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Review Article

Solubility Enhancement Strategies for BCS Class II Drugs in Orally Disintegrating Tablet Platforms: A Review

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Abstract

Objective(s): To critically review and synthesize solubility enhancement strategies applied to Biopharmaceutics Classification System (BCS) Class II drugs formulated as orally disintegrating tablets (ODTs), with particular attention to how dissolution-rate-limiting solubility constraints are addressed without compromising the rapid disintegration performance that defines this dosage form.

Data sources: Peer-reviewed primary and review literature (2013-2026) on BCS classification, solid dispersion technology, sublimation- and lyophilisation-based pore-forming techniques, particle size reduction and nanocrystal engineering, cyclodextrin complexation, and self-emulsifying systems, together with published formulation and evaluation studies on rapid-melt ODTs of representative BCS Class II lipid-lowering agents.

Study selection: Publications addressing the mechanistic basis of solubility enhancement, its integration with ODT manufacturing platforms (direct compression, sublimation/lyophilisation, solid dispersion, nanocrystal freeze-drying), and comparative in vitro performance (disintegration time, dissolution efficiency, drug release) were prioritized, including case-level formulation studies on rosuvastatin, simvastatin, and ezetimibe rapid-melt systems, supplemented by recent (2021-2026) literature to reflect current developments in the field.

Summary of contents: This review outlines the biopharmaceutical rationale for combining solubility enhancement with ODT technology, describes the principal solubility enhancement strategies (solid dispersion, sublimation-assisted pore formation, particle size reduction/nanocrystal engineering, cyclodextrin inclusion complexation, and surfactant/self-emulsifying approaches), and examines their integration into ODT matrices through a series of case studies on statin and cholesterol-lowering rapid-melt formulations, together with recently reported BCS Class II ODT systems. Evaluation parameters specific to solubilized-drug ODT systems, formulation-process trade-offs, regulatory considerations, and future directions are also discussed.

Conclusion: The convergence of solubility enhancement technology with ODT platforms offers a rational route to improving both the dissolution rate and patient acceptability of BCS Class II drugs, provided that the porosity and disintegration performance of the tablet matrix are preserved during incorporation of the solubilized drug intermediate.

Keywords: BCS Class II; solubility enhancement; solid dispersion; orally disintegrating tablets; rapid melts; sublimation; nanocrystal; dissolution rate

1. INTRODUCTION

The Biopharmaceutics Classification System (BCS), introduced as a scientific framework for correlating in vitro drug dissolution with in vivo bioavailability, classifies drugs into four categories on the basis of aqueous solubility and intestinal permeability. BCS Class II drugs, characterized by high permeability but low aqueous solubility, present a dissolution-rate-limited absorption profile, such that oral bioavailability is governed primarily by the rate at which drug particles dissolve in gastrointestinal fluid rather than by membrane permeation.[1]

A substantial proportion of drugs in current clinical use, and an even larger proportion of new chemical entities in development, fall within BCS Class II, making solubility enhancement one of the central technical challenges in modern oral dosage form design.[1-3] This challenge is compounded when the target dosage form is an orally disintegrating tablet (ODT), since the very features that make an ODT rapidly disintegrate in the oral cavity, namely a porous, low-density matrix and rapid saliva penetration, do not by themselves address the intrinsic dissolution-rate limitation of a poorly soluble drug once released from the tablet.

This review examines how solubility enhancement strategies have been applied to BCS Class II drugs within ODT platforms, drawing on both the broader pharmaceutical literature and a series of case-level formulation studies on statin and cholesterol-lowering agents, to outline a rational, mechanistically grounded

approach to designing rapid-melt formulations for poorly soluble drugs.

