SUMMARY
and general conclusions

Despite the widespread use in the plastics industry, hot-melt extrusion processability and material behaviour of pharmaceutical formulations during melt processing is still insufficiently understood. Furthermore, in the early stage of development, only limited and expensive drug substance is available and restricts the number of performable tests. Given the latter issues, there is a need for rational assessment of the processability and potential of the drug formulation before conducting large scale extrusion experiments. Moreover, the impact of scale-up to larger equipment on the material and process properties is poorly understood. Hereby, the overall aim of this doctoral study is to improve understanding of pharmaceutical melt processability and scale-up to support rational development of drug products via melt processing techniques (e.g. hot-melt extrusion and injection molding).

Chapter 1 provided a general introduction to the concept of pharmaceutical hot melt extrusion, pharmaceutical continuous manufacturing and two quality by design tools which were comprehensively used throughout this doctoral thesis: rheology and process analytical technology.

Chapter 2 investigated (i) the influence of the drug solid-state (crystalline or dissolved in the polymer matrix) on the melt viscosity and (ii) the influence of the drug concentration, temperature and shear rate on polymer crystallization using rheological tests. Poly (ethylene oxide) (PEO) (100.000 g/mol) and physical mixtures (PM) containing 10-20-30-40% (w/w) ketoprofen or 10% (w/w) theophylline in PEO were rheologically characterized. Rheological tests were performed (frequency and temperature sweeps in oscillatory shear as well as flow-induced crystallization experiments) to obtain a thorough understanding of the flow behaviour and crystallization of PEO-drug dispersions. It was found that theophylline did not dissolve in PEO as the complex viscosity

(η*) of the drug-polymer mixture increased as compared to that of neat PEO. In contrast, ketoprofen dissolved in PEO and acted as a plasticizer, decreasing η*. Acting as a nucleating agent, theophylline induced the crystallization of PEO upon cooling from the melt. On the other hand, ketoprofen inhibited crystallization upon cooling. Moreover, higher concentrations of ketoprofen in the drug-polymer mixture increasingly inhibited polymer crystallization. However, flow-induced crystallization was observed for all tested mixtures containing ketoprofen. The obtained rheological results are relevant for understanding and predicting HME processability (e.g., barrel temperature selection) and downstream processing such as injection molding (e.g., mold temperature selection). It can be concluded that rheology is an indispensable characterization toolbox to predict the processability of drug-polymer melt formulations.

Chapter 3 elucidated the impact of the injection mold temperature upon the polymer crystallinity, its microstructure and the resulting drug release from immediate and sustained release tablets containing semi-crystalline polymers. The study investigated an immediate release formulation containing 20% (w/w) ketoprofen (KETO) in poly (ethylene oxide) (PEO) and a sustained release formulation containing 20 - 40% (w/w) metoprolol tartrate (MPT) in polycaprolactone (PCL). The physical mixtures of drug-polymer were characterized via isothermal crystallization experiments using DSC and rheological measurements to elucidate the impact of the drug solid-state upon the crystallization kinetics. Tablets were prepared using various thermal histories, i.e. extrusion barrel temperature and injection mold temperatures were selected based on the rheological characterization. Polymer crystallinity and microstructure in the tablets was characterized via DSC and polarized optical microscopy. The results showed that the differences in PEO crystallinity induced by the various mold temperatures did not affect the KETO dissolution from the tablets. On the other hand, MPT (20 - 40% w/w) dissolution from the PCL matrix when extruded at 80 °C and injection molded at 25 and 35 °C was significantly different due to the changes in the polymer microstructure. Moreover, more perfect polymer crystals are obtained with higher mold temperatures, decreasing the drug diffusion rate through the PCL matrix. The results presented in chapter 3 imply that the injection mold temperature should be carefully controlled for sustained release formulations containing hydrophobic semi-crystalline polymers.

Chapter 4 investigated the use of a mini melt extruder to study the impact of process conditions (temperature and shear rate) during processing. In-line Raman spectroscopy was implemented in

the barrels, allowing to monitor the melt during processing. The aim of this study was twofold: to investigate (I) the influence of key process parameters (screw speed - barrel temperature) upon the product solid-state transformation during processing of a sustained release formulation in recirculation mode; (II) the influence of process parameters (screw speed - barrel temperature - recirculation time) upon mixing of a crystalline drug (tracer) in an amorphous polymer carrier by means of residence time distribution (RTD) measurements. The results indicated a faster mixing endpoint with increasing screw speed. Processing a high drug load formulation above the drug melting temperature resulted in the production of amorphous drug whereas processing below the drug melting point produced solid dispersions with partially amorphous/crystalline drug. Furthermore, increasing the screw speed resulted in lower drug crystallinity of the solid dispersion. RTD measurements elucidated the improved mixing capacity when using the recirculation channel. In-line Raman spectroscopy has shown to be an adequate PAT-tool for drug product solid-state monitoring and elucidation of the mixing behavior during processing in a mini extruder. The implementation of Raman spectroscopy in a mini scale extruder is an asset in the early stage of product development.

