WHITEPAPER

How to Overcome Solubility Challenges by Applying Amorphous Solid Dispersion: An End-to-End Solution

PRESENTED BY:

Syngene

PUBLISHED BY:

FIERCE Pharma

No matter how much potential a molecule exhibits for treating a disease or condition, if it doesn't reach its biological destination, efficacy is weakened. A number of factors influence bioavailability, including the extent of absorption in the gastrointestinal tract, the type of formulation and even the physical characteristics of the patient.[1]

Poor solubility is among the primary causes of low bioavailability for orally administered drugs.[2] Because over 85% of pharmaceuticals are administered orally, improving solubility is a top priority among drug developers. A few approaches for improving either water solubility or dissolution rate include chemical modifications such as using salts, co-crystals or prodrugs, as well as physical modifications such as complexation and nanocrystals.[2]

Another strategy—converting drug products to amorphous form—has gained popularity in recent years for its potential to overcome the oral absorption issues that slow drug development. About 30% of the marketed products that require solubility enhancement use amorphous solid dispersion (ASD), making it the most frequently used technology from 2000 to 2020.[2]

Converting a crystalline form of a drug to an ASD form has improved bioavailability and solubility for many products; to date, the FDA has approved 29 drugs based on ASDs.[3] However, because amorphous forms are thermodynamically unstable, the materials and technologies that enable ASD formation, the subsequent dosage form design and the methods of characterization of these systems all play a critical role in defining quality, stability, processability and performance.

This white paper describes a successful approach for preparing, screening, characterizing and dosing ASDs in preclinical and early clinical development.

Amorphous solid dispersions (ASDs) are a popular mechanism for enhancing the solubility and bioavailability of drugs that are poorly soluble in water.

The Growing Prevalence of ASD Formulations

Amorphous solid dispersions (ASDs) are a popular mechanism for enhancing the solubility and bioavailability of drugs that are poorly soluble in water. Drugs that treat cancer, cystic fibrosis and organ transplant rejection, to name a few, use ASDs in their formulation to help overcome the molecules' solubility limitations.[4]

In ASDs, the drug homogenously dispersed in a carrier in an amorphous state. The amorphous form of API enhances solubility because it lacks crystalline lattices and has an inherently disordered arrangement. Apart from improving the solubility, ASDs enhance the wettability, rate of dissolution and supersaturation of drugs, thereby promoting the membrane flux, ultimately leading to improved oral bioavailability.[3]

As formulation strategies improved, ASD forms have become more widely studied in early-phase drug development. “In preclinical studies, ASD is a valuable tool for us to get the desired therapeutic margins needed to determine safe and effective dose range,” said Shaik Shahe Mahammad, senior team leader at Syngene, a global contract research, development and manufacturing organization headquartered in Bangalore, India.

Strengths and Limitations of ASD

ASD is an effective method for overcoming solubility and bioavailability challenges of poorly water-soluble compounds. As with any formulation strategy, ASD has its advantages and disadvantages.

Strengths

- An ASD product maintains supersaturation in the gastrointestinal (GI) tract, improving bioavailability.[5]
- The products tend to be well tolerated *in vivo*.[6]
- Scientists can formulate ASDs using well-characterized, off-the-shelf excipients, processes, and screening methods.
- Processes typically used to produce ASDs, including spray-drying and melt-extrusion, are well established and scalable to commercial levels.

Limitations

- ASDs tend to be thermodynamically unstable.
- Solid-state physical instabilities associated with ASDs include amorphous–amorphous phase separation (AAPS) and/or conversion of the amorphous drug to a crystalline form (crystallization), both of which negate the solubility advantage.[6]

Methods and technologies used to develop ASDs influence instability. For this and other reasons, an understanding of ASD preparation and characterization, as well as an understanding of the chemistry underlying these products, is essential for successful early development. “We need to assess the physical stability of the ASD in question,” said Shahe Mahammad. “It’s important to select a right polymer and right methodology to produce these products. They have a tendency to pick the moisture, and need an adequate packing configuration to ensure its native form on storage”.

As with any formulation strategy, **ASD has its advantages and disadvantages**.

Early and Preclinical ASD Development

Spray-drying and hot-melt extrusion account for about 60% of marketed drug products.[2]

During the spray-drying method, the drug and polymer are dissolved or suspended in a common solvent or solvent mixture. It's then dried over a stream of controlled heated inert gas to remove the solvent. Rapid evaporation of solvent causes a sudden rise in viscosity which leads to the entrapment of drug molecules within the polymer matrix.[2]

Here, we describe Syngene's criteria and process for developing and manufacturing ASD products using a spray-drying process.