2. THE BCS CLASS II SOLUBILITY CHALLENGE

For a BCS Class II drug, the rate of dissolution, and hence the rate of drug available for absorption, is described by the Noyes-Whitney relationship, in which dissolution rate is directly proportional to the exposed surface area of drug particles and to the concentration gradient between the diffusion layer adjacent to the particle surface and the bulk medium, and inversely proportional to the diffusion layer thickness. Because intestinal permeability is not limiting for these drugs, any formulation intervention that increases effective surface area, improves wettability, or increases apparent saturation solubility can translate directly into improved dissolution rate and, in many cases, improved oral bioavailability.[1]

The practical consequence for formulators is that BCS Class II drugs are disproportionately dependent on formulation strategy relative to BCS Class I drugs, and the choice of solubility enhancement technique must be reconciled with any other functional requirements of the dosage form, such as the rapid disintegration and low mechanical robustness characteristic of ODTs.

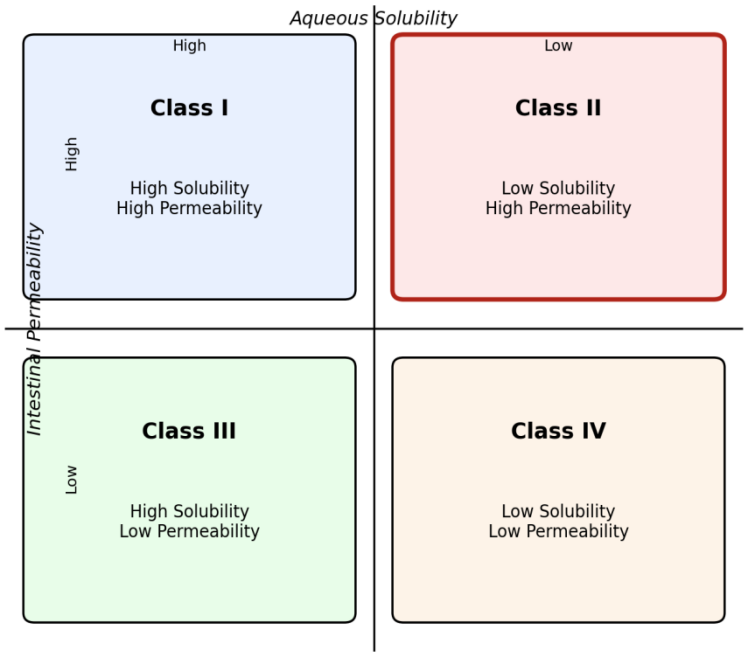

Figure 1. The Biopharmaceutics Classification System (BCS), showing the dissolution-rate-limited absorption profile characteristic of Class II drugs (high permeability, low solubility). Original schematic prepared by the author, adapted conceptually from the BCS framework of Amidon et al.[1]; not reproduced from any copyrighted source.

3. RATIONALE FOR COMBINING SOLUBILITY ENHANCEMENT WITH ODT TECHNOLOGY

Combining solubility enhancement with ODT design is motivated by a biopharmaceutical synergy: rapid tablet disintegration exposes drug particles to saliva and, subsequently, gastrointestinal fluid within seconds, but this advantage is only fully realized if the drug itself dissolves rapidly once exposed.[20] For a BCS Class I drug, rapid disintegration alone is generally sufficient to achieve a fast, near-complete dissolution profile. For a BCS Class II drug, rapid disintegration without a complementary solubility enhancement strategy simply shifts the rate-limiting step from tablet breakup to drug particle dissolution, without meaningfully improving overall drug release kinetics.

Formulating a solubility-enhanced BCS Class II drug as an ODT therefore requires the simultaneous optimization of two, at times competing, objectives: preserving the high matrix porosity and low interparticulate bonding needed for rapid wicking-driven disintegration, while incorporating a solubilized or particle-size-reduced drug intermediate (solid dispersion granulate, nanocrystal powder, or inclusion complex) without compromising flow, compressibility, or content uniformity. Much of the formulation science described in this review is concerned with reconciling this trade-off.

