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ACCELERATING DEVELOPMENT OF POORLY SOLUBLE DRUG CANDIDATES THROUGH QUALITY-BY-DESIGN

THE SOLUBILITY CHALLENGE IN TODAY'S R&D PIPELINES

The pharmaceutical industry is facing a tremendous challenge in its R&D pipelines—the overwhelming prevalence of poorly soluble drug candidates. More than 80% of candidate drugs fall into either the Biopharmaceutics Classification System (BCS) Class II (poor solubility, high permeability) or Class IV (poor solubility, low permeability) categories (Figure 1).[1, 2] Many of these poorly soluble compounds target areas of high unmet medical need, requiring accelerated development timelines to bring these critical therapies to patients faster.

"The formulation and technology platforms we use today are different from the ones we used 10 to 20 years ago," says Klaus Pollinger, group director global product development at Aenova Group. Drug developers need to widen the range of techniques to address solubility challenges presented by new generations of drug candidates. "We must go for a science-based, data-driven approach to formulation," adds Pollinger. In addition, comprehensive preformulation programs that use active pharmaceutical ingredients (APIs) sparingly for technology screening are critical to meeting the challenges of bringing new, poorly soluble drug candidates to clinic.

FORMULATION STRATEGIES TO ADDRESS SOLUBILITY CHALLENGES

Standard API formulation approaches include techniques such as micronization and particle design (e.g., dry and wet milling or micro/nanoparticle formation) and excipient- or additive-based formulations (e.g., solubilization or complexation).

Many new drug candidates have such low aqueous solubility that even reducing particle size through micronization or adding solubilizing excipients is not enough to achieve good bioavailability at an optimal dose. In such cases, more advanced technologies are necessary to achieve the desired therapeutic outcomes.

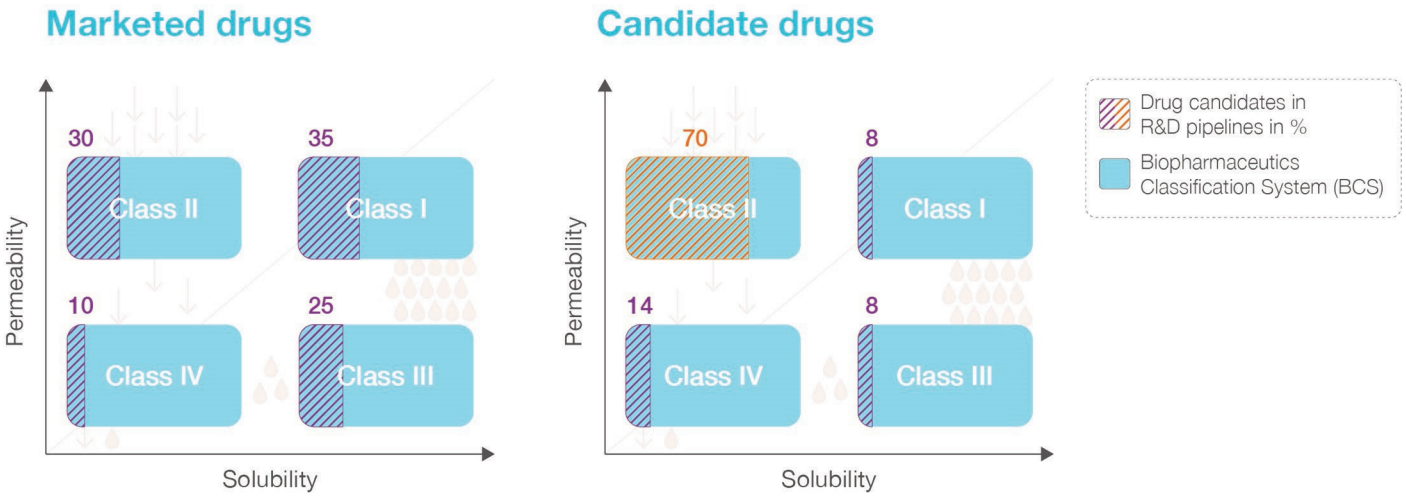

Figure 1: Poorly soluble drug candidates dominate R&D pipelines (right). Classes II (low solubility, high permeability) and IV (low solubility, low permeability) together represent over 80% of drug candidates, while classes I (high solubility, high permeability) and III (high solubility, low permeability) each constitute around 8%. Class II (yellow shading) alone represents about 70% of drug candidates. In contrast, a much smaller percentage of approved drugs are poorly soluble (left).

