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Nanoformed API: A Superior Alternative to Solid Dispersions

Cutting-edge nanotechnology is now emerging, with strong clinical evidence, as an alternative to amorphous solid dispersion (ASD), able to not only address bioavailability challenges but also deliver higher drug loads in much more patient-friendly formats with fewer and smaller pills and easier regimens.

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Estimates suggest that fewer than one in twenty potential drug candidates progress through preclinical studies to a positive Phase 3 outcome, with oncology drugs suffering from the highest rate of attrition.[1] A significant contributor to the number of failed programs is a lack of efficacy caused by poor drug bioavailability.

Poor aqueous solubility of drugs is a challenge to drug delivery, bioavailability, and absorption. It is occasionally spoken about as an "unwritten rule" in drug product development.[2]

Pharmaceutically active molecules with low solubility convey a higher risk of failure for drug innovation and development. Pharmacokinetics, pharmacodynamics, and several other parameters, such as drug distribution, protein binding and absorption, are majorly affected by their solubility.[3]

Amplifying the challenge to developers, there has been a significant increase in the percentage of new chemical entities (NCEs) in the pipeline that display poor physicochemical and biopharmaceutical properties, falling into biopharmaceutics classification system (BCS) classes II and IV. This has undoubtedly played a significant role in attributing to those high failure rates.[4]

Table 1 – The increased proportion of new chemical entities (NCEs) in BCS classes II & IV. 2006 vs. 2019.

2006: 30-35% in Top 200 **Class I** High Solubility High Permeability **2019:** 5-10% in NCEs	**2006: 30-35% in Top 200** **Class II** Low Solubility High Permeability **2019: 60-70% in NCEs**
2006: 25-30% in Top 200 **Class III** High Solubility Low Permeability **2019:** 5-10% in NCEs	**2006: 5% in Top 200** **Class IV** Low Solubility Low Permeability **2019: 10-20% in NCEs**

The latest generation of small molecule drugs exhibit increased molecular weights and lipophilicity compared to those discovered in the 1990s and earlier.[5,6] Today's novel, complex molecules present not only biopharmaceutical challenges such as poor solubility and bioavailability, but also handling and manufacturing challenges. Less than 30% of new chemical entities in drug development pipelines are readily bioavailable when administered orally.[7] When orally dosed, they are less likely to achieve sufficient exposure (efficacy) and are likely to exhibit higher variability and food effects.

Amplifying the impact of such failures, sub-optimal performance may not become apparent until relatively late in a development program, when attempts are made to scale production for larger clinical trials. To avoid escalating the overall time and cost of a project, or even seeing the program fail altogether, it is therefore important that developers conduct a comprehensive assessment of a drug molecule's solid-state properties and give careful regard to the selection of appropriate solubility-enhancing technologies.

Typical Drug Formulation Strategies

Overcoming poor solubility may be achieved through modifications to the crystal form, and solid-state techniques utilized for solubility enhancement including the formation of salts, polymorphic or amorphous forms, and co-crystals. Each technique has specific advantages and, in some cases, disadvantages that may prevent its successful use.[8]

For instance, turning a crystalline API, which most poorly soluble APIs tend to be, into an amorphous form using a carrier that is usually a polymer. This results in the formation of amorphous, high-energy states that enhance solubility. This can be achieved through various techniques such as spray-drying and hot-melt extrusion and is referred to as an Amorphous Solid Dispersion (ASD).[9]

It is important to note that given the broad nature of poorly soluble APIs, no single technique has universal application.[10] Therefore, the choice of technique depends on the specific properties of the API and the desired characteristics of the final drug product.

When Salts & Micronized Formulations Fail

When traditional formulation techniques such as the use of salts and micronized formulations fail to enhance solubility and bioavailability, formulators often turn to advanced formulation strategies, including amorphous solid dispersions (ASD).

Amorphous solid dispersion techniques can be used to scatter API in amorphous state within a hydrophilic polymer matrix. Due to the formulation's higher energy and lack of a fixed lattice structure this can lead to an increase in the apparent solubility and dissolution rate and consequently, the bioavailability of the active substance.

The hydrophilic polymer matrix in ASDs serves multiple purposes. It can prevent the drug from reverting back to its less soluble crystalline form, enhance the wettability of the drug, and can also interact with the gastrointestinal fluids to aid in its dissolution.

While ASDs are a proven approach to tackle solubility and bioavailability challenges in drug formulation, their successful development requires a deep understanding of both the drug and the polymer, as well as the interactions between them.

"When salts and micronized formulations fail, amorphous solid dispersions are generally selected as advanced formulations to tackle poor solubility and bioavailability. However, developing one may come at the cost of sacrificing drug load."

Beyond ASDs

Spray dried and melt extruded ASDs have enabled the druggability of dozens of APIs, however, their development often comes with compromises to environmental and patient considerations.

Nanoform's **controlled expansion of supercritical solutions (CESS®)** technology is an alternative to amorphous solid dispersions.

The CESS method of recrystallization works by controlling the solubility of an API in supercritical carbon dioxide ($scCO_2$), enabling crystallization or precipitation at a range of temperatures and pressures. The CESS process provides a significant improvement over previous supercritical technologies due to the reproducible controlled nucleation and particle formation enabled by controlled mass transfer, flow and pressure reduction.

The use of $scCO_2$ facilitates a green particle engineering process with pharmaceutical CO_2 that is free from excipients and organic solvents.