4. SOLUBILITY ENHANCEMENT STRATEGIES

4.1 Solid Dispersion Technique

Solid dispersion involves dispersing a poorly soluble drug at the molecular, amorphous, or fine crystalline level within an inert, typically hydrophilic, carrier matrix, thereby increasing effective surface area, improving wettability, and, in the case of amorphous or molecular dispersions, eliminating the crystal lattice energy barrier to dissolution.[4] Commonly used carriers include polyvinylpyrrolidone (PVP), polyethylene glycols (PEG) of varying molecular weight, and poloxamers, selected according to the drug's melting point, thermal stability, and compatibility with the chosen preparation method (solvent evaporation, melting/fusion, or kneading).[4,5]

Solid dispersion approaches have been applied to improve the aqueous solubility of ezetimibe, a poorly water-soluble cholesterol absorption inhibitor, using carrier-based dispersion techniques that markedly increased apparent solubility and dissolution rate relative to the unprocessed drug, providing an intermediate suitable for downstream incorporation into a rapidly disintegrating tablet matrix.[6]

A parallel approach applied to simvastatin, a widely prescribed BCS Class II lipid-lowering agent, similarly demonstrated that solid dispersion technique can substantially improve the solubility of poorly soluble statins, supporting the general applicability of this strategy across structurally related lipid-lowering actives.[7]

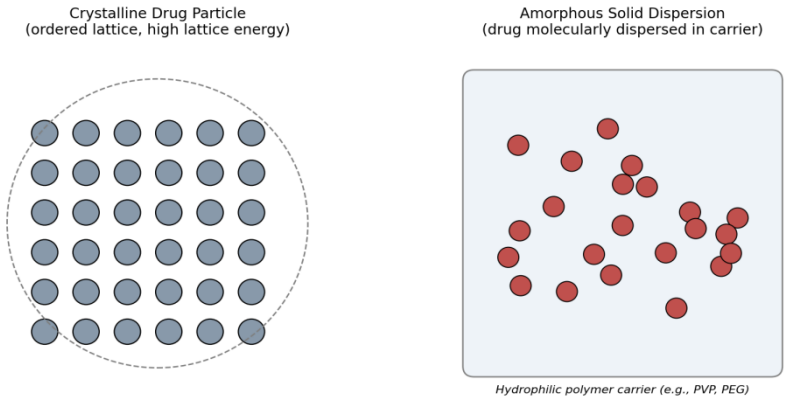

Figure 2. Schematic comparison of a crystalline drug particle, in which the ordered lattice imposes a high lattice energy barrier to dissolution, and an amorphous solid dispersion, in which drug molecules are dispersed within a hydrophilic carrier without long-range crystalline order. Original schematic prepared by the author; not reproduced from any copyrighted source.

From a thermodynamic standpoint, the enhanced apparent solubility of an amorphous or molecularly dispersed drug arises because the amorphous state possesses a higher Gibbs free energy than the corresponding crystalline lattice, eliminating the lattice energy that must otherwise be overcome for dissolution to proceed. This same elevated free energy, however, renders amorphous dispersions thermodynamically metastable, and physical stability is governed in large part by the glass transition temperature (Tg) of the dispersion; as a general formulation rule, storage temperatures are kept well below the system Tg to minimise molecular mobility and the associated risk of recrystallisation over shelf life. Because amorphous systems characteristically generate a transient, supersaturated solution on dissolution before re-equilibrating toward the thermodynamic solubility of the crystalline form, many solid dispersion formulations incorporate a precipitation inhibitor (commonly a cellulosic polymer such as HPMC or HPMCAS) to prolong this supersaturated state for long enough to permit absorption, a strategy conceptually described in the pharmaceutical literature as the "spring and parachute" approach to solubility enhancement.[5]