Credit: Aenova

Two frequently applied approaches to improve solubility and bioavailability are lipid-based formulations and amorphous solid dispersions.

- *Lipid-based formulations:* This approach involves dissolving poorly soluble APIs in a lipid vehicle, often combined with surfactants and cosolvents like propylene glycol, ethanol, polyethylene glycol (PEG), and glycerol, and are typically filled into soft gelatin capsules. This approach enhances solubility by aiding the dispersion and absorption of the API in the intestinal tract. Lipid-based formulations are particularly effective for poorly soluble small molecules as well as peptides and polypeptides.

- *Amorphous solid dispersions:* These formulations embed the API in a polymer matrix, converting the compound from a crystalline to an amorphous state, thereby enhancing its solubility and bioavailability. Technologies like hot melt extrusion, spray drying, and solvent evaporation are commonly used to create amorphous solid dispersions. This approach is scalable and economically viable, making it suitable for a range of poorly soluble small molecules. However, the process may involve extensive heat, which could affect the stability of some APIs or require careful handling of organic solvents.

"The Aenova team has decades of experience in applying these technologies to meet the formulation demands of today's oral solid dosage forms," says George Shlieout, head of manufacturing science and technology at Aenova Group. Choosing the right formulation strategy for a drug candidate is essential for successful development, and it requires a thorough understanding of the API's properties and the strengths and limitations of each technology.

A QUALITY-BY-DESIGN APPROACH TO FORMULATION

Quality-by-Design (QbD) is a structured pharmaceutical development approach that ensures quality is built into the product from the beginning by thoroughly understanding product properties and process controls.[3] This approach emphasizes continuous improvement and regulatory alignment to facilitate product safety and efficacy.

QbD is particularly valuable in the formulation development of poorly soluble drugs, helping developers identify key parameters influencing solubility and bioavailability. Aenova scientists integrate QbD throughout their formulation strategy, providing data-driven solutions that align with current regulatory standards (Figure 2).

Preformulation

The process starts with a thorough characterization of the API's physical and chemical properties. Pollinger explains, "We want to understand the API, its physical chemistry— and we have established protocols that help us do that." Aenova scientists then leverage theoretical models and computer-based screening to narrow down the most appropriate formulation technology for a given API.

This in-silico evaluation is followed by an experimental screening of solvents, polymers, and surfactants at microgram and milligram scales, which allows Aenova scientists to minimize API usage. Small-scale experimental screening is of high value, especially during the candidate selection phase of a new chemical entity, where API availability is often limited.

Formulation development

"Based on the preformulation data, we select the appropriate formulation platform, be it lipid-based or amorphous solid dispersion," says Pollinger. Before working with larger quantities of an API, Aenova scientists first simulate the selected formulation approach with simpler tools that require less material (often only a few milligrams). For example, they can mimic hot melt extrusion using tools like vacuum compression molding.[4,5] Similarly, they simulate spray drying by dissolving the API and polymer support in a common organic solvent.

In these trials, the team evaluates the API's solubility and how it behaves within the simulated formulation system, among other physical properties.

Process development

The final step involves optimizing the manufacturing process, such as hot melt extrusion or spray drying, at the pilot lab scale. Understanding the critical process parameters (CPP) and the related critical quality attributes (CQAs) ensures a seamless transition from development to commercial-scale production.

"Our goal is to deliver a formulation that succeeds on the first attempt, reducing the risk of discovering issues such as poor absorption or bioavailability during first-in-human trials," explains Shlieout. "We focus on establishing

