexation) or secondary nanocarriers, can achieve comparable or superior fold-increases in bioavailability, narrowing or even reversing this apparent advantage for specific molecules such as irbesartan [26].

Third, manufacturing and regulatory practicality considerations, rather than purely physicochemical performance, often determine the platform selected in industrial practice. The lower capital equipment burden and more straightforward analytical characterization of inclusion complexation may favor its selection during early formulation screening or for smaller-scale manufacturers, whereas the carrier-free, high-drug-loading character of nanocrystals makes them the default choice for high-dose BCS Class II compounds where excipient bulk is a binding constraint, as exemplified by the commercial success of fenofibrate and sirolimus nanocrystal products [14,15].

A limitation of the current evidence base, and a recurring theme across the reviewed literature, is the scarcity of head-to-head comparative studies in which the same BCS Class II drug is formulated as both a nanocrystal and an inclusion complex under matched experimental conditions and evaluated in the same in vivo model. Most of the comparative inferences drawn in this review, including those summarized in Table 6 and Figure 2, are therefore necessarily cross-study comparisons subject to confounding by differences in species, dosing, analytical methodology, and formulation optimization effort. Future research employing matched, within-study comparisons across a panel of representative BCS Class II drugs would substantially strengthen the evidence base available for rational, mechanism-informed technology selection.

Finally, the emergence of hybrid platforms cyclodextrin nanosponges, cyclodextrin-complexed lipid nanoparticles, and related combination strategies suggests that the dichotomy between nanocrystal and inclusion-complex technologies may become progressively less sharp over time, with formulation science increasingly favoring rationally designed combination systems that capture complementary mechanisms of solubilization within a single delivery platform [24,26,27].

X. CONCLUSION

Nanocrystal engineering and cyclodextrin-based inclusion complexation remain the two most extensively validated and commercially translated technologies for addressing the dissolution-rate-limited absorption that characterizes BCS Class II drugs. Nanocrystals achieve solubility and dissolution enhancement primarily through particle-size-driven increases in surface area and surface free energy, offer near-complete drug loading well suited to higher-dose compounds, and have an extensive regulatory track record spanning oral and parenteral products. Inclusion complexes achieve enhancement through host–guest molecular encapsulation, offer high reproducibility and well-established analytical characterization methods, and provide valuable ancillary benefits including chemical and photostabilization and taste masking, but are constrained by cyclodextrin cavity-size selectivity and the comparatively larger excipient mass required per dose.

No single technology is universally optimal across the chemically diverse BCS Class II drug class; technology selection should be guided by the specific molecular size and lipophilicity profile, intended dose, manufacturing infrastructure, and regulatory strategy relevant to the candidate drug. The growing body of evidence on hybrid systems combining nanocrystal- and inclusion-complex-based mechanisms indicates a promising direction for future formulation

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development, particularly for the most challenging poorly soluble drug candidates where neither technology alone achieves a fully satisfactory solubility or bioavailability profile.

