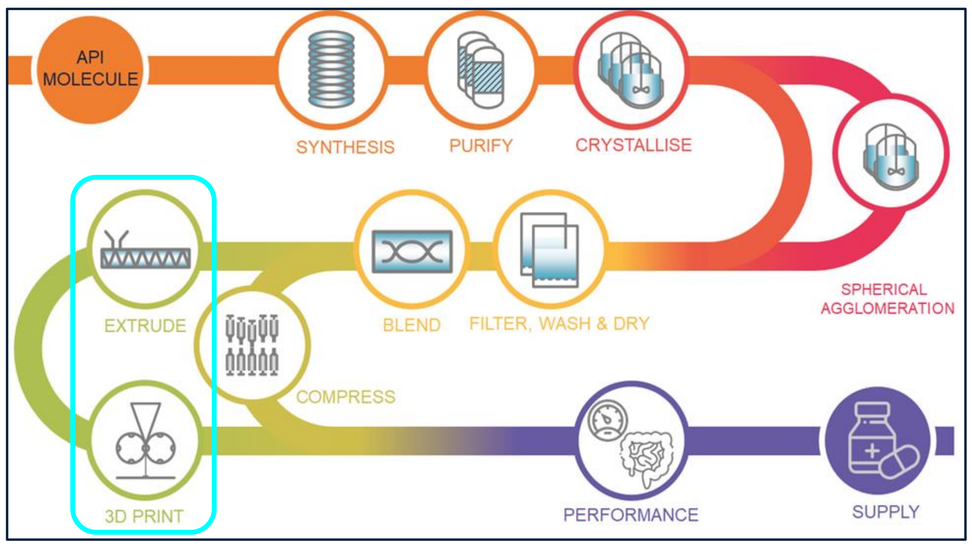
3D Printing MicroFactory for Amorphous Solid Dispersion formulations

Elke Prasad[a,b*], Jill Hueckman[a,b,c], Ecaterina Bordos[a,b], John Robertson[a,b], Gavin W. Halbert[a,b]

[a]EPSRC Future Manufacturing Research Hub, University of Strathclyde, Technology and Innovation Centre, 99 George Street, Glasgow, G1 1RD, UK
[b]Strathclyde Institute for Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, UK
[c]University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences, 12850 East Montview Boulevard Aurora, CO 80045, USA
*elke.prasad@strath.ac.uk



Context and Aim of Work

This study utilised the **HUB Additive-Manufacturing-MicroFactory** as an enabler for streamlined manufacture of Amorphous Solid Dispersion (ASD) formulation of the model compound Ritonavir with an immediate release polymer Soluplus® (BASF). The Digital Design and Manufacture of Amorphous Pharmaceuticals (DDMAP) research program identified Soluplus® as a superior polymer to form stable ASD formulation with Ritonavir.

The drug release from 3D printed (3DP) Ritonavir ASD formulations with Soluplus® were compared to a commercial product (Norvir, 100mg, Abbvie Ltd).

Filament Free Printing

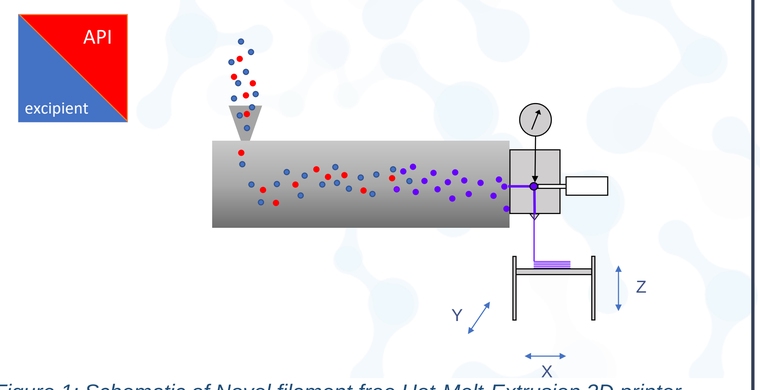


Figure 1: Schematic of Novel filament free Hot-Melt-Extrusion 3D printer.