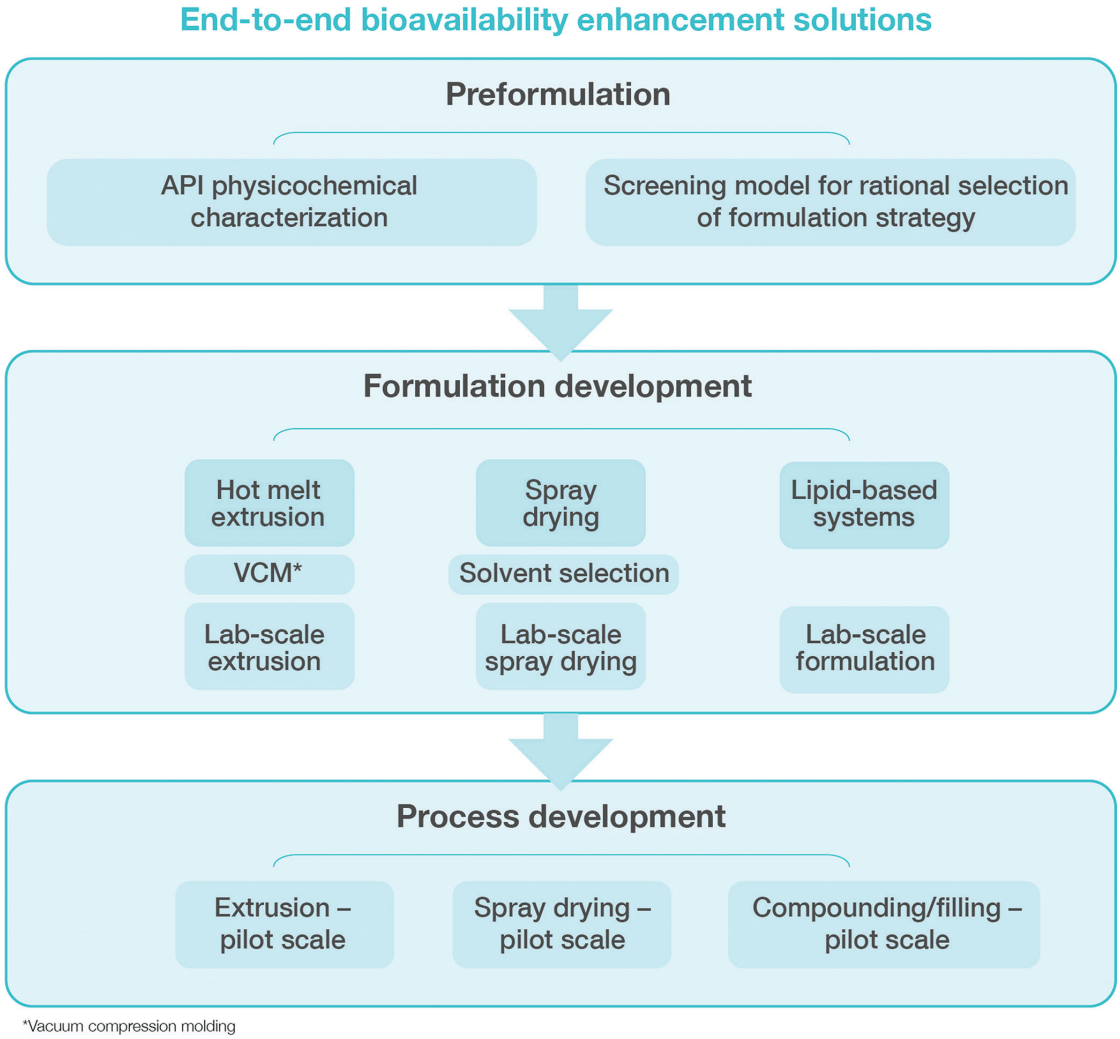

Figure 2: Aenova's end-to-end bioavailability enhancement solutions.

Credit: Aenova

proof-of-principle to ensure confidence in the formulation as it moves into clinical development." By incorporating a data-driven QbD approach, developers can mitigate the cost and time implications of late-stage setbacks.

ACCELERATING TIME-TO-CLINIC AND TIME-TO-MARKET

A comprehensive QbD approach to formulation development, like the one designed by Aenova experts, enables pharmaceutical companies to accelerate their drug candidates' journey from the preclinical stage to the clinic and, ultimately, to the market.

Early development

At the preclinical stage, selecting the most appropriate formulation based on empirical evidence is crucial. Shlieout says, "The best approach is when we have an early understanding of the API and its characteristics. Then we can find the best [formulation] technology for the API. We strive to get it right from the start."

A PHASE 1 STUDY DEMONSTRATING IMPROVED SOLUBILITY AND ENHANCED BIOAVAILABILITY WITH HOT MELT EXTRUSION

Several studies have been conducted to establish the bioavailability improvements enabled by hot melt extrusion. The study referenced here is a compelling example of the technology's potential.