Excipient and Polymer Selection Criteria

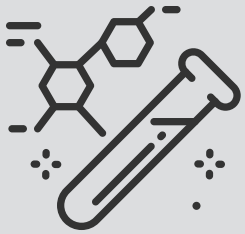
Excipient selection for ASD depends on several factors, including:

- The ability of the polymer/s to form miscible molecular solid dispersion with drug, and physical/chemical stability of solid dispersion
- Excipients (solubilizers, hydrophilic polymers, plasticizers, as required) needed to meet the target product requirement
- Polymers with higher glass transition temperature with lesser hygroscopicity is preferred.
- Maximum permissible limit for excipients available for human adult administration per the FDA's Inactive Ingredient Database (IIG), as well as for respective animal species to be used in Good Laboratory Practice (GLP) preclinical toxicity studies
- Selection of safer solvent/solvent mixtures as per ICH class-2 and -3 for spray-dried dispersions

Polymers are selected based on their ability to provide a stable amorphous solid dispersion of drug. Polymers/solubilizers such as PVPK30, PVP K90, Copovidone, hydroxypropyl beta cyclodextrin, HPMC-AS, HPC and Eudragit copolymers can be evaluated. Plasticizers such as glyceryl monostearate (GMS) and tributyl citrate (TBC), polyethylene glycol and triethyl citrate can be evaluated as required.

Theoretical Miscibility Assessment

Theoretical miscibility of drug and polymers can be evaluated using the group contribution method of Hansen's solubility parameter. The difference between the solubility parameters of drug (δ_D) and polymer (δ_P) can be a preliminary selection criteria, where δ D-P ≤7MPa was identified as a cutoff for miscibility, whereas $\delta_{D\text{-}P} > 10$MPa can be expected to indicate immiscibility.[7]



Spray-drying and hot-melt extrusion account for about **60% of marketed drug products**.[2]

In-situ amorphonisation by DSC/mDSC

Heat-cool-heat experiments followed by a Modulated DSC (mDSC) run should be performed on the drug with various polymers. Considerations include:

- An endotherm (sharper) indicates melting point of the compound.
- Glass transition temperature (Tg) indicates the amorphous form of the solid dispersion
- A single Tg: The higher the Tg, the higher the physical stability of ASD.
- Multiple Tg values indicate the heterogeneity or biphasic amorphous solid dispersion formation, that infers that there is a chance of phase separation or lack of miscibility between the drug/compound and the polymer that can further result in recrystallisation upon storage.[8]

Melting point depression is one of the indicators to assess the drug-polymer miscibility. Melting point of the drug (Tm) should be higher than the glass transition temperature of the polymer (Tg) to observe such depression in melting point in the presence of the polymer.[8]

Generation and evaluation

The polymers selected based on preliminary miscibility assessment should be selected for feasibility trials. We prepare up to eight prototypes of ASDs using a rotary evaporation technique. Spray-drying is used as required for feasibility trials and informal stability at a 1:3 drug-to-polymer ratio. Other drug loads (1:1 and 1:2) are evaluated with the respective polymers only when 1:3 ASD trials show amorphous nature, as confirmed by powder X-ray diffraction.

ASDs are characterized using the following techniques:

- Weight loss using thermogravimetric analysis covering the degradation/decomposition
- Characterization of Tg by differential scanning calorimeter (mDSC/DSC)
- Total water content by Karl Fisher Titration (KFT)
- Powder X-ray diffraction (PXRD) pattern
- Solubility studies in biorelevant media, e.g., solubility in simulated gastric fluid (SGF) and transfer to Fasted State Simulated Intestinal Fluid (FaSSIF) and/or Fed State Simulated Intestinal Fluid (FeSSIF) to understand super saturation of spray-dried dispersions (SDD) vs crystalline and their impact on fed vs fasted state
- Residual solvents by gas chromatography (for SDD): This evaluation is not performed during initial screening experiments. Residual solvents are evaluated for the spray-dried ASDs only once the prototypes are shortlisted and spray dried.

Amorphous Form Stabilization

We typically establish the following parameters to evaluate the amorphous form stabilization:

- Physical stability of ASD (at 40 °C/75% RH or 25 °C/60% RH) for at least 2 or 4 weeks. Up to four prototypes are considered
- Effect of temperature and humidity
- Storage temperature (Tg – 50 °C). The product should be stored at about 50 °C below the Tg of the ASD
- Drug-to-polymer ratio and miscibility
- Minimum water/solvent content in SDD – with no increase/change in Tg and no risk of nucleation/recrystallization or phase separation
- Packaging of solid dispersion—with or without desiccants based on stability

We target this approach to provide appropriately stable solid dispersion with the desired solubility enhancement. The shortlisted ASD prototypes are manufactured with the help of a lab-scale spray-drier using relevant process parameters (optimization of the solids percentage in the solvents, atomization, inlet temperature, drying temperature and drying time) and staged for informal stability. Secondary drying of the spray-dried ASD shall be optimized to bring down the residual solvent content as low as possible within ICH limits.

