Q&A with Ardena Experts

From concept to commercialization:

A CDMO's insight on amorphous solid dispersions

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Nearly 90 % of new chemical entities (NCEs) in development have inadequate aqueous solubility and bioavailability properties, critical for their efficacy and commercialization. Over the past two decades, there has therefore been a substantial rise in the adoption of amorphous solid dispersion (ASD) and amorphous APIs as enabling technologies by pharmaceutical companies seeking to tackle these inadequacies (see Figure 1). To shed some light on why, when, and how to exploit the amorphous state of active pharmaceutical ingredients (APIs), we ask our formulation experts Oluwatomide Adeoye, Formulation Scientist, and Timothy Pas, Group Leader - Formulation Development and Production at Ardena, for their qualified opinion on the advantages, challenges, and strategies for utilizing ASD technology in early drug development through regulatory approval and commercialization.

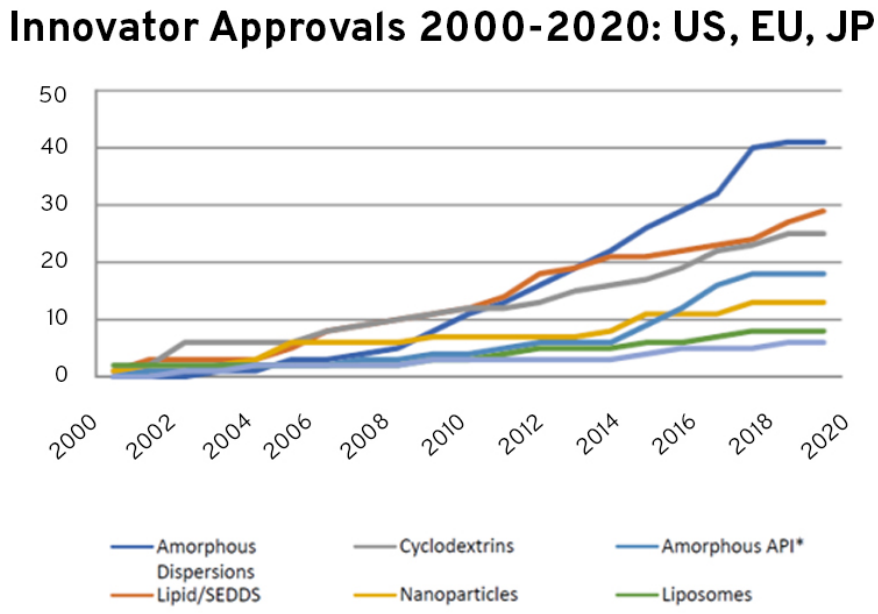

Figure 1: Enabling solubilization technologies used on approved marketed product from 2000 to 2020.

* Drug substance formulated as pure amorphous form instead of ASD.
Source: Bilgili et al, 2021, Pharmaceutics (13(10): 1682).

Why would you recommend companies to explore the amorphous state for their poorly soluble NCEs?

Timothy

Since the turn of the millennium, new and very potent (in-vitro) lead molecules have been identified by the implementation of combinatorial chemistry and high throughput screening. However, their aqueous solubility, which is still the first hurdle when it comes to oral delivery, has been neglected. Thus, many of these NCEs are incapable of becoming orally bioavailable without intervention. Hence, formulators around the globe have searched for enabling technologies of which the discovery of ASDs represents a very strong tool in making poorly soluble NCEs more orally bioavailable. In ASDs, a poorly soluble drug is molecularly dispersed in an inert polymeric matrix to create a so-called glass solution with improved solubility, dissolution rate, stabilization of the supersaturated state, enhanced bioavailability, and ultimately efficacy. In essence, these factors contribute to making ASDs a very powerful tool that can enable poorly soluble NCE to become the next blockbuster molecule.

Why would you consider ASDs as the technology of choice for a new chemical entity (NCE) to overcome poor solubility?

Oluwatomide

Compared to other solubility and oral bioavailability enhancing technologies, a higher number of innovative NCEs utilizing ASD technology have received regulatory approval over the past two decades. Due to their ability to achieve and maintain supersaturation for a certain duration, ASDs produce a substantially higher apparent water solubility, faster dissolution, higher membrane flux and, consequently, enhanced oral bioavailability when administered to patients. This renders them a very valuable strategy to bring poorly soluble compounds to the market. Nevertheless, the decision to use this technology still depends on a thorough evaluation and understanding of the biopharmaceutical aspects of the concerned NCE.

What biopharmaceutical aspects are you referring to?

Oluwatomide

Since each NCE is defined by its own unique set of physicochemical properties (e.g., LogP, melting point, pH-dependent solubility behaviour, etc.), ASD development does not always represent the best strategy for developing a molecule. Sometimes lipid-based formulations or nanosuspensions might be more suitable. Hence, it is key to identify this at an early stage.