Study overview

This first-in-human, single-dose, open-label Phase 1 study evaluated the pharmacokinetic profile of a hot melt extrusion formulation (compressed tablet) compared to a standard formulation (direct compression tablet). The study enrolled 13 adult male and female participants in a randomized crossover design with two arms: one testing standard formulation in participants who had a meal beforehand (fed) and the other testing hot melt extrusion tablet in both fed and fasted participants. The primary objective was to assess the effect of the hot melt extrusion technology on drug absorption and bioavailability.

Key findings

- Improved pharmacokinetic performance: The hot melt extrusion formulation showed a >40% increase in maximum plasma concentration (C_{max}) and in the area under the curve (AUC) compared to the standard formulation, indicating significantly enhanced bioavailability (Figure 3).

- Minimized food effects: The hot melt extrusion formulation exhibited consistent bioavailability regardless of food intake (fasted vs fed) (Figure 3).

Conclusion

The results showed a marked improvement in plasma concentration with the hot melt extrusion formulation, demonstrating its ability to enhance bioavailability and minimize the effect of food. Enhanced bioavailability could potentially reduce dose requirements, improving the compound's safety profile.[6]

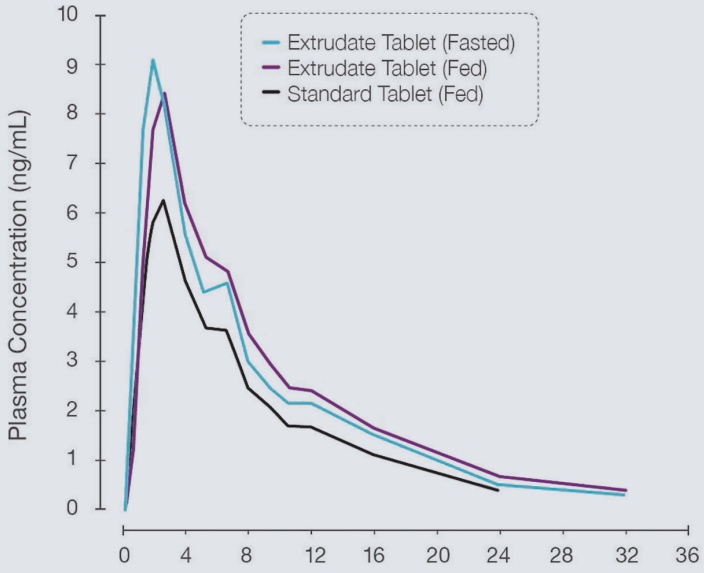

Figure 3: Pharmacokinetic profile of a hot melt extrusion formulation compared to a standard formulation.

Source: George Shlieout et al., "New Aspects and Challenges in modern Solid Dosage Forms Development and processing" (webinar series organized by Pozlab Ltd. and Applied Manufacturing Science Ltd., May–June, 2022).

Aenova scientists rapidly screen and select the optimal formulation strategy for each API, minimizing the risk of bioavailability challenges at the preclinical or later stages of development. By entering preclinical studies with an optimal formulation approach for a given API, pharmaceutical companies can optimize their preclinical safety studies and lay a solid foundation for successful clinical development.

Clinical development

Transitioning from API development to scaled production for clinical testing can be time-consuming and introduce risks. To simplify that transition, Aenova scientists use the same equipment and personnel to prepare technical and clinical batches. Pollinger explains, "From our experience, we know that having the same project team, the same project manager, same formulation scientists, same analytical scientists, and even the same operators and technicians can greatly benefit our customers." This continuity offers drug developers more confidence that the formulation and process used during the early development stage will be successfully translated to the clinical stage, ultimately reducing the time it takes innovative therapies to reach patients.