Rheology screening

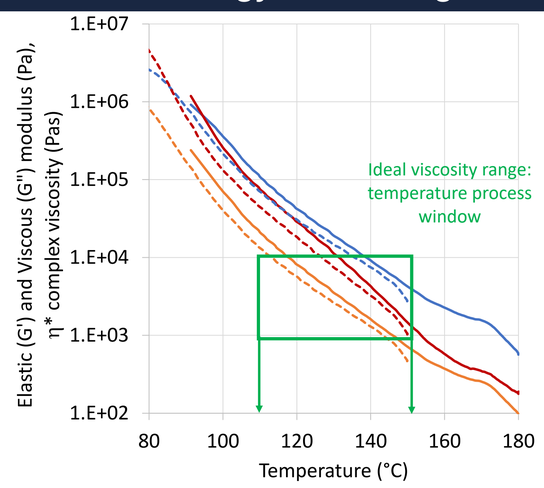


Figure 2: Oscillatory Temperature Sweep: Elastic (G', red) and Viscous (G", blue) modulus and complex viscosity (η, orange) versus temperature of 20% w/w Ritonavir – Soluplus® extrudate.*

Process development

- Material ageing
- Discolouration
- Increase in viscosity / die pressure
- One tablet per piston stroke -> slow
- Ritonavir VERY static

- Temperature: 145°C
- Feed rate: 0.1kg/h
- Screw speed: 50 rpm
- Print Bed: 60C
- Nozzle: 0.4 mm
- Speed: 40 mm/s
- Fill pressure: 14 bar
- Gcode 'A length' proportional to mass
- Good uniformity of mass

Process data

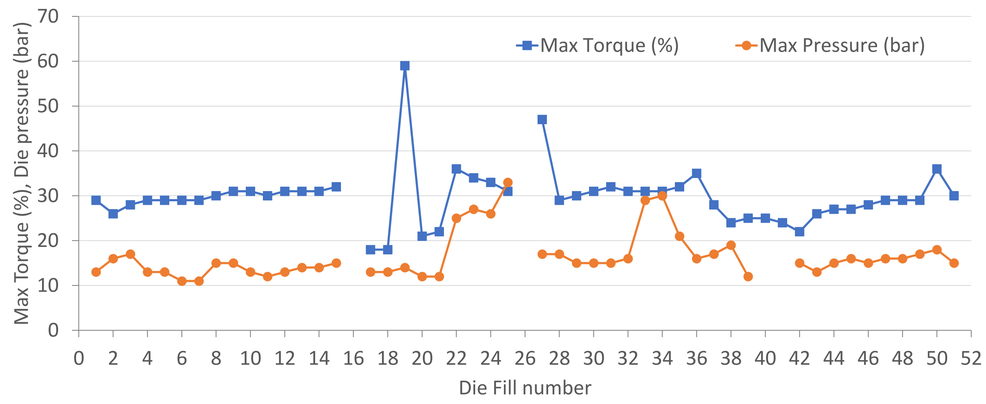


Figure 3: Process data from MicroFactory operated at 145°C. Orange circles: maximum die pressure (bar) during die fill; blue squares – Max torque (%) during die fill.

3DP dose forms

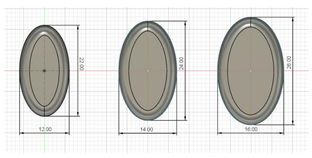


Figure 4: Digital tablet designs: elliptically shaped tablets with rounded edges from left to right: 22mm x 12mm x 5mm (E22); 24mm x 14mm x 5mm (E24) and 26mm x 16mm x 5mm (E26).

Figure 5: 3D printed tablets with 20% w/w Ritonavir - Soluplus®: E22 with 58% Infill, E24 with 42.5% and E26 with 32% Infill.

