



Why Drug Solubility Matters: Understanding its Central Role in Bioavailability and Successful DS/DP Development

As part of our small molecule technical insights series
Terry Ernest and Jonathan Loughrey explain **Why Drug Solubility Matters** and why choosing the right development partner is critical for project success.

Terry Ernest, Director of Manufacturing Science & Technology:

Terry has spent more than 30 years shaping the world of pharmaceutical development and manufacturing. With hands-on experience across a variety of dosage forms, modified-release formulations, tablets, capsules, oral liquids, and sterile liquids, Terry brings practical insight and deep technical knowledge into every discussion. In 2025, he joined the Board of the Academy of Pharmaceutical Sciences (APS), continuing a passion for driving innovation and advancing human health.

Jonathan Loughrey, Director of Chemical Development:

As a Chartered Chemist with a PhD in organic chemistry, Jonathan brings over 18 years of experience in the pharmaceutical industry across innovators, large pharma and CDMOs, specialising in development from the discovery phase through Phase I/IIa including full synthetic routes, physical sciences, preformulation and advanced formulations for bioavailability enhancement.

Introduction

For organisations outsourcing drug substance (DS) and drug product (DP) development, bioavailability remains one of the most persistent and commercially significant challenges in pharmaceutical development. Many drug candidates demonstrate strong biological activity *in vitro*, yet fail to deliver adequate exposure *in vivo*. In a large proportion of these cases, poor solubility is the root cause.

Understanding why solubility matters, how it influences bioavailability and what development strategies are available to address it, is essential for outsourcers making informed decisions about formulation pathways and service provider selection. The complexity of modern molecules – particularly those in BCS/DCS Classes 2–4 – means that solubility challenges are no longer exceptional but routine. Addressing them effectively requires a structured, data driven approach that integrates DS characterisation with DP design from the earliest stages.

This article explores the scientific basis linking solubility and bioavailability, outlines the formulation and screening strategies used to address poor solubility and highlights the development capabilities outsourcers should evaluate when selecting a partner.



Oral Drug Delivery and the Solubility Challenge

Oral administration remains the most common route for pharmaceuticals due to its convenience, patient acceptance and cost effectiveness. However, oral delivery places significant physicochemical demands on the drug substance. Once administered, a drug must traverse the gastrointestinal (GI) tract, encountering dramatic pH changes, enzymatic environments and absorption barriers.

In the stomach, the acidic environment can enhance the solubility of weakly basic drugs through protonation. As the drug progresses into the duodenum, jejunum and ileum, the pH increases towards neutral. Under these conditions, many molecules revert to a neutral form that exhibits markedly lower solubility. It is often at this point (where absorption primarily occurs) that solubility becomes limiting.

A drug that cannot remain sufficiently dissolved at the site of absorption will not achieve adequate systemic exposure, regardless of its intrinsic potency. As a result, solubility is not merely a formulation inconvenience; it is a determinant of clinical success.

Why Bioavailability Needs to Be Enhanced

From a development and commercial perspective, enhancing bioavailability serves several critical objectives:

- **Achieving dose linear exposure**, which supports predictable pharmacokinetics and robust clinical modelling
- **Reducing inter and intra subject variability**, improving confidence in clinical outcomes
- **Ensuring sufficient exposure** to elicit the desired pharmacological effect
- **Minimising off target toxicity** by enabling lower administered doses
- **Reducing cost of goods**, as less active pharmaceutical ingredient (API) may be required per dose

Different formulation approaches can produce widely varying bioavailability profiles. Comparative pharmacokinetic models demonstrate substantial differences between suspensions, oil solutions and lipid-based systems such as Self-MicroEmulsifying Drug Delivery System (SMEDDS), underscoring the importance of selecting the right platform for a given molecule.

For outsourcers, this highlights a key consideration: **a formulation partner's ability to evaluate and compare multiple bio enhancement strategies is often more important than any single technology offering.**

Solubility, Permeability and the Developability Classification System

Solubility alone does not determine bioavailability. A drug must also permeate the intestinal epithelium. To integrate these two parameters, the Developability Classification System (DCS) is widely used to guide formulation strategy.

The DCS categorises molecules into several classes:

- **Class 1:** High solubility, high permeability – generally straightforward to formulate
- **Class 2a:** Dissolution rate limited molecules, often amenable to particle size reduction
- **Class 2b:** Solubility limited molecules requiring advanced bio enhancement strategies
- **Class 3:** High solubility but poor permeability
- **Class 4:** Poor solubility and poor permeability, representing the greatest challenge

Most modern development candidates fall into Classes 2–4, where standard formulation approaches are insufficient. For outsourcers, understanding where a molecule sits within this framework enables more realistic expectations of development complexity, timelines and cost. It also provides a basis for evaluating whether a service provider has appropriate capabilities.



