SEVER PHARMA SOLUTIONS

A COMPARISON OF SATURATED SOLUBILITY ENHANCEMENT VIA SPRAY DRYING AND HOT MELT EXTRUSION PROCESSING

Tony Listro, Sever Pharma Solutions, Putnam, Connecticut
tlistro@severpharmasolutions.com

Michael M. Crowley, Theridian Technologies, LLC, Austin, Texas.
mcrowley@theridian.com

SEVER PHARMA SOLUTIONS

A COMPARISON OF SATURATED SOLUBILITY ENHANCEMENT VIA SPRAY DRYING AND HOT MELT EXTRUSION PROCESSING

INTRODUCTION

The permeability and solubility of a drug are key determinants of its oral bioavailability. Many new active pharmaceutical ingredients exhibit poor bioavailability due to limited aqueous solubility and thus has been recognized as a common and significant challenge for industry [1]. Several techniques have been developed to enhance solubility including (a) salt formation (b) solutions in solvents and cosolvents (c) micelle systems and self-emulsifying drug delivery systems (d) particle size reduction and nanoparticles (e) complexation (f) pro-drugs and (g) amorphous solids and solid dispersions.

Solid solutions are similar to liquid solutions and consist of a single phase irrespective of the number of components. A solid solution of a poorly water soluble drug dissolved in a carrier is of particular interest as a means of improving oral bioavailability. In a solid solution, the drug's particle size has been reduced to its molecular dimensions resulting in a more rapid dissolution rate. By judicious selection of a carrier, the dissolution rate of the drug can be increased by up to several orders of magnitude. Spray drying and hot melt extrusion are two common processing approaches for the formation of solid dispersions and solid solutions [2-4]. We report a comparison of saturated solubility enhancement between spray drying and hot melt extrusion for a poorly soluble, new active pharmaceutical ingredient.

MATERIALS AND METHODS

Study compounds were characterized and used as received from their suppliers. The polymers included Hypromellose Acetate Succinate (HPMCAS, Shin-Etsu), Eudragit RL (Evonik), Eudragit E (Evonik), Kollidon (PVP K90, BASF) Kollidon VA 64 (BASF) and SoluPlus (BASF).

Spray Drying

Spray dried samples of FSR-101 were prepared from a 10% solution of the drug and polymer in methanol using a Buchi B-290. The following conditions were used: Aspirator flow–100%, Nitrogen Gas flow rate: 550 – 600 L/hr at 6 bar, solution flow rate 2-3 mL/min and a 0.7 mm nozzle tip diameter. The inlet temperature adjusted to maintain the outlet temp at 50-55 °C. The resultant dispersions were then dried in a vacuum oven at 35 - 40°C for 24 hours.

Hot Melt Extrusion

Powders of the drug and polymer (25% w/w drug content) were blended in the Turbula mixer (Turbula Type T2 F) and introduced to the Haake Mixing Bowl (Haake Polylab OS Rheo Drive 4 and Rheomix OS Mixing Bowl). The initial temperature was set according the glass transition temperature of each polymer, generally about 25-50 °C above the Tg. The mixing speed was set at 100 rpm.

Powder X-Ray Diffraction (PXRD) Analysis

A Bruker D8 Advance diffractometer equipped with a VANTEC-1 detector was utilized. Samples weighing approximately 100 mg were packed in 0.5-mm-deep cups and were spun at 15 rpm to minimize crystal orientation effects. The X-ray source was operated at 45 kV and 40 mA. Data for each sample were collected from 3° to 40° on the 2□ scale in continuous detector scan mode at a scan speed of 2 s/step and a step size of 0.04°/ step.

Differential Scanning Calorimetry (DSC)

DSC analyses were performed using a Thermal Analysis Q2000 differential scanning calorimeter equipped with an autosampler. Samples were equilibrated at the desired RH overnight then crimped into hermetic aluminum pans with a pinhole lead. The samples were equilibrated at 25°C for 5 minutes followed by modulating the temperature at 0.32°C/min while increasing the temperature to 200°C using dry nitrogen at 40 mL/min.

Saturated Solubility Testing

Saturated solubility was measured by adding an excess of drug or dispersion to PBS solution at 37°C. The suspension was agitated at 37°C for at least 1 h and then centrifuged and filtered with a 0.45 µm membrane. The concentration of the supernatant was measured by HPLC.

HPLC

Drug purity was determined using a Waters Alliance system with 2695XC Separations Module, 2489 UV Vis Detector and Empower software. A gradient method was used, the column was XBridge phenyl with a 3.5 µm particle size, the flow rate was 1 mL/min, the column temperature was 30 °C and the injection volume was 10 µL. The method was qualified for specificity (against the polymers), linearity, accuracy and precision.

RESULTS AND DISCUSSION

FSR-101 is a poorly water soluble with a log P = 3.46 and solubility parameter = 31.1 MPa0.5. FSR-101 is a white crystalline solid with rectangular plate morphology, an atomic weight of 510.81 Daltons and melting point of 174 °C. The water solubility is <0.1mg/mL. FSR-101 exhibits solubility in PEG 400, Ethyl Acetate, Ethanol, Acetone, Toluene and MEK.