4.2 Sublimation-Assisted Pore Formation Combined with Direct Compression

An alternative, and in several respects complementary, strategy incorporates a volatile, subliming pore-former (such as camphor or menthol) directly into a direct-compression tablet blend containing the drug and superdisintegrant system; removal of the subliming agent by vacuum drying generates a highly porous matrix that increases both the rate of saliva wicking (accelerating disintegration) and the effective surface area of drug particles exposed on disintegration (accelerating dissolution). This technique has been applied to rosuvastatin rapid melts prepared by direct compression and sublimation, and to ezetimibe rapidmelts designed using an analogous sublimation-based pore-forming approach, with both formulations demonstrating improved in vitro disintegration and dissolution relative to conventionally compressed tablets of the same drug.[9,10]

More recently, a dual-porogen strategy combining a subliming agent with a second, complementary pore-former has been applied to cilostazol, a structurally unrelated BCS Class II drug, in an ODT prepared for buccal delivery by both lyophilisation and direct compression; the optimised formulation achieved a markedly faster early-time-point dissolution than the corresponding conventional tablet, underscoring the continued relevance of porogen-based porosity engineering to BCS Class II ODT design.[8]

Complementary work on rosuvastatin rapid melts, evaluated for both formulation performance and in vivo behaviour, and on ezetimibe rapidmelts assessed by in vitro evaluation, has further characterized the disintegration and dissolution advantages achievable through this combined direct-compression–sublimation approach for BCS Class II statins and cholesterol absorption inhibitors.[11,12,13]

4.3 Particle Size Reduction and Nanocrystal Approaches

Micronization and nanocrystallization techniques reduce drug particle size into the low-micron or nanometre range, directly increasing surface-area-to-volume ratio in accordance with the Noyes-Whitney relationship.

Techniques include wet milling, high-pressure homogenization, and controlled precipitation (bottom-up crystallization), each producing a stabilized particle suspension that is typically converted to a solid intermediate by spray drying or lyophilization prior to incorporation into a tablet blend.[14]

The direct integration of nanocrystal technology with ODT platforms has recently been demonstrated for aprepitant, a poorly soluble antiemetic, in which an optimised nanocrystal suspension was spray-dried and subsequently freeze-dried into an ODT matrix, achieving rapid disintegration (over 95% within two minutes) together with the dissolution advantage conferred by nanocrystal-scale particle size, illustrating the convergence of particle engineering and ODT design discussed conceptually in Section 3.[15]

An additional, particle-size-dependent contribution to solubility enhancement at the nanoscale is described by the Ostwald-Freundlich equation, which predicts that the apparent equilibrium solubility of a solid particle increases as particle radius decreases below approximately one micrometre, owing to the increasing contribution of surface free energy relative to bulk free energy. This effect is generally modest in absolute terms compared with the surface-area-driven kinetic dissolution rate advantage of nanocrystals, but is nonetheless a recognised mechanistic contributor, and formulators must additionally guard against Ostwald ripening (the tendency of larger particles to grow at the expense of smaller ones during storage of a nanosuspension) through appropriate choice of stabilising surfactant or polymer.

4.4 Cyclodextrin Inclusion Complexation

Cyclodextrins, cyclic oligosaccharides possessing a hydrophobic internal cavity and hydrophilic outer surface, can form inclusion complexes with lipophilic drug molecules, increasing apparent aqueous solubility through a combination of molecular encapsulation and disruption of crystal lattice packing. This approach is particularly useful where thermal processing (as used in fusion-based solid dispersion) is undesirable owing to drug thermolability.[16,17]

4.5 Surfactant Incorporation and Self-Emulsifying Approaches

Incorporation of surfactants or self-emulsifying drug delivery system (SEDDS) pre-concentrates, adsorbed onto a solid carrier for subsequent tabletting, can improve both wettability and effective solubility of highly lipophilic BCS Class II drugs, generating fine oil-in-water dispersions on contact with aqueous fluid. While less commonly reported for ODT-specific applications than solid dispersion or sublimation-based techniques, this approach represents a viable option for drugs with very low aqueous solubility that respond poorly to carrier-based dispersion alone.[18]

Table 1. Comparative summary of solubility enhancement strategies applied to BCS Class II drugs in ODT platforms, with key supporting references.

