Upscaling of hot-melt extrusion for the manufacturing of solid dispersions: a case study with poly(ethyleneglycol-g-vinylalcohol) and miconazole

S. Guns\textsuperscript{a}, J. Vangoidtsenhoven\textsuperscript{a}, J. Martens\textsuperscript{b}, V.B.F. Mathot\textsuperscript{c}, G. Van den Mooter\textsuperscript{a}

\textsuperscript{a} Laboratory for Pharmaceutical and Biopharmacy, University of Leuven Herestraat 49, box 921, 3000 Leuven, Belgium.
\textsuperscript{b} Centre for Surface Chemistry and Catalysis, University of Leuven, Kasteelpark Arenberg 23, 3001 Heverlee, Belgium.
\textsuperscript{c} SciTe B.V., Ridderlaan 6, 6162 AK Geleen, the Netherlands; Department of Chemistry, University of Leuven, Celestijnenlaan 200f, box 2404, 3001 Heverlee, Belgium.

**Purpose**

To investigate the effect of upscaling the hot-melt extrusion process on the kinetic miscibility of solid dispersions of a poorly soluble drug (miconazole) and a semi-crystalline copolymer (poly(ethyleneglycol-g-vinylalcohol), EG/VA) as drug polymer system (EPS). The drug-polymer demixing was observed from a drug content of 47\% w/w miconazole (polymorph II) (confirmed with XRPD).

**Methods**

Solid dispersions made up of miconazole and EG/VA were prepared by hot-melt extrusion. The first type of extruder was a lab scale co-rotating, internal circulating mini extruder (Sci Micro compounding, DSM-Explore, The Netherlands) (batch size 4.5g). The internal circulation time was 1 min, screw speed was 200rpm and the temperature was set at 170\(^\circ\)C. These solid dispersions were prepared with respectively 9, 15, 20, 25, 31, 35, 41, 47 and 50\% w/w of miconazole. These samples are referred to as sample L9, L15, L20, L25, L31, L35, L41, L47 and L50 respectively.

The second type of extruder was a co-rotating pilot scale extruder (AMP19PC, APV Baker Ltd, UK) with a continuous throughput. The speed was set at 200rpm, feed rate at 3.1kg/h, and the temperature was 160\(^\circ\)C. These solid dispersions were prepared with respectively 9, 18, 29, 34, 39, 45, 50, 55 and 60\% w/w of miconazole. These samples are referred to as sample P9, P18, P29, P34, P39, P45, P50, P55 and P60 respectively.

**Stability**

After 24h: Crystalline miconazole was observed from a drug concentration of 35\% w/w.

An amorphous miconazole rich-phase could be detected in the 50\% w/w sample.

After 15 days: Crystalline miconazole was observed from a drug concentration of 31\% w/w.

An amorphous miconazole rich-phase could be detected in the 50\% w/w sample.

**Results: Hot-melt extrusion with lab scale extruder**

**Results: Hot-melt extrusion with pilot scale extruder**

**Temperature control**

**Shear and temperature**

Lab scale extruder:

40\% w/w MICO 170\(^\circ\)C 200rpm

\begin{itemize}
  \item No denaturing
  \item 130\(^\circ\)C – 200rpm: Crystalline MICO & amorphous miconazole rich-phase
  \item 170\(^\circ\)C – 400rpm: Crystalline miconazole
\end{itemize}

Importance of shear forces and operating temperature!

**Conclusions**

The kinetic miscibility of the samples prepared with the lab scale extruder was slightly higher than the samples prepared with the pilot scale extruder. As the solid dispersions with high drug load were unstable over time, demixing occurred, slightly faster for the samples prepared with the lab scale extruder. After 15 days, the levels of molecular mixing were comparable, pointing to the predictive value of samples prepared on laboratory scale.

Additionally the lab scale extruder proved to be a very useful tool to find a suitable operating window for the production of solid dispersions with hot-melt extrusion.