Title

Solid dispersions: Improving drug performance through tablet micro-structure design

Author

Elke Prasad[a], John Robertson[a], Gavin W. Halbert[a]

Affiliation

[a]*EPSRC Future Manufacturing Research Hub in Continuous Manufacturing and Advanced Crystallisation, University of Strathclyde, Technology and Innovation Centre, 99 George Street, Glasgow, G1 1RD, UK*

Purpose

Solid dispersions formulations manufactured by Hot-Melt-Extrusion (HME) have shown to improve drug release for BCS class II drugs, such as Mefenamic acid (MFA). Drug release for MFA is highly dependent on particle size. Commercially available MFA capsules have shown high variability in their drug release profile[1] which may lead to variable efficacy. This study shows how solid dispersion formulations and microstructure design significantly improve product performance.

Methods

Solid dispersion formulation of 50% w/w Mefenamic acid (MFA, Sigma Aldrich) and Soluplus (BASF) containing 15% w/w Sorbitol (Merck) as plasticiser (SOL15) was prepared by HME (Process 11, Thermofisher). The formulation was a) pelletised and hand filled into size 0 hard gelatine capsules and b) 3D printed (3DP) with a porous core exposed to the surface (Figure 1) to achieve a MFA dose of 250mg. Neat MFA powder and a physical mixture (PM) of 50% (w/w) MFA and SOL15 powder were also hand filled into size 0 hard gelatine capsules to generate a MFA dose of 250mg.

Pellets were prepared by cutting the HME filament (~2 mm diameter) to the length of approximately ~2mm. The 3DP tablets were printed with a novel in-house designed integrated HME-3D printer (Intellectual Property Office UK, patent application number 2101534.2). The 3D printed tablet shape was elliptical with a length of 22 mm, width of 12 mm and height of 5mm. The Infill % was set to 47.3%, which equated to an infill line distance of 0.85 mm (gap between infill lines). No top or bottom layer were printed to create a porous tablet core.

Drug release profiles of all three formulations were established by performing a Dissolution test based on USP 37 of Mefenamic acid capsules (n=6) in Tris buffer pH 9 and UV analysis. The % drug release (normalised to tablet weight) was calculated and reported.

Results

Whilst MFA powder achieved a very consistent released, it failed to release >85 % content within 60 minutes (Figure 2A). The physical mixture showed greater variation between the 6 tablets, but released >85% content at 55 minutes. The pelletised solid dispersion formulation significantly improved drug release compared to neat MFA powder and the PM, >85% drug release within 35 minutes and therefore complying with pharmacopeial release requirements (>85% at 45 minutes) (Figure 2B). The variation between individual tablets was also lower compared to the PM. The 3DP tablet, with a highly controlled microstructure, achieved complete drug release at 20 minutes

(91.6%). The variation in drug release was very high at 10 minutes only and very low at all other data points.

Conclusions

Solid dispersion formulation significantly improved the drug release profile by increasing the consistency and reducing the time to achieve complete drug release (>85%) to 35 minutes and 20 minutes for the 3DP tablet.

This demonstrates the possibility of fine tuning drug release profiles through micro-structure control by 3DP

Images

Figure 1: 3D printed tablet with porous core: elliptical shape with dimensions of 22 mm length, 12 mm width and 5 mm height. Infill percentage 47.3%. No top or bottom layer were printed.

Table/Charts

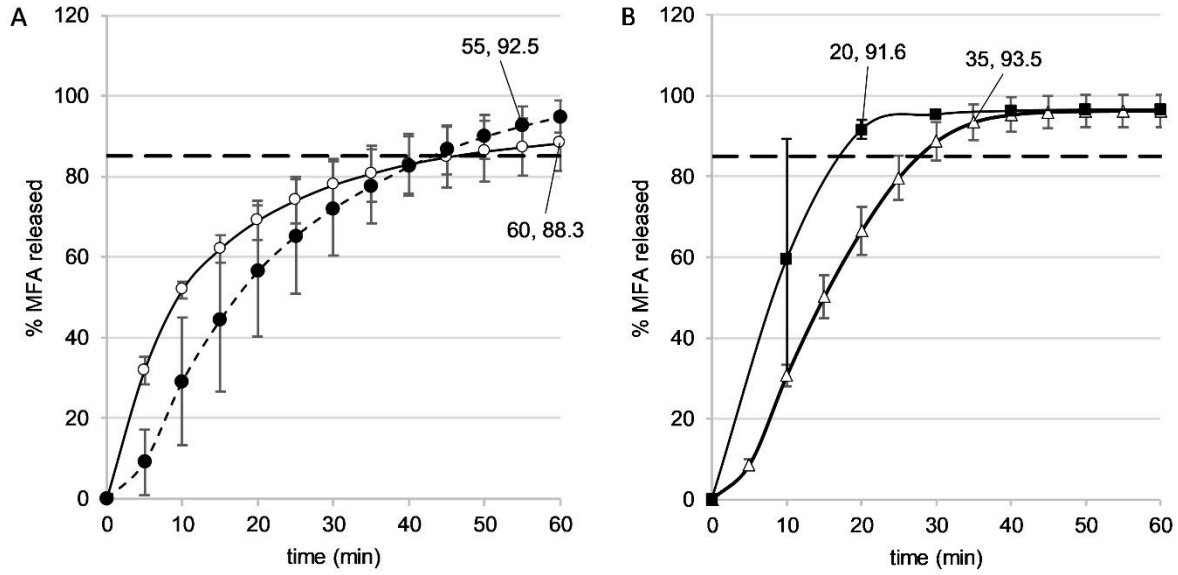

Figure 2: % drug release over time for A) MFA powder - open circle; Physical mixture of 50% w/w MFA and SOL15 – closed circle and B) pelletised extrudate of 50% w/w MFA and SOL15[1] – open triangle and 3D printed tablet of 50% w/w MFA and SOL15 – closed square. Data labels: (minutes, % MFA released (mean ± standard deviation) (n=6).

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 and Corin Mack for their support in this project. We would also like to thank BASF for the donation of Soluplus® polymer.

References

1. Prasad E, Robertson J, Halbert GW 2020. Improving consistency for a Mefenamic acid immediate release formulation. J Pharm Sci 109(11):3462-3470.