Strategy	Primary Mechanism	Key Advantage	Key Limitation	Key Reference(s)
Solid dispersion	Amorphisation / molecular dispersion; eliminates lattice energy barrier	Large solubility gain; well-established carriers	Physical instability (recrystallisation) on storage	4-7
Sublimation-assisted pore formation	Increased matrix porosity; simultaneous disintegration and dissolution benefit	Simple integration with direct compression	Requires vacuum-drying/lyophilisation step; pore-former residue control	8-13
Particle size reduction (nano/micro)	Increased surface-area-to-volume ratio (Noyes-Whitney); minor Ostwald-Freundlich contribution	Applicable to thermolabile drugs	Risk of Ostwald ripening; specialised equipment	14,15
Cyclodextrin complexation	Molecular inclusion; disruption of crystal packing	Avoids thermal processing	Drug loading capacity limited by resin/cavity size	16,17
Surfactant / SEDDS	Improved wettability; in-situ micro/nano-emulsification	Effective for very lipophilic actives	Limited ODT-specific precedent; taste/texture considerations	18

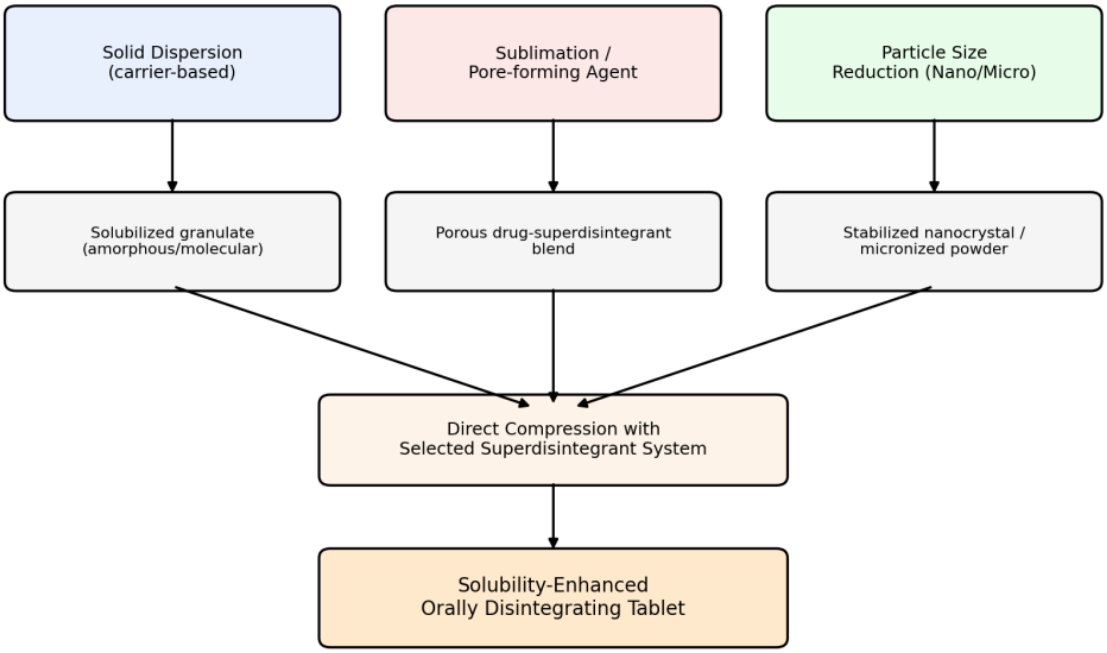

Figure 3. Generalised process-integration pathway by which solid dispersion, sublimation-assisted pore formation, and particle size reduction converge on a solubility-enhanced orally disintegrating tablet. Original schematic prepared by the author; not reproduced from any copyrighted source.

