HUB Microfactory – PPA 1 – Mefenamic acid – HME – 3D printing process stream

E. Prasad, J. Robertson, G. Halbert
CMAC Future Manufacturing Research Hub, Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow, UK
*elke.prasad@strath.ac.uk e-mail of Corresponding Author

HUB Microfactory - Product-Process Archetype 1:

continuous crystallisation 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.

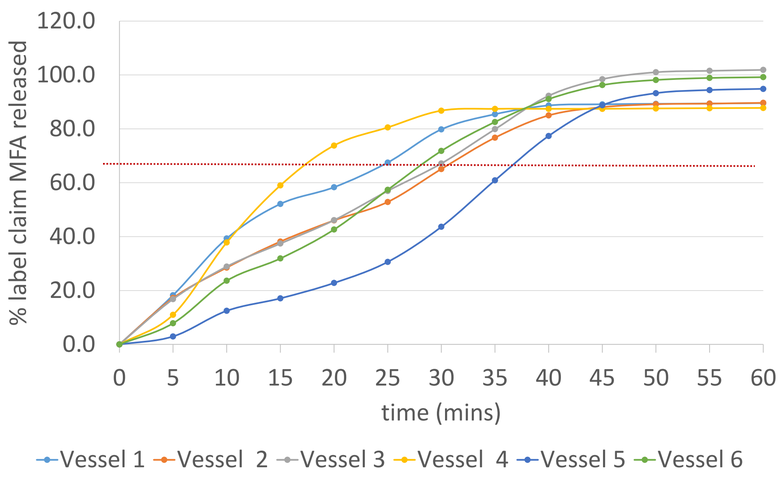
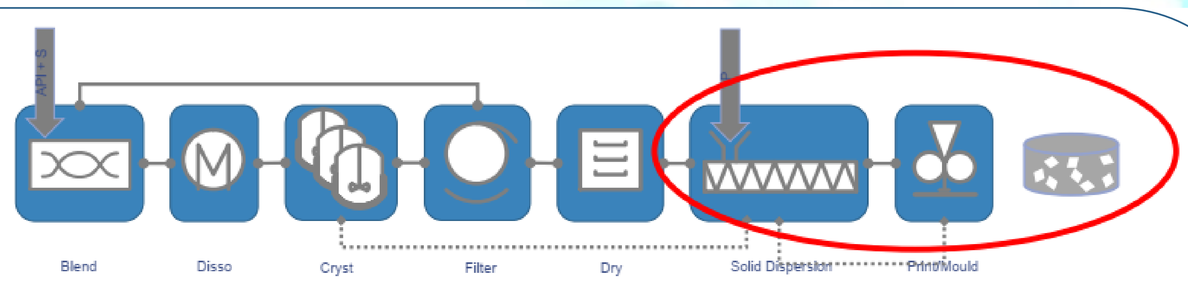


Figure 1: USP II dissolution test (pH 9) of 250mg MFA casules, Pharmavit Limited (PVL), Batch 4348



Formulation approach: precisely controlled primary particles (D90<42µm) within a polymer matrix will deliver optimised physical properties for biopharmaceutics performance from a simplified formulation avoiding the need for multiple excipients.

Deliverables PPA3: improved product manufacturability, simplified formulation with consistent dosage form performance, manufactured from a less complex process chain

Target: oral solid dose form with IR release profile at a dose of 250/500mg

Manufacture PPA1: HME – 3DP fused filament fabrication (FFF)/Injection molding

Formulation: crystalline solid dispersion

Predictive approach:

- Target particle size of D_{90} = 42 µm was calculated based on the Development Classification system (Butler 2010) with a target dose of 250mg.
- Hansen solubility parameters were determined to identify lowest solubility of MFA in a range of polymers

Results - HME

MFA – Affinisol 15LV (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, 150C°C and PM
- Extruded MFA-Affinisol 15LV 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 15LV content seen as a shift of Tg from 127°C to 148°C (not seen in PM)
- Tg of API-polymer system higher than polymer only (~100°C) (MFA non-glass former)
- At PT >160C: only crystalline Form in system is Form I

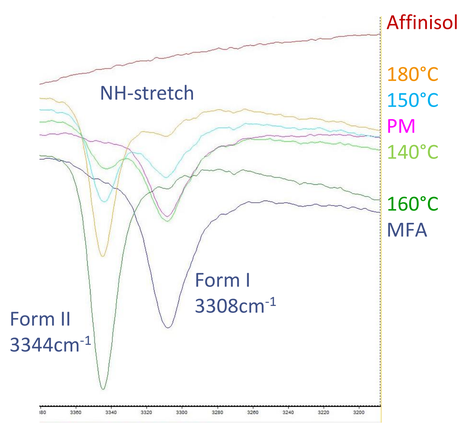


Figure 2: FTIR spectrum of 50% MFA-Affinisol extrudates processed at 140°C, 150°C, 160°C, 180°C, the Physical mixture (PM) and MFA only.