In **Chapter 5**, the volumetric scale-up law was assessed for its applicability to scale-up from a laboratory-scale extruder (11 mm diameter) to a pilot-scale extruder (16 mm diameter) with geometric similarity using low feed rates (0.1-0.26 kg/h at lab-scale). A sustained release formulation was extruded on both scales using scaled feed rates according to the volumetric scale-up law. The specific mechanical energies, drug solid-state, drug dissolution and the residence time distribution responses (i.e. axial mixing degree, mean residence time, width of distribution) were compared between both scales. The results showed that the difference in mean residence time between both scale extruders reduced with higher throughput and thus fill level. Overall, the specific mechanical energies (SME) were comparable between scales when using the volumetric scale-up law (i.e. applying scaling factor $q = 3$) and were exactly matching with a scaling factor of $q = 2.6$. It was found that plug flow conditions at lab-scale should be avoided before scaling up to obtain similar SMEs. The same degree of axial mixing (represented by the Peclet number) was demonstrated at a scaling factor of $q = 2$. If drug solid-state is a critical quality attribute (CQA), focus should be on the screw speed and cooling capacity of the larger scale extruder. The drug dissolution showed similarity between scales and was independent of drug solid-state for this formulation, indicating that successful scale-up was possible.

Chapter 6 studied the transfer of in-line Raman spectroscopic models for API quantification and solid-state classification from a mini to a pilot-scale hot-melt extruder. Raman spectra were continuously collected in the extrusion die while processing calibration and validation physical mixtures in a mini extruder, yielding a calibration spectral data set (miniCal) and a validation spectral data set (miniVal). Similar calibration and validation physical mixtures were processed in a pilot-scale extruder in an earlier study by Saerens et al. (pilotCal and pilotVal spectral data sets). A PLS model was developed by regressing the preprocessed miniCal spectra (SNV - spectral region 1550-1780 cm^{-1} of miniCal) versus the API concentration. Various standardization techniques were used to perform the calibration transfer to the pilot-scale extruder: Direct Standardization (DS) and Piecewise direct standardization (PDS) and slope/bias correction of predictions. Validation of the method was done by means of accuracy profiles. Furthermore, a Raman classification model for solid-state prediction was developed on the mini extruder using Celecoxib and Eudragit® E PO. Barrel temperature (130-150°C) and physical mixture composition (30-50% CEL in Eudragit® E PO) were varied to obtain extrudates with different solid-state (crystalline solid dispersion or glassy solid solution). The same physical mixtures were processed in a pilot-scale extruder in an earlier study. A PLS-DA model was developed with the Raman spectra collected on the mini extruder. Calibration transfer of the classification model to the pilot scale extruder was attempted by spectral preprocessing, DS and PDS. The classification results from the transferred pilot scale spectra were evaluated using the misclassification table. A good transfer of the Raman calibration model for API quantification from the mini to the pilot-scale extruder was obtained in a certain concentration range (25 - 32.5 %w/w) via univariate slope/bias correction. Also, a good transfer of the solid-state classification model was obtained for all transfer methods (preprocessing, DS and PDS). This study showed that it is possible to develop empirical models for API quantification and solid-state classification on a mini scale which are usable on a larger scale extruder.

Chapter 7 outlines the broader international context, relevance and future perspectives.

It can be concluded that rational development of drug formulations for pharmaceutical melt processing should contain a thorough rheological characterization of the drug-polymer melt mixture in combination with an investigation of the physicochemical properties of the raw materials. A logical next step should be to investigate the drug formulation on a mini scale extruder at relevant process conditions (temperature and shear rates). In-line Raman spectroscopy can

provide additional chemical information during processing on a mini scale to verify if the quality of the product is sufficient before further scale-up. This thesis also improved understanding of scale-up for parallel extruders and identified key process conditions for successful scale-up (i.e. adequate axial mixing and shear rate). Moreover, the collected spectra on a smaller scale extruder can further be used to develop empirical models that are usable on a larger scale extruder to facilitate the scale-up and process control without extensive use of product.