Spray dried dispersions of FSR-101 were prepared and several polymers were screened. The lead spray dried dispersion (SDD) contained HPMCAS with 25% w/w drug content. The SDD was confirmed to be amorphous by PXRD, DSC and SEM. FSR-101 chemical stability was confirmed by HPLC. The saturated solubility of the SDD was found to be 0.42 mg/mL and had a single phase

glass transition temperature of 94 °C. Forced crystallization studies determined the SDD exhibited moisture associated re-crystallization. Thus, HME was selected as an alternate technique to prepare an FSR-101 amorphous dispersion.

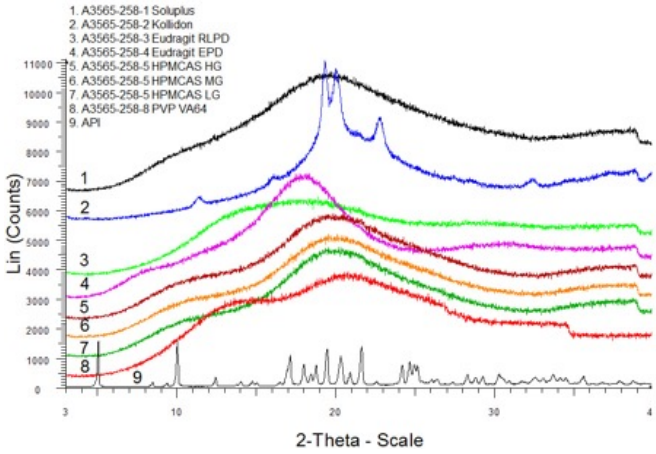

Figure 1. PXRD Results of FSR-101 Hot Melt Extrudates

The HME samples were analyzed by PXRD (Figure 1). All were found to be amorphous except for Kollidon 90. A single phase glass transition temperature was observed by DSC for the SoluPlus, Eudragit RL, Eudragit E and Kollidon VA-64 samples (Table 1). FSR-101 purity was determined to be acceptable for all samples except for the HPMCAS sample, which had ~20% degradation (Table 1). This observation is in contrast to the chemical stability of the spray dried dispersion.

SamplePurity	(HPLC)	HME Tg
SoluPlus	99.5%	82 °C
Eudragit RL	99.8%	84 °C
Eudragit E	99.4%	73 °C
HPMCAS HG	80.1%	109 °C
VA-64	99.8%	104 °C

Table 1. Purity & DSC Results of Hot Melt Extrudates.

The saturated solubility and morphology following a 10 day stability study of the HME samples was determined and is reported in Table 2. The saturated solubility of the SoluPlus, Eudragit RL, Eudragit E and Kollidon VA-64 samples was exceptional, and were greater than the spray dried dispersion. These samples were confirmed to be amorphous following a 10 day stability study.

Sample	Saturated Solubility	Morphology (10 Days @ 60 °C / 75%RH)
SDD	0.42 mg/mL	Crystalline
SoluPlus HME	3.1 mg/mL	Amorphous
Eudragit RL HME	0.45 mg/mL	Amorphous
Eudragit E HME	0.58 mg/mL	Amorphous
VA-64 HME	4.4 mg/mL	Amorphous

Table 2. Saturated Solubility & Morphology Stability

CONCLUSIONS

Amorphous dispersions were successfully prepared by both spray drying and melt extrusion. HPMCAS was found to have the best stability and saturated solubility from the spray drying process. However, FSR-101 was found to degrade when processed by melt extrusion with this polymer. The saturated solubility of the amorphous dispersions prepared by melt extrusion exceeded those prepared by spray drying. This study demonstrates that amorphous dispersion can be prepared by spray drying and melt extrusion but the physicochemical properties of the dispersion are dependent upon the process.

REFERENCES

1. Leuner, C. and J. Dressman, Improving drug solubility for oral delivery using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics, 2000. 50(1): p. 47-60.
2. Paudel, A., et al., Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: Formulation and process considerations. International Journal of Pharmaceutics, 2013. 453(1): p. 253-284.
3. Breitenbach, J., Melt extrusion: from process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics, 2002. 54(2): p. 107-117.
4. Patterson, J.E., et al., Melt extrusion and spray drying of carbamazepine and dipyridamole with polyvinylpyrrolidone/vinyl acetate copolymers. Drug Development and Industrial Pharmacy, 2008. 34(1): p. 95-106.

Postal address
Box 590
201 25 Malmö
Sweden
info@severpharmasolutions.com

Headquarters
Sever Pharma Solutions
Agneslundsvägen 27
212 15 Malmö
Sweden
+46 (0)40 36 18 00

Dutch Site
Sever Pharma Solutions
Tolweg 15
3741 LM Baarn
The Netherlands
+31 (0)35 52 80 400

US Site
Sever Pharma Solutions
36 Ridge Road | US-06260
Putnam (CT)
USA
+1 860-541-5280