Effect of Processing Methods on Physical Stability of Amorphous Solid Dispersions Consisting of Naproxen and Povidone

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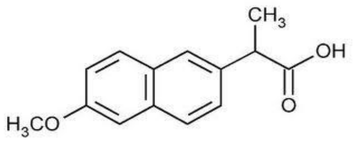
Introduction

Hot melt extrusion (HME) and spray drying (SD) are both widely used to prepare amorphous solid dispersions (ASDs). The mechanisms are different for both processes. In HME, mechanical and thermal heat are applied to the materials. Molten drug or drug crystals dissolve in molten polymer. SD involves thermal energy applied to atomized droplets of organic solution of drug and polymer. Processing method is found to have profound impact on physicochemical properties and physical stability of ASDs

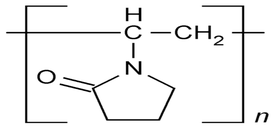
Materials

Naproxen :
Tg = 7.8C
MP = 155 ºC
Weak acid (pKa 4.2)
H Bond Donor
Fast crystallizer



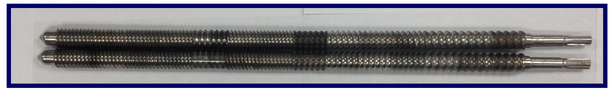
***liq. Nitrogen quench required to make amorphous**

Povidone (Kollidon®25):
Tg = 156 ºC
Amorphous
Water Soluble
H Bond Acceptor



Methods

- Low and high drug levels: 30% and 60% naproxen
- SD: Ethanol feed solution 10% (w/v) solids concentration, outlet temperature at 60 ºC
- HME: Leistritz Nano16 twin screw extruder with 25:1 L/D
- Stored at ambient, 40, and 60 °C for one month



- Characterized physical stability with modulated differential scanning calorimetry (mDSC) and powder x-ray diffraction (PXRD)
- Quantified crystalline material from PXRD

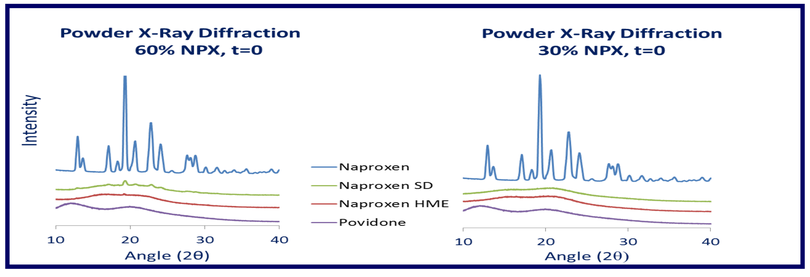
Hypothesis

Our hypothesis is that an ASD consisting of a drug that crystallizes rapidly is more stable when melt extruded than spray dried.

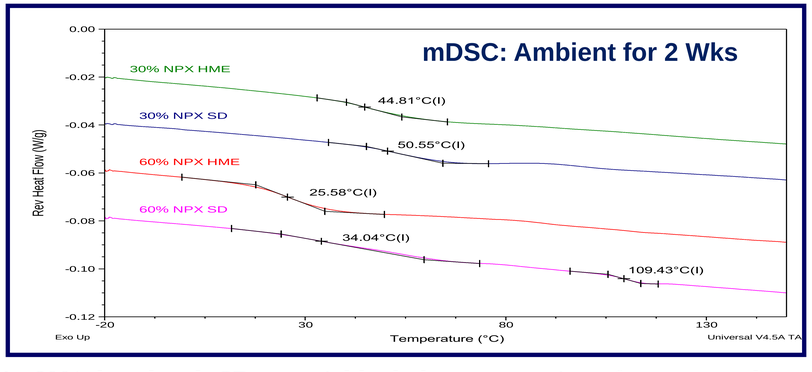
Purpose

- Understanding of processing method impact on the physical stability of naproxen ASDs
- Identify if stronger interactions during processing result in increased stability of ASDs

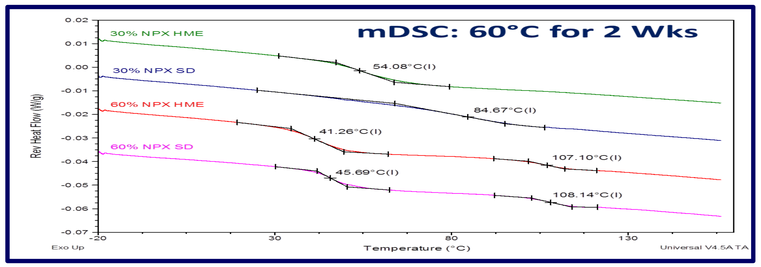
Results



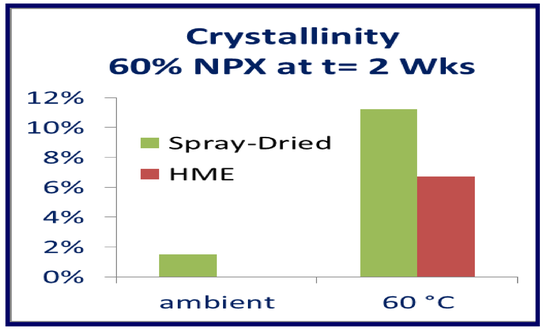
At t=0, PXRD of low drug level remained amorphous for both SD and HME materials. At high drug level, crystalline content was observed.



At 60% drug level, SD material had phase separation after two weeks storage at ambient while HME material did not. Both materials at 30% drug level did not have phase separation as confirmed by single glass transition temperature (Tg).



After two weeks at 60 ºC, low drug level ASDs remained amorphous. The Tg's of SD and HME ASDs increased 34 ºC and 9 ºC respectively. The high drug level ASDs both had phase separation and similar Tgs.



Both materials re-crystallized after two week storage at 60 ºC. Spray dried material had a greater extent of crystallinity at both storage conditions.

Conclusion

This study demonstrated the unique advantage of melt extrusion over spray drying to prepare ASDs. Melt extruded ASDs containing drugs with high crystallization rate are more physically stable than those prepared using the spray drying process.

References

1. Crowley MM, Zhang F, Repka MA, et al. Pharmaceutical Applications of Hot-Melt Extrusion: Part I. *Drug Development and Industrial Pharmacy.* 2007;33(9):909-926.
2. Paudel A, Van den Mooter G. Influence of Solvent Composition on the Miscibility and Physical Stability of Naproxen/PVP K 25 Solid Dispersions Prepared by Cosolvent Spray-Drying. *Pharmaceutical research.* 2012/01/01 2012;29(1):251-270.
3. Agrawal AM, Dudhedia MS, Patel AD, Raikes MS. Characterization and performance assessment of solid dispersions prepared by hot melt extrusion and spray drying process. *International journal of pharmaceutics.* 11/30/ 2013;457(1):71-81.