The technology offers several advantages over ASDs:

Smaller or fewer pills

Two thirds of marketed solid dispersion intermediates are at least two-thirds excipients. This can translate to extreme pill burdens, or may even render the development unviable because it is impossible to achieve the dose loading required for the final drug product. A prime example is Carogra® (carotegrast

methyl formulated into an ASD), which is approved in Japan for ulcerative colitis with adult daily dosing of 2,880 mg, representing 24 pills a day. To make things worse, Carogra is to be taken after a meal.

As the CESS technology does not rely on the use of polymers, it is possible to develop pills that are smaller than their ASD counterparts, and/or reduce pill burden through high drug loading in nanocrystals and nanocrystalline intermediates.

Improved long term storage stability

Most solid dispersions are not thermodynamically stable, thus, the API will tend to aggregate and recrystallize within the polymer matrix leading to impaired *in vivo* performance.[11]

Nanocrystalline APIs produced by CESS exhibit excellent long term physical and chemical stability, warranting longer shelf life.

Better processing characteristics

Handling and downstream processing properties of drug product intermediates can be improved using the CESS technology.

Typically, solid dispersion intermediates contain upwards of 75 percent water-soluble, hygroscopic polymers. These intermediates are prone to absorb water, yielding tacky, unprocessable materials. Moreover, the water absorbed plasticizes the systems posing further stability challenges.[12,13]

Nanoform's CESS process produces neat API nanocrystals that are non-hygroscopic, alleviating the need for humidity controls and enabling simple blending and processing steps.

Free from volatile organic solvents

At least 24 marketed ASDs are produced by spray drying method. In general, methanol, acetone and dichloromethane solvents are used in the process posing health, environment and safety hazards. Dichloromethane has been banned by the U.S. Environmental Protection Agency (US EPA) since April 2024, with the solvent being phase out in the next two years.[14]

The CESS technology uses recycled carbon dioxide in supercritical state ($scCO_2$) as a solvent. The dry ice formed at the end of the process sublimates to yield an API dry powder with no residual solvents.

Case Study: Nanocrystalline Enzalutamide

Enzalutamide, marketed as Xtandi®[15], is the number one prescribed androgen receptor inhibitor.[16] It was first approved to treat prostate cancer by the U.S. Food and Drug Administration (FDA) in 2012, and by the European Medicines Agency (EMA) in 2013. Enzalutamide is a poorly soluble compound, and so it was originally developed and marketed as a lipid-based soft capsule (Xtandi capsule), and then as a spray dried amorphous solid dispersion-based formulation, launched as Xtandi tablet. The ASD exhibits a good pharmacokinetic (PK) profile, but is administered as 4 x 40 mg, or 2 x 80 mg tablets, representing a significant pill burden to prostate cancer patients, for whom tablet-burden and dysphagia are well-documented challenges.

Together with its ONConcept® Consortium partners: Bluepharma – Indústria Farmacêutica, SA; Helm AG; and Welding GmbH & Co. KG, Nanoform has developed a nanoenzalutamide tablet formulation that reduces tablet burden to a single 160mg tablet per day regimen, which may be preferable for patients in need of reducing their total number of daily pills.

In an *in vivo* rodent study, the nanocrystalline formulations matched the performance of the marketed amorphous solid dispersion. Moreover, in a comparative bioavailability study in humans, the 160 mg tablet performed similarly to the marketed ASD.

	Group	AUC0-last (h·µg/ml)	Cmax (µg/ml)
—	ASD in suspension	208 ± 47.4	12.1 ± 2.3
---	Nanocrystals 1	189 ± 22.4	10.5 ± 1.5
—	Nanocrystals 2	193 ± 35.2	9.89 ± 1.0

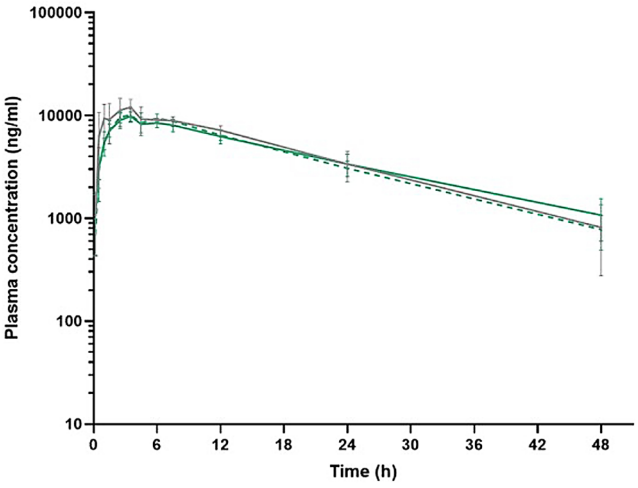

Figure 1 – Enzalutamide plasma concentrations after oral administration of suspended Xtandi and nanocrystals

The consortium partners anticipate executing licensing deals and commercialising nanoenzalutamide.

Summary

Whilst solid dispersions prepared by spray drying, hot melt extrusion and other techniques are on the market as proven formulations to tackle solubility and bioavailability issues, nanoforming by CESS can provide a better alternative.

CESS nanocrystals can match the *in vivo* performance of ASDs, and the process avoids organic solvents and eliminates residual solvents from the drug product. The nanocrystal-based final formulations usually exhibit excellent physical and chemical stability and have much higher drug loadings compared to most of the ASDs, translating to smaller pills and lower pill burden.

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[15] Xtandi® is a registered trademark of Astellas Pharma, Inc.

[16] Source: xtandi.com

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