HUB Microfactory – Product-Process Archetype 1:

Continuous crystallization and crystal engineering coupled with polymer processing steps to produce a particle suspension amenable to a range of post-processing e.g., moulding or additive-layer printing of solid oral dosage form.

Problem statement for Model Drug Mefenamic acid (MFA): Oral bioavailability of Mefenamic acid shows significant dependence on particle size leading to variable efficacy.

Results - HME

MFA – Affinisol 15V (1:1) was extruded on a Process 11 Parallel Twin Screw Extruder at processing temperatures (PT) of 140°C, 150°C, 160°C, and 180°C. FTIR analysis (Bruker Tensor II, ATR; Figure 2) and thermal analysis (Netzsch DSC Polyma24, Figure 3) of extrudates, physical mixture and MFA showed the following properties:

- MFA Form I is stable at ambient temperatures and transforms to Form II via sublimation-condensation at elevated temperatures (~172°C) observed for PT 140°C, 150°C and PM.
- Extruded MFA-Affinisol 15V systems exhibit several amorphous (Tg's) and crystalline species (Transition and Tm) within the API-polymer system.
- Increasing the HME PT resulted in an increase in amorphous MFA-Affinisol 15V content seen as a shift of Tg from 127°C to 148°C (not seen in PM I).
- Tg of API-polymer system higher than polymer only (~100°C) (MFA non-glass former).
- At PT >160°C: only crystalline Form I in system is Form I.

Results – Product performance

MFA is a weak acid with a pKa of 4.2 and a BCS class II drug. The dissolution profile is therefore highly dependent on particle size and pH.

The dissolution rate was assessed with the Pion Inform (Pion Inc) across a range of physiologically relevant pHs as well as pH 9, the recommended test conditions for QC testing (USP 35).

Two batches with different PSD were prepared by a linear cooling crystallisation: Batch A with a D90 of 271µm and Batch B with a D90 of 64µm (wet-milled) (Figure 6). The dissolution rate of these MFA powders, commercially available MFA powder (Sigma, D90 = 371µm) and a 6mm MFA Sigma powder compact show the impact of particle size on dissolution behaviour across a pH range of 6.5 – 9 (Figure 4).

HME extrudates show an improved dissolution behaviour across a much wider pH range (pH 2-9, Figure 5).

Conclusion

The present API-polymer extrudate systems consist of a variety of amorphous and crystalline species. Particle size, presence of polymer and amorphous and crystalline forms impact the dissolution behaviour of MFA.