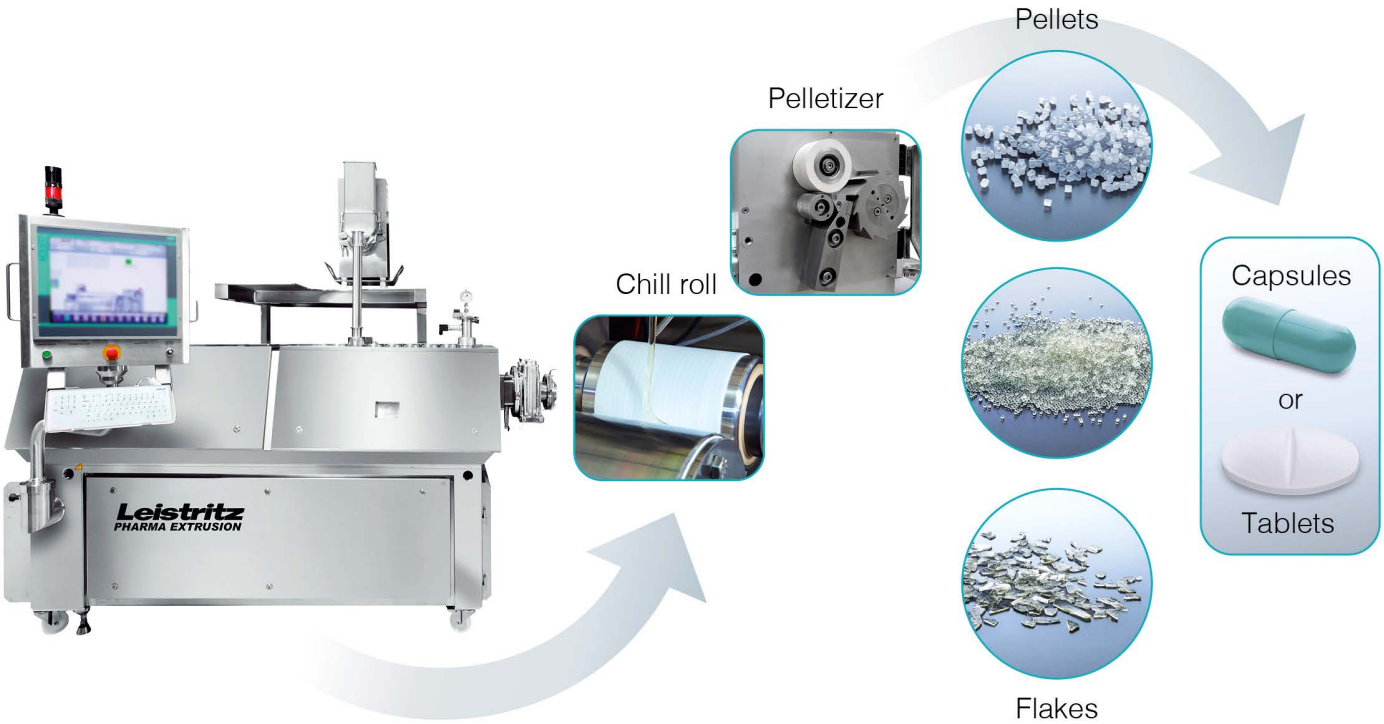

Figure 4. Choosing the right formulation and technology for a drug candidate can expedite its journey from the lab to the clinic. The HME process includes extrusion, pelletization, and preparation of the final drug product.

Credits: Leistritz©, Aenova

Commercialization

Having end-to-end capabilities beyond candidate selection, early development, and clinical development is crucial for the reliable supply of the final drug product with optimized solubility profiles. "Aenova offers integrated product development, and this is the preferred option for the majority of the companies we work with," says Shlieout. "We will be able to serve them through all development stages to commercialization."

Additionally, Aenova's formulation development platform can bring differentiation to established generic drug products by improving their solubility and safety profiles. "It's also possible to work with generics to reduce the API content, which will improve the safety profile," Shlieout notes.

By integrating advanced formulation technologies and maintaining continuity across development and commercialization stages, poorly soluble APIs can be optimized for therapeutic benefit. This holistic approach not only accelerates the drug development timeline but also enhances the quality and safety of the final drug products, enabling pharmaceutical companies to address the unmet needs of patients more efficiently. Aenova's end-to-end formulation development capabilities, built on QbD principles, address critical solubility and bioavailability challenges that dominate today's pharmaceutical R&D pipelines.

ABOUT AENOVA GROUP:

The Aenova Group is a leading global contract development and manufacturing service provider for the pharmaceutical and healthcare industries. Aenova develops, produces, and packages all common dosage forms, product groups, and active ingredient classes from pharmaceuticals to dietary supplements for human and animal health: solid, semisolid and liquid, sterile and nonsterile, high and low dose, OEB 1 to 5 (occupational exposure band). Four thousand employees at 14 sites in Europe and the US contribute to the success of the Aenova Group. Learn more at www.aenova-group.com.

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