Translating Solubility Data into Formulation Strategy

A central challenge in development is translating pH dependent solubility data into predictive bioavailability outcomes. Solubility profiles often show steep declines as pH approaches neutrality, mirroring conditions in the intestine. If these profiles are not understood early, formulation strategies may fail late in development.

Effective service providers therefore integrate:

- **Biorelevant solubility testing** (e.g. FaSSIF, simulated gastric fluid)
- **Permeability assessment**, often using in vitro monolayer models
- **Non sink dissolution and biphasic dissolution testing**, to understand precipitation risk and absorption potential

This integrated data set informs whether solubility enhancement alone is sufficient, or whether permeability focused strategies must also be deployed.

Bioavailability Enhancement Strategies

Salt Formation and Cocrystals

Salt screening and cocrystal formation are frequently used to improve aqueous solubility by pairing the API with a pharmaceutically acceptable counter ion. When successful, these approaches can stabilise the ionised form of the drug under near neutral conditions. However, they are not universally applicable and require careful toxicity and stability assessment.

Particle Size Reduction

Micronisation and other particle size reduction techniques increase surface area, improving dissolution rate. This approach is particularly effective for Class 2a molecules, where dissolution – not intrinsic solubility – is the primary limitation. For pharmaceutical and biotechnology companies wishing to outsource, evaluating a partner's control over particle size distribution and downstream handling is critical.

Lipid Based Formulations

Lipid formulations, including oil solutions and liquid filled capsules, can significantly enhance solubility and absorption for lipophilic drugs. These systems often require specialised equipment and expertise in phase behaviour, lipolysis and capsule filling.

Amorphous Solid Dispersions (ASDs)

Amorphous dispersions produced via spray drying or hot melt extrusion encapsulate the drug in a polymeric matrix, maintaining molecular separation and inhibiting crystallisation. When the matrix dissolves, it “drags” the drug into solution, enhancing apparent solubility and maintaining supersaturation.

ASDs are powerful but complex, requiring careful polymer selection, solvent compatibility studies, stability assessment and process optimisation.

Excipient and Polymer Screening: Reducing Risk Early

One of the most effective ways to de risk development is high throughput excipient screening. By testing a wide range of excipients and polymers at defined ratios, developers can rapidly identify systems that meet target dose requirements under biorelevant conditions.

Techniques described in the source include:

- UV/VIS precipitation screening
- Solvent casting followed by biorelevant solubility testing
- Evaluation of hydrogen bonding potential, miscibility and crystallisation risk



For outsourcers, this highlights an important differentiator between providers: **the breadth and depth of their screening capability** and their ability to narrow options efficiently before scale up.



Performance Testing and Stability Considerations

Bio enhanced formulations must demonstrate not only improved solubility but also physical and chemical stability. Characterisation typically includes:

- XRPD to confirm amorphous state
- DSC and modulated DSC for glass transition
- Residual solvent analysis (HPLC, TGA, QNMR)
- Particle size distribution and flowability
- Hygroscopicity assessment via GVS/DVS

Performance testing under non sink conditions and biphasic dissolution provides insight into precipitation risk and permeability enhancement. These data are essential for confident progression into clinical manufacturing.

Integration Across DS and DP Development

Partners which offer fully integrated DS and DP development brings many benefits. Early collaboration between scientists, analysts, pharmacists and engineers enables formulation decisions to be informed by realistic manufacturing constraints and regulatory expectations.

For outsourcers, integration reduces hand off risk, improves knowledge transfer and shortens timelines; particularly when transitioning from development scale to GMP manufacture.



Almac's Expertise in Bioavailability Driven Development

Almac combines DS characterisation, formulation screening, analytical development and GMP manufacturing across bio enhanced platforms including micronisation, spray drying, hot melt extrusion and lipid based dosage forms.

Notably, the integration between Almac's DS and DP services enables:

- Early excipient and polymer selection aligned with downstream manufacturability
- Seamless transfer from small scale development to clinical and commercial production
- Consistent analytical methodologies across development stages

For outsourcers, the key takeaway is not exclusivity, **but the importance of evaluating whether a provider can offer similar integration and continuity.**

Find formulation development service partners at www.pharmaserviceshub.com



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