An Informal Stability Study of Development Prototypes of Spray-Dried Dispersions

Samples from spray-dried development batches are packed in a double-lined polyethylene bag with or without desiccant and placed in either a high-density polyethylene or aluminum pouch and staged for stability.

Stability studies are continued for up to six months under conditions of 25 °C/60% RH or 30 °C/75% RH and 40 °C/75% RH.

Tests conducted during ASD stability studies

Parameter	Initial testing	During stability
Description	✓	✓
PXRD	✓	✓
Tg (mDSC) (if required)	✓	-
Assay	✓	✓
Related substances	✓	✓
Water content	✓	✓
Residual solvent	✓	-

We target this approach to provide appropriately **stable solid dispersion** with the desired **solubility enhancement**.

Preclinical Pharmacokinetic Studies

With shortlisted prototypes determined, we conduct a pharmacokinetic (PK) study to determine the anticipated active drug level. We typically use LC-MS/MS for bioanalysis and conduct data analysis using Phoenix WinNonlin software. Clients are presented with a PK study report detailing our findings (crystalline vs ASD-based formulation). The prototype is selected based on PK study inferences where:

- Bioavailability enhancement is achieved with ASD in comparison with crystalline drug-based formulation
- Dose-proportional bioavailability with dose escalation, which can ensure desired tox margins.

Scaling Up Spray-Dried Solid Dispersion

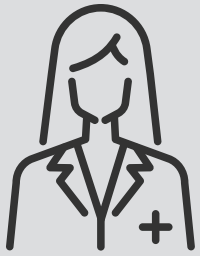
All scale-up activities are performed by an experienced team of formulation and chemical manufacturing personnel. Experts in quality control, quality assurance, environmental health, safety and sustainability, engineering and maintenance, and supply chain management help support the chemical manufacturing team.

To scale up from benchtop to commercial levels, our scientists first evaluate one selected SDD prototype in the scale-up batch. The scale-up batch is evaluated at the scale required for manufacture for preclinical and phase 1 clinical studies, e.g., 5% solids content in spraying solution at the spraying rate of 25 to 30 ml/minute. Sub lots are manufactured under GMP requirements depending on the feasibility of continuous manufacture. API requirements are discussed when presenting the finalized prototype and drug-to-polymer ratio.

Critical process parameters for scale-up batch study are evaluated using similar batch composition parameters as studied in stability and PK studies. The following parameters are considered for process optimization during scale-up:

- Inlet temperature
- Spray Flow rate
- Atomisation pressure
- Drying time

Key process parameters such as drying air flow, aspirator rate and raw material characteristics are kept constant. Critical quality attributes for ASDs such as particle size distribution, water content, bulk density and PXRD are also evaluated. Drying time using a vacuum tray dryer is established by monitoring residual solvent content (one of the critical quality attribute).



To scale up from benchtop to commercial levels, our scientists first evaluate one selected SDD prototype in the scale-up batch.

Scale-up process for ASDs

Process	Process Parameter	Test
Solid dispersion	Solvent, solids content in solvent, spray drying process parameters	Physical nature of solid dispersion, residual solvent, bulk volume, water content, supersaturation, PXRD, assay and related substances

Batch Size Consideration

Because of the equipment capacity and operational ranges, ASD products are manufactured as sublots. In-process testing for all sublots is conducted for assay, PXRD and residual solvents. All sublots are tested for release testing parameters defined under the Certificate of Analysis.

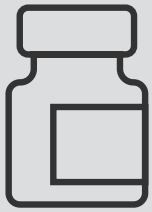
The ASDs generated and tested for the quality parameters shall be further used in the dosage form development (capsules, tablets, powder for suspension/solution) as required for clinical studies. Based on the learnings from preclinical PK studies, the SDD should be designed into the suitable dosage form.

The Advantage of End-to-End Capabilities

While a significant percentage of molecules benefit from ASD to improve solubility, development and manufacturing require specialized expertise and equipment. To ensure a product has the best chance of moving from discovery through to preclinical and clinical trials, pharmaceutical companies must partner with CDMOs that understand the processes used to prepare solid dispersion and which technique best suits the application.