5. CASE STUDIES: STATIN AND CHOLESTEROL-LOWERING RAPID-MELT FORMULATIONS

The formulation studies summarised in this section, spanning rosuvastatin, simvastatin, and ezetimibe, together illustrate how the strategies described in Section 4 have been applied, in combination, to a structurally related family of BCS Class II lipid-lowering agents, and provide a coherent basis for the general formulation principles proposed later in this review.

5.1 Rosuvastatin Rapid Melts

Rosuvastatin, a poorly water-soluble HMG-CoA reductase inhibitor, has been formulated as a rapid-melt tablet using combined direct compression and sublimation methodology, with in vivo evaluation supporting the biopharmaceutical relevance of the resulting formulation, and separately characterized and optimized with respect to in vitro disintegration and dissolution performance.[9,11,12]

5.2 Ezetimibe Rapid Melts and Solid Dispersion

Ezetimibe rapidmelts have been developed using both a sublimation-based direct-compression approach and a solid dispersion route intended primarily to enhance solubility ahead of tablet compression, with in vitro evaluation confirming improved disintegration and dissolution relative to conventional tablets, and dedicated solid-dispersion work demonstrating a marked increase in apparent solubility of the drug when dispersed within a hydrophilic carrier matrix.[6,10,13]

5.3 Simvastatin Rapid Melts and Solid Dispersion

Simvastatin rapidmelts have similarly been developed and evaluated, with a complementary solid dispersion study demonstrating improved solubility of simvastatin when processed with a suitable hydrophilic carrier, supporting the general principle that solubility enhancement upstream of tablet compression, whether by solid dispersion or by sublimation-assisted pore formation, materially improves the dissolution performance achievable in the finished rapid-melt product.[4,7]

Taken together, these formulation studies, together with an earlier general review of rapid-melt dosage form technology and more recent literature on ODT formulation strategy, indicate a consistent pattern across this class of drugs: solubility enhancement (by solid dispersion or particle engineering) and disintegration enhancement (by superdisintegrant selection and, where used, sublimation-based pore formation) act on distinct, complementary rate-limiting steps, and their combined application yields greater improvement in overall drug release than either strategy applied in isolation.[20,21]

6. FORMULATION-PROCESS INTEGRATION CHALLENGES

- Flow and compressibility: solid dispersion granulates and nanocrystal-derived powders often exhibit poor flow relative to free-flowing directly compressible diluents, necessitating careful excipient selection or co-processing to maintain acceptable tablet weight uniformity.

- Preservation of matrix porosity: incorporation of a dense, solubilized drug intermediate can reduce the interconnected pore volume of the compact, partially offsetting the disintegration benefit of the superdisintegrant system; formulators must therefore re-optimize disintegrant type and level for each

solubility-enhanced intermediate rather than assuming performance parity with the unprocessed drug.

• Physical stability of the amorphous state: amorphous solid dispersions are thermodynamically metastable and prone to recrystallization on storage, particularly under elevated humidity, which is a specific concern for ODTs given their inherently higher moisture sensitivity and typically less protective packaging than conventional film-coated tablets.[5]

• Taste masking interactions: several solubility enhancement techniques (solid dispersion, cyclodextrin complexation) can inadvertently increase the rate of drug release in the oral cavity itself, increasing the risk of an unpleasant taste being perceived during the brief oral residence time of the tablet, and requiring taste-masking measures to be re-evaluated for the solubility-enhanced intermediate rather than the parent drug.

7. EVALUATION PARAMETERS FOR SOLUBILIZED-DRUG ODT SYSTEMS

In addition to the standard ODT evaluation parameters (disintegration time, wetting time, friability, hardness, content uniformity), formulations incorporating a solubility-enhanced drug intermediate are typically further characterized using saturation solubility studies (to confirm the magnitude of solubility improvement achieved), differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) to confirm the amorphous or molecularly dispersed state of the drug and to monitor physical stability on storage, and comparative dissolution efficiency or similarity factor (f2) analysis against both the solubility-enhanced intermediate alone and the finished ODT, to quantify the incremental contribution of tablet disintegration to overall release kinetics.[20]