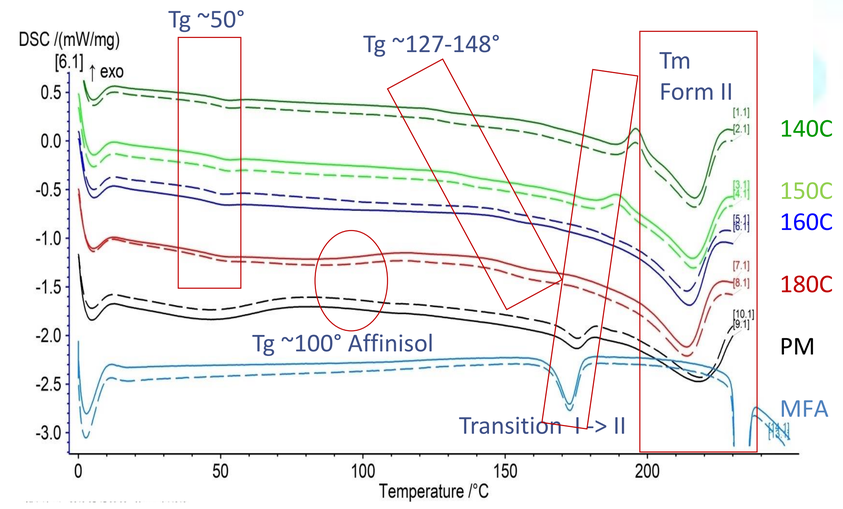


Figure 3: Thermogram of extrudates 50% MFA-Affinisol 15LV processed at 140°C, 150°C, 160°C, 180°C, Physical mixture (PM) and MFA only.

Results – Product performance

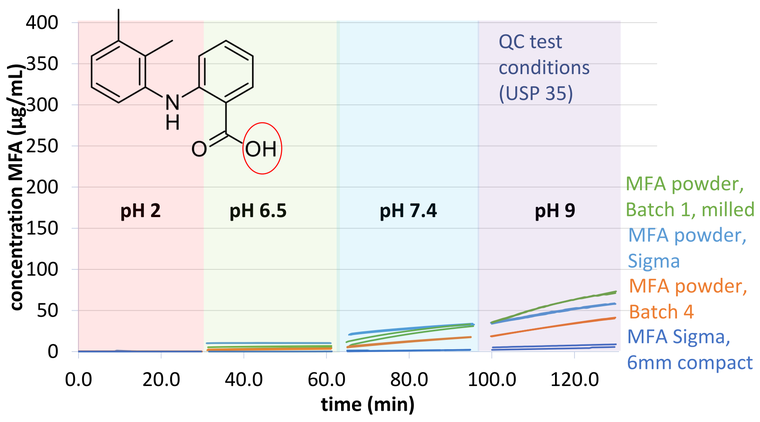
MFA is a weak acid with a pK_a of 4.2 and a BCS class II drug. The dissolution profile is therefore highly dependant on particle size and pH.

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 4 with a D90 of 271um and Batch 1 with a D90 of 64um (wet-milled) (Figure 6). The dissolution rate of these MFA powders, commercially available MFA powder (Sigma, D90 = 371um) 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).

Figure 4: Dissolution MFA powder particle size vs compact



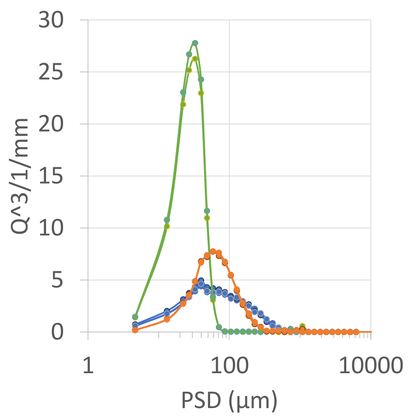
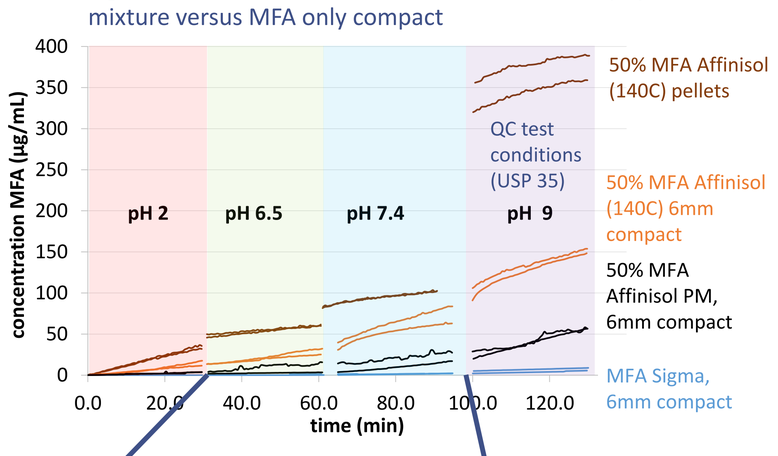
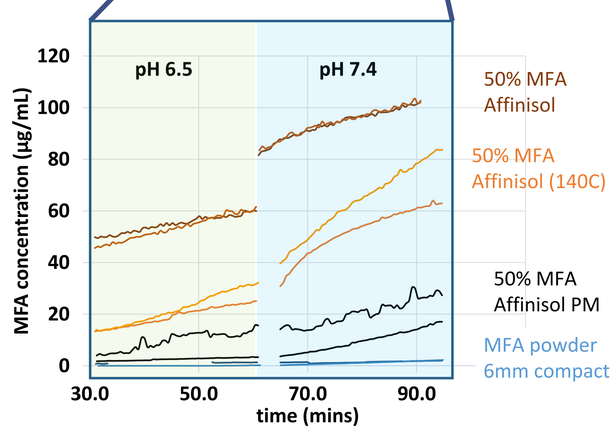


Figure 6: Particle size distribution of MFA, Sigma, MFA Batch 1 milled, MFA Batch 4

Figure 5: Dissolution MFA-Affinisol extrudate and physical mixture versus MFA only compact





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.

Next steps

Assessing the impact of amorphous and crystalline forms I and II on dissolution behaviour
MFA - Polymer "in-solubility" screening: To increase the crystalline MFA content within the API polymer system