“With experience and the right platform technology, a CDMO can apply its learnings in ASD to new compounds, improving bioavailability there by efficacy,” said Shahe Mahammad. “That’s how we are able to manufacture product with limited API (mg scale). We identify a suitable formulation approach—conventional or enabling techniques—for the drug candidate earlier. Clients in the discovery stage that want to establish proof of concept benefit from this approach.”

It’s also cost-effective and efficient for drug developers to work with a CDMO that not only handles ASD formulation, but also has experience in the steps that occur before and after. Under one roof with a unified team, a drug developer can move from proof-of-concept, to understanding how the product behaves *in vivo*, to preclinical drug metabolism and pharmacokinetics (DMPK) studies, and on to GMP manufacturing and clinical trials.



While a significant percentage of molecules benefit from ASD to **improve solubility,** development and manufacturing require specialized expertise and equipment.

A company like Syngene, for example, not only develops ASD product, but it can also offer end-to-end support, including:

- ASD development
- In-vivo pharmacokinetic studies to assess the exposures
- ASD process optimization
- GMP supply of ASD
- Converting ASD to suitable dosage form for the clinical studies

“When the compound is not amenable for development, we have the technology—whether ASD or lipid-based formulation—to make it enabled,” said Shahe Mahammad.

The Future of ASD in Drug Development

Over the past two decades, ASD has emerged as one of the most promising approaches for improving the solubility of molecules developed for oral administration. Advances in science and technology have allowed scientists to improve ASD strategies and resolve limitations such as instability. For drug developers who want to ensure optimal bioavailability of novel compounds or improve the bioavailability of existing compounds, ASD is a viable solution.

Advances in science and technology have allowed scientists to **improve ASD strategies** and **resolve limitations** such as instability.

References

1. Le, Jennifer, et al. Drug Bioavailability. Merck Manual, professional version. https://www.merckmanuals.com/professional/clinical-pharmacology/pharmacokinetics/drug-bioavailability

2. Iyer R, Petrovska Jovanovska V, Berginc K, et al. Amorphous Solid Dispersions (ASDs): The Influence of Material Properties, Manufacturing Processes and Analytical Technologies in Drug Product Development. *Pharmaceutics*. 2021;13(10):1682. Published 2021 Oct 14. doi:10.3390/pharmaceutics13101682

3. Tambe S, Jain D, Meruva SK, et al. Recent Advances in Amorphous Solid Dispersions: Preformulation, Formulation Strategies, Technological Advancements and Characterization. *Pharmaceutics*. 2022;14(10):2203. Published 2022 Oct 16. doi:10.3390/pharmaceutics14102203

4. Formulating Drug Products for Optimized Absorption: Elucidating Amorphous Solid Dispersions. U.S. Food & Drug Administration, August 30, 2022. https://www.fda.gov/drugs/regulatory-science-action/formulating-drug-products-optimized-absorption-elucidating-amorphous-solid-dispersions

5. Pandi P, Bulusu R, Kommineni N, Khan W, Singh M. Amorphous solid dispersions: An update for preparation, characterization, mechanism on bioavailability, stability, regulatory considerations and marketed products. *Int J Pharm*. 2020;586:119560. doi:10.1016/j.ijpharm.2020.119560

6. Bhujbal SV, Mitra B, Jain U, et al. Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies. *Acta Pharm Sin B*. 2021;11(8):2505-2536. doi:10.1016/j.apsb.2021.05.014

7. DeBoyace K, Wildfong PLD. The Application of Modeling and Prediction to the Formation and Stability of Amorphous Solid Dispersions. *J Pharm Sci*. 2018;107(1):57-74. doi:10.1016/j.xphs.2017.03.029

8. Iyer R, Petrovska Jovanovska V, Berginc K, et al. Amorphous Solid Dispersions (ASDs): The Influence of Material Properties, Manufacturing Processes and Analytical Technologies in Drug Product Development. *Pharmaceutics*. 2021;13(10):1682. Published 2021 Oct 14. doi:10.3390/pharmaceutics13101682

Syngene

Syngene International Ltd. (BSE: 539268, NSE: SYNGENE, ISIN: INE398R01022) is an integrated research, development, and manufacturing services company serving the global pharmaceutical, biotechnology, nutrition, animal health, consumer goods, and specialty chemical sectors. Syngene's more than 5200 scientists offer both skills and the capacity to deliver great science, robust data management, and IP security and quality manufacturing at speed to improve time-tomarket and lower the cost of innovation. With a combination of dedicated research facilities for Amgen, Baxter, and Bristol-Myers Squibb as well as 2 Mn sq. ft of specialist discovery, development, and manufacturing facilities, Syngene works with biotech companies pursuing leading-edge science as well as multinationals, including GSK, Zoetis, and Merck KGaA. For more details, visit www.syngeneintl.com