For ASDs it is very important to check whether the physicochemical properties of the NCE (enthalpy relaxation, glass transition and melting temperature, etc.) favor the amorphous form. What is the intended quality target product profile? Can ASD technology support the intended dose of the NCE? For instance, most of the currently marketed ASDs contain drug loads (less than or) equal to 30 % w/w.

If the intended dose of the NCE is (too) high, it may be impossible to formulate the API as powder-in-capsule, which is usually preferred during phase I and/or phase II clinical trials. Even if tablet development is chosen, the pill mass and/or pill burden may still present significant problems for commercial viability. Hence, it remains important to have some subject matter experts on ASD technology on board to define a fit-for-purpose technology for an NCE.

What is the ideal polymer or carrier to be included in an ASD and how do you identify it?

Timothy

In ASDs, the crystal lattice of the concerning API is de facto "broken" when it is molecularly dispersed in a suitable polymer. Because an amorphous API by itself is usually thermodynamically unstable, the primary consideration in choosing a polymer matrix for ASD development is its ability to prevent the recrystallization of the dispersed API in the solid state. Since this ability is API concentration dependent, the ideal polymer should also maintain high doses of the API in the amorphous form which translates into reduced pill burdens.

Since ASDs are meant to generate supersaturated solutions, another important consideration is the ability of the polymer matrix to prevent API recrystallization upon dissolution within the gastrointestinal media for the timescales required for optimal oral absorption and bioavailability. In addition, the final selected polymer should also be inert.

What are the main technologies for manufacturing ASDs?

Oluwatomide

Solvent evaporation via spray drying and thermal based methods such as hot melt extrusion (HME) are the two leading technologies for industrial-scale manufacturing of ASDs. Of course, many more technologies exist, like cryomilling, freeze drying, electro spraying, electrospinning, spray congealing or supercritical carbon dioxide impregnation. However, they are currently less viable for commercial manufacturing. Of the two main technologies, spray drying is particularly useful for quick screening in early drug development where the quantity of API is low, as well as for thermolabile compounds. It is important to note that the choice of manufacturing technology and processing variables can affect the physical and functional properties of the ASDs.

What are the main challenges of developing ASDs for early development?

Timothy

The main challenge involves finding the ideal polymer that meets all the requirements for a clinically effective and commercially viable ASD. Considering most pharmaceutical and biotech clients prefer polymers already approved by regulatory agencies to avoid excipient toxicity studies, there is sometimes a limited number of excipients applicable to a specific API. Another challenge is that speed is often a priority in early development for most companies, which is driven by their investors. This can limit the time requirement for generating detailed data in early development. At Ardena, we like to be focused and fast and have created a strategy for finding a perfect equilibrium between early developments costs and fast clinical translation.

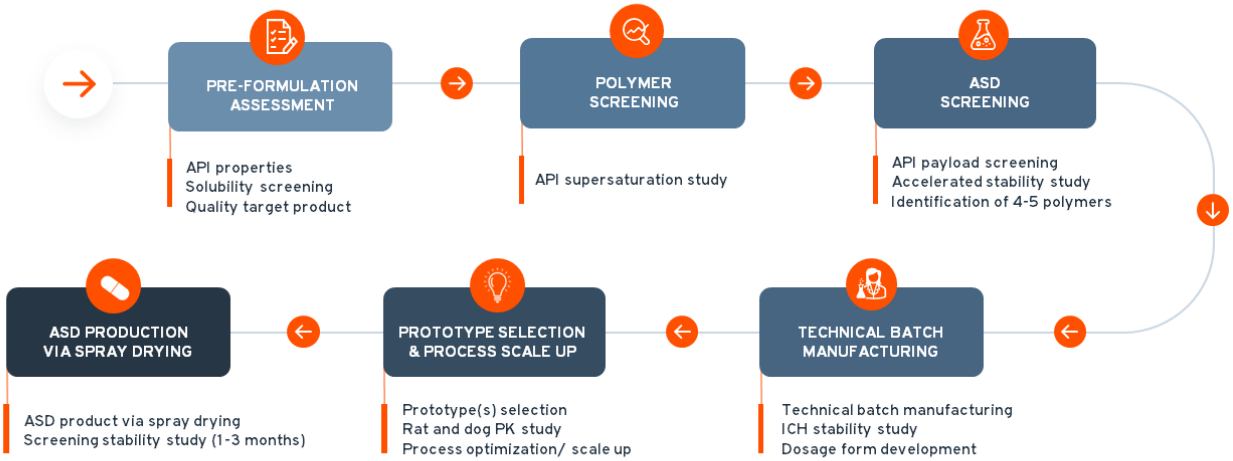

Figure 2: Amorphous solid dispersion development workflow

Navigating you through drug development