REFERENCES

1. Amidon, G.L.; Lennernäs, H.; Shah, V.P.; Crison, J.R. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 1995, 12, 413–420.
2. FDA. Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (Guidance for Industry); U.S. Food and Drug Administration: Silver Spring, MD, 2017.
3. Butler, J.M.; Dressman, J.B. The developability classification system: application of biopharmaceutics concepts to formulation development. J. Pharm. Sci. 2010, 99, 4940–4954.
4. Blagden, N.; de Matas, M.; Gavan, P.T.; York, P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv. Drug Deliv. Rev. 2007, 59, 617–630.
5. Savjani, K.T.; Gajjar, A.K.; Savjani, J.K. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012, 2012, 195727.
6. Xia, D.; Cui, F.; Piao, H.; Cun, D.; Jiang, Y.; Ouyang, M.; Quan, P. Effect of crystal size on the in vitro dissolution and oral absorption of nitrendipine in rats. Pharm. Res. 2010, 27, 1965–1976.
7. Vij, M.; Dand, N.; Kumar, L.; Wadhwa, P.; Wani, S.U.D.; Mahdi, W.A.; Alshehri, S.; Alam, P.; Shakeel, F. Optimisation of a greener-approach for the synthesis of cyclodextrin-based nanosponges for the solubility enhancement of domperidone, a BCS class II drug. Pharmaceuticals 2023, 16, 567.
8. Mishra, D.K.; Shandilya, R.; Mishra, P.K. Lipid based nanocarriers: a translational perspective. Nanomedicine 2018, 14, 2023–2050.
9. Junyaprasert, V.B.; Morakul, B. Nanocrystals for enhancement of oral bioavailability of poorly water-soluble drugs. Asian J. Pharm. Sci. 2015, 10, 13–23.
10. Möschwitzer, J.P. Drug nanocrystals in the commercial pharmaceutical development process. Int. J. Pharm. 2013, 453, 142–156.
11. Mosharraf, M.; Nyström, C. The effect of particle size and shape on the surface specific dissolution rate of microsized practically insoluble drugs. Int. J. Pharm. 1995, 122, 35–47.
12. Sinha, B.; Müller, R.H.; Möschwitzer, J.P. Bottom-up approaches for preparing drug nanocrystals: formulations and factors affecting particle size. Int. J. Pharm. 2013, 453, 126–141.
13. Khan, S.; Patil, K.; Yeole, P.; Gaikwad, R. Formulation and characterization of carbopol-934 based kojic acid-loaded smart nanocrystals: a solubility enhancement approach. Pharmaceutics 2022, 14, 770.
14. Junghanns, J.U.; Müller, R.H. Nanocrystal technology, drug delivery and clinical applications. Int. J. Nanomedicine 2008, 3, 295–309.
15. Gao, L.; Liu, G.; Ma, J.; Wang, X.; Zhou, L.; Li, X. Drug nanocrystals: in vivo performances. J. Control. Release 2012, 160, 418–430.
16. Patel, V.R.; Agrawal, Y.K. Nanosuspension: an approach to enhance solubility of drugs. J. Adv. Pharm. Technol. Res. 2011, 2, 81–87.
17. Loftsson, T.; Brewster, M.E. Pharmaceutical applications of cyclodextrins: basic science and product development. J. Pharm. Pharmacol. 2010, 62, 1607–1621.
18. Jambhekar, S.S.; Breen, P. Cyclodextrins in pharmaceutical formulations I: structure and physicochemical properties, formation of complexes, and types of complex. Drug Discov. Today 2016, 21, 356–362.
19. Pinho, E.; Grootveld, M.; Soares, G.; Henriques, M. Cyclodextrins as encapsulation agents for plant bioactive compounds. Carbohydr. Polym. 2014, 101, 121–135.

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20. Brewster, M.E.; Loftsson, T. Cyclodextrins as pharmaceutical solubilizers. Adv. Drug Deliv. Rev. 2007, 59, 645–666.
21. Stella, V.J.; He, Q. Cyclodextrins. Toxicol. Pathol. 2008, 36, 30–42.
22. Conceição, J.; Adeoye, O.; Cabral-Marques, H.M.; Lobo, J.M.S. Cyclodextrins as excipients in tablet formulations. Drug Discov. Today 2018, 23, 1274–1284.
23. Singh, R.; Bharti, N.; Madan, J.; Hiremath, S.N. Characterization of cyclodextrin inclusion complexes a review. J. Pharm. Sci. Technol. 2010, 2, 171–183.
24. Tiwari, R.; Pathak, K. Nanosponges: an emerging drug delivery system for enhancement of solubility and bioavailability. Int. J. Pharm. Sci. Nanotechnol. 2011, 4, 1483–1494.
25. Khalid, A.; et al. Effect of hydrophilic polymers on the solubility and dissolution enhancement of rivaroxaban/beta-cyclodextrin inclusion complexes. Saudi Pharm. J. 2023, 31, 1018–1027.