Amorphous Solid Dispersion: Improving Dissolution Rate of Poorly Water-Soluble Drug Substance

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BACKGROUND AND OBJECTIVES

Research studies show that the majority of API candidates in the development pipeline have a BCS Class II rating, which means those APIs need a solubilization strategy to promote the bioavailability to improve their chance of clinical success.

One commercially validated technique to improve the solubility of poorly-soluble APIs is to prepare them as amorphous solid dispersions (ASD). J-star Research Inc. has spray drying (SD), hot melt extrusion (HME) and co-processing in house to establish ASD technique. This case study is focused on the preparation and evaluation of one model ASD produced at J-Star using Spry Drying.

METHODS

Active pharmaceutical Ingredient (API) molecules intended for oral administration are often categorized into four classes using the Biopharmaceutical Classification System (BCS) as shown in Figure 1. They are classified based on their aqueous solubility across the gastrointestinal (GI) pH range and their permeability across the GI mucosa. This classification guides the direction of the formulation strategy to develop API candidates in the pipeline into drug products.

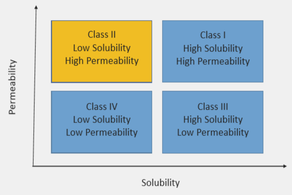

Figure 1. Biopharmaceutical Classification System

ASD Formulation Development

The formulation for ASD includes solvent, API, polymer and surfactant. The selection of the polymer is critical to generating an ASD that is physically stable and achieves the desired API dissolution profile The selection of the solvent or the solvent mixture is to ensure that both API and polymer/surfactant will dissolve to form a homogeneous solution. The surfactant enhances the solubility of the drug in the gastric fluid.

Spray Drying Process Development

The preparation of ASD was accomplished by using a small-scale spray dryer, Buchi B290, a schematic of the spray drying process is shown in Figure 2. The rate of the solvent removal from the rotary evaporator is slow, which may cause some phase separation, while the rate of the solvent removal from SD is rapid. The ASD samples generated from SD may have some residual solvent, and a secondary drying in a vacuumed oven was used for residual solvent removal.

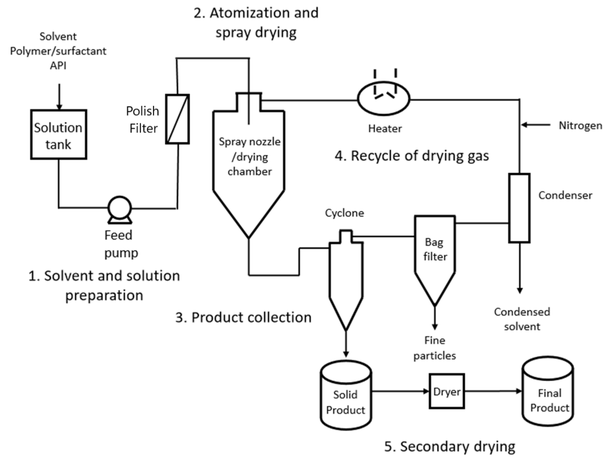

Figure 2. Spray drying process flow diagram

There are 5 steps (unit operations) in SD process:

1. Solvent and solution preparation 2. Atomization and spray drying: 3. Product collection 4. Recycle and drying gas 5. Secondary drying

RESULTS

- Nifedipine (a typical BCS II compound) was used as the drug substance model in this case study
- HPMCAS-MG and PVP K30 were used as the polymers for the ASD
- Dichloromethane (DCM) and Ethanol (1:1 w/w) were used as the solvent.
- ASDs were produced and evaluated using 40% drug load with both polymers.
- Residual solvent, dissolution rates and stability tests were performed on API crystalline and ASDs.

1. Residual Solvent

ASD Products	Residual Solvent/ICH Limit (ppm)	
	DCM	Ethanol
40% NIF – 60% PVP K30	<60*/600	349/5000
40% NIF – 60% HPMCAS	<60*/600	178/5000

*: Based on ICH Q3C (R6), the concentration limit for DCM is 600 ppm while the residual DCM in the ASD products are under LOQ 60 ppm.

2. Dissolution Rate

Experimental Setup (as shown in figure 3)

- USP 0.03 M Phosphate buffer solution (pH: 6.8)
- Temperature: 37 ± 0.2 °C
- Volume: 500 mL
- Apparatus 2: 50 rpm
- Time: 4 hour
- Collecting Point: 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 180 min, 240min (12 data points)
- 175 mg of powder materials (NIF crystalline/ ASD products)
- 8ml of sample was collected at each time point for concentration test
- Analytical Method: UV (a standard curve was built with NIF crystalline)
- All measurements were carried out in triplicate.

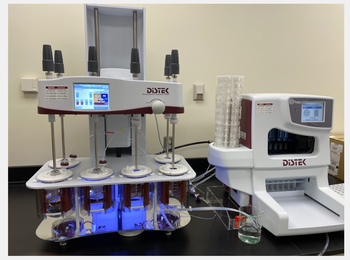

Figure 3. Experimental setup for dissolution tests on the Nifedipine Crystalline and ASDs.

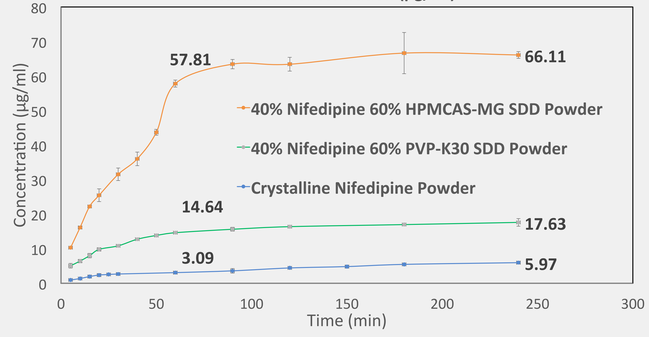

Figure 4. Dissolution profile of NIF crystalline and NIF ASDs with PVP and HPMCAS at 40% drug load.

3. Stability Test

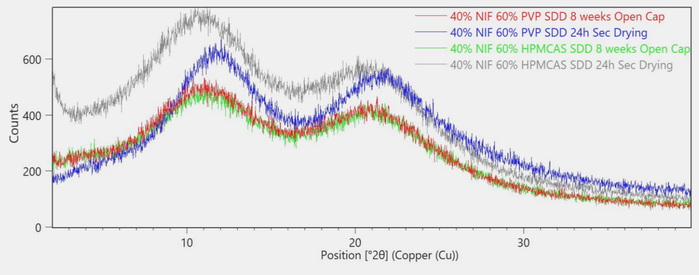

Figure 5. Powder X-ray diffraction patterns for stability tests on Nifedipine PVP/HPMCAS solid dispersions: right after second drying and 8 weeks room temperature and relative humidity.

CONCLUSIONS

1. This case study has showed that the technique of improving the dissolution rate of poorly-soluble drug substance by making them into Amorphous Solid Dispersion (ASD) using spray drying has been successfully applied on a certain drug substance (Nifedipine) at J-Star Research Inc.

2. The residual solvent of the ASDs are under the concentration limit based on ICH guideline.

Figure 6. ASD made by spray drying

3. The dissolution rate and concentration has been greatly improved by ASDs produced using a spray dryer compared to the original crystal API.

4. The ASDs produced at J-Star Research Inc. has established a high level of purity and stability.

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