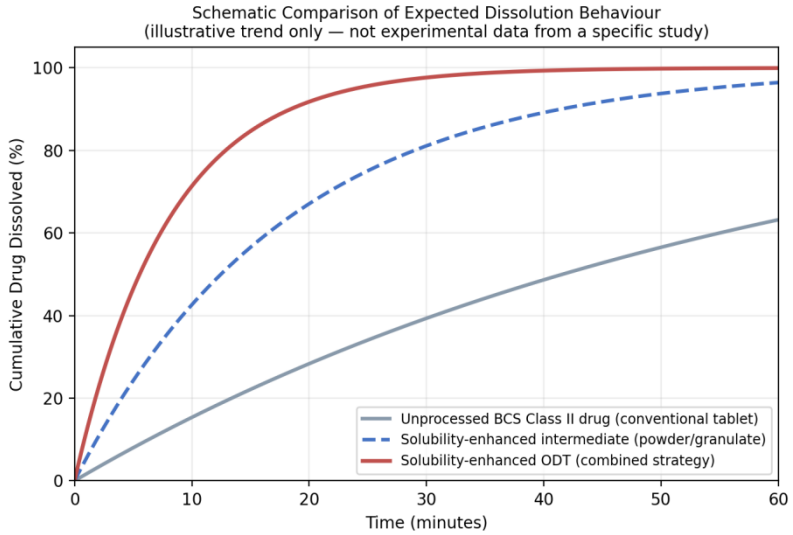

Figure 4. Schematic representation of the expected dissolution advantage conferred by combining solubility enhancement with rapid tablet disintegration, relative to either the unprocessed drug or the solubility-enhanced intermediate alone. Curves are illustrative of the mechanistic rationale described in Sections 3–6 and are not experimental data from a specific cited study. Original schematic prepared by the author; not reproduced from any copyrighted source.

8. REGULATORY CONSIDERATIONS

BCS Class II drugs are not generally eligible for a biopharmaceutics-based biowaiver of in vivo bioequivalence studies, since their absorption is dissolution-rate limited rather than solubility- and permeability-independent as required for Class I biowaiver eligibility.[1] Consequently, formal in vivo bioequivalence data are typically required to support generic or line-extension approval of a solubility-enhanced BCS Class II ODT product, even where in vitro dissolution profiles closely match the reference product. Regulatory dossiers are therefore expected to include a well-justified formulation and process development rationale, ideally within a Quality-by-Design framework, linking the chosen solubility enhancement technique and its critical process parameters to the resulting critical quality attributes of the finished tablet.

9. FUTURE PERSPECTIVES

Continued development in this area is likely to focus on co-processed intermediates that combine solubility enhancement and disintegration-promoting functionality within a single engineered particle, reducing the formulation trade-offs described in Section 6, together with expanded application of nanocrystal[15] and lipid-based/self-emulsifying[18] approaches to BCS Class II actives for which solid dispersion technology alone provides insufficient solubility improvement. Systematic, Quality-by-Design-driven comparison of solubility enhancement techniques across a wider range of BCS Class II drugs would further strengthen the evidence base for rational technique selection in ODT development.

10. CONCLUSION

Solubility enhancement is a necessary, rather than optional, companion to disintegration enhancement

when formulating BCS Class II drugs as orally disintegrating tablets, since rapid tablet breakup alone does not resolve the dissolution-rate limitation intrinsic to these actives. The case studies reviewed here, spanning rosuvastatin, simvastatin, and ezetimibe, together with recently reported nanocrystal- and porogen-based ODT systems for other BCS Class II drugs, demonstrate that combining solid dispersion, nanocrystal engineering, or sublimation-assisted pore formation with appropriately selected superdisintegrant systems yields rapid-melt formulations with meaningfully improved dissolution performance relative to conventionally compressed tablets. Continued refinement of co-processed, multifunctional intermediates is expected to further improve the robustness and manufacturability of this formulation approach.

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