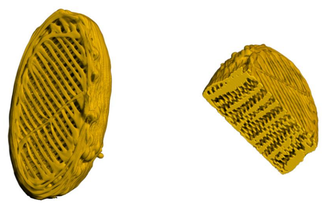


*Figure 6: Micro CT analysis of 3D printed tablet (E22, 58%) to determine porosity, volume and surface area **(in progress)**.*

Solid state analysis

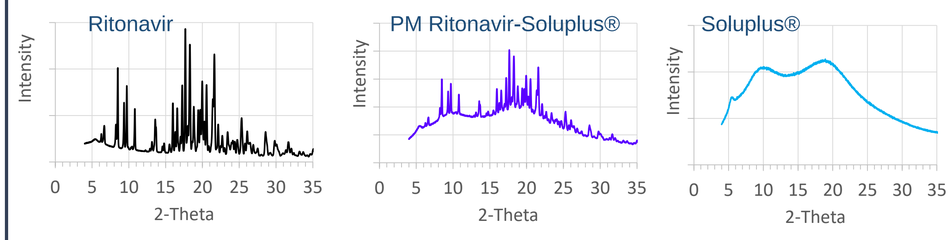


Figure 7: Diffraction pattern of Ritonavir (left), PM 20% w/w RIT-SOL (middle) and Soluplus® (right).

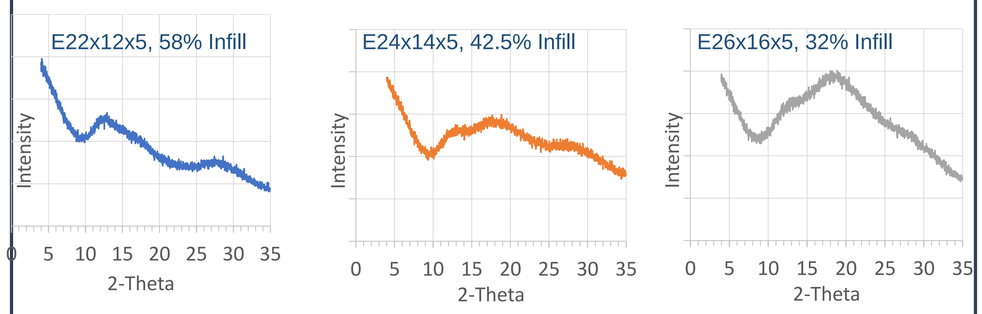


Figure 8: Diffraction pattern of 3DP tablets: E22 – blue, E24 – orange and E26 – grey.

Tablet uniformity

AC8404, E22x12x5, 58%			
	average	stdev	%RSD
Width (mm)	10.06	0.20	1.96
Length (mm)	20.03	0.17	0.84
Height (mm)	4.60	0.09	1.93

AC8404, E24x14x5, 42.5%			
	average	stdev	%RSD
Width (mm)	12.47	0.14	1.09
Length (mm)	22.53	0.18	0.78
Height (mm)	4.54	0.07	1.64

AC8404, E26x16x5, 32%			
	average	stdev	%RSD
Width (mm)	14.37	0.08	0.53
Length (mm)	24.45	0.17	0.70
Height (mm)	4.71	0.09	1.96

Figure 9: Uniformity of tablet dimensions (average, standard deviation and % relative standard deviation (RSD) for with, length and height of 3DP tablets.

Content and degradation analysis

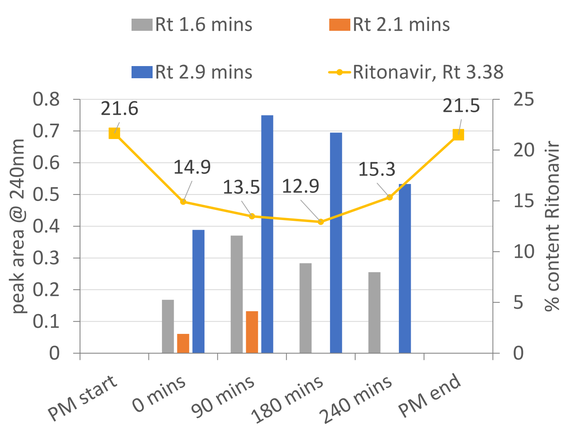


Figure 10: Ritonavir (yellow squares) content of powder blend physical mixtures (PM) and extruded samples (EX) versus time. Main degradation peaks versus time, eluting at 1.6 mins (grey), 2.1 mins (orange) and 3.38 mins (blue).

Linking degradation with SIFT-MS

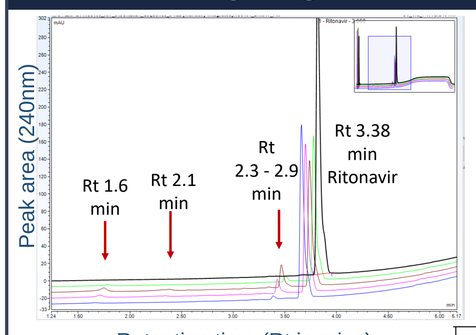


Figure 11: HPLC chromatogram of Ritonavir (Rt 3.38mins) and main degradation peaks (Rt 1.6, 2.1 and 2.9mins) from extrudate samples.

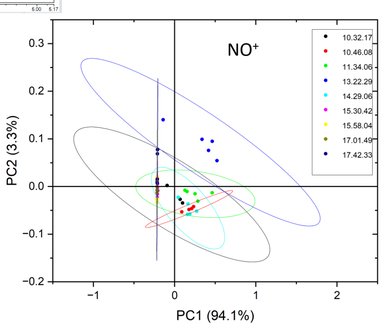


Figure 12: SIFT-MS analysis: PCA score plot (NO^+ reagent ion) volatile organic compounds detected during 3DP manufacture of Ritonavir – Soluplus® tablets.
Analysis in progress.

Product performance

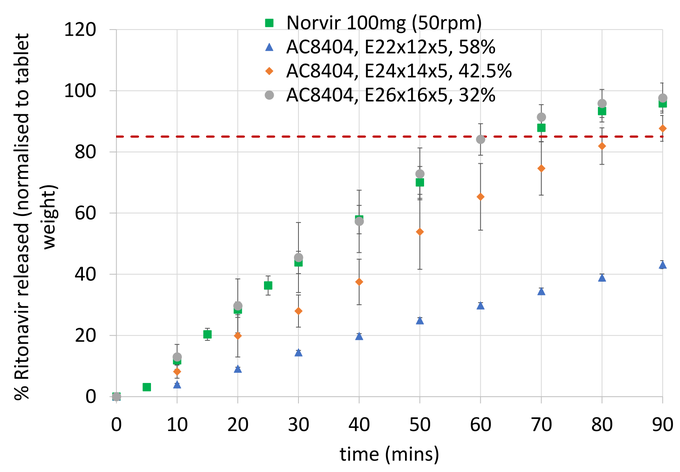


Figure 13: Product performance - % Ritonavir released (normalised to tablet weight) versus time. Norvir 100mg, Abbvie (green square), 3DP tablet E22 (blue triangle), 3DP tablet E24 (orange diamond), 3DP tablet E26 (grey circle). Red dashed line – 85% released.

References

1. Prasad E, Islam MT, Goodwin DJ, Megarry AJ, Halbert GW, Florence AJ, Robertson J 2019. Development of a hot-melt extrusion (HME) process to produce drug loaded Affinisol™ 15LV filaments for fused filament fabrication (FFF) 3D printing. Additive Manufacturing 29:100776.

Conclusion

A novel integrated HME-3D printer, the HUB 'Additive-Manufacturing-MicroFactory' enabled streamlined manufacture and performance testing of ASD formulation consisting of Ritonavir in Soluplus® polymer. By altering the porosity of the tablet core through additive manufacturing, product performance equivalent to a commercial product was obtained.

Acknowledgements The authors would like to acknowledge that this work was carried out in the CMAC National Facility supported by the EPSRC (Grant ref EP/P006965/1) and by UKRPIF (UK Research Partnership Fund) award from the Higher Education Funding Council for England (HEFCE) (Grant ref HH13054). G. W. Halbert is funded by Cancer Research UK (C149/A20496). We would like to thank the National Facility team, in particular Martin Ward, Rachel Feeney and Thomas McGlone, for their support in this project. We would also like to thank BASF for the donation of the Soluplus® polymer.