

Investigation of pharmaceutical hot-melts using Rheo-microscopy

Authors: Fritz Soergel, Dirk Hauch, Matthias Jährling, Katharina Paulsen, Astrid Weber-Kleemann, Thorsten Cech, Andreas Gryczke, Stefan Schmölzer and Damir Zecevic

Overview

Purpose: Provide on the one hand an efficient screening tool for hot-melt extrusion (HME) formulation development and make available on the other hand rheological parameters for process development and optimization, as well as for modeling calculations for compounding and extrusion.

Methods: Rheometry and polarization light microscopy up to 300 °C with well-defined heating and cooling rates, temperature profiles and shear rates as well as oscillatory testing.

Results: This combined method requires only a small sample volume and delivers efficiently significant and well-correlated rheological data and microscopic images, which allow to investigate formation and stability of solid solutions or crystalline dispersions. Moreover these results deliver at the same time meaningful parameters for extruder dimensioning and processability and for simulation calculations of the pharmaceutical HME process.

Introduction

The simultaneous acquisition of rheological data and microscopic images is already an established research tool for a variety of applications in industries like e.g. food, petrochemicals and cosmetics. This combined method is applied to investigate processes like emulsification, coalescence, foaming and crystallization as well as for the determination of number, morphology and size distribution of crystals.^{1,2}

Formulation development

More recently, the pharmaceutical industry faces the challenge to find the right solubilizers and processing

equipment/ parameters for newly developed Active Pharmaceutical Ingredients (APIs) to be able to process them and achieve high bioavailability, long term stability as well as good drug release characteristics. In order to produce a stable drug, the goal in R&D is to develop a formulation containing the API, suitable polymers or waxes (as solubilizers), plasticizers and processing additives, leading to a solid solution which does not show recrystallization.^{3,4} With other APIs, the formulation of a crystalline dispersion may be the goal, because for those APIs crystal ripening may be less fatal regarding long term stability and drug release than a potential recrystallization of a solid dispersion.

Traditionally, different measurements have to be made parallel to each other, for example with a hot stage microscope with heating/cooling capability (to determine crystals and their melting and recrystallization behavior) or a Kofler Bench (metal plate with defined temperature gradient to determine softening and melting ranges in a subjective way). More comprehensive analytical methods are Differential Scanning Calorimetry (DSC; determines glass transition, melting/crystallization temperatures, melting/crystallization enthalpies) and Thermogravimetric Analysis (TGA; determines water content, thermal degradation).⁵

For hot melt extrusion, a screening tool is most beneficial which delivers consistent information about crystallinity in dependence of temperature and at the same time relevant parameters for processability – like softening, melting and degradation temperature and the information, how viscosity changes with temperature and with shear rate.

Process development/optimization and modeling
 Simultaneous rheometry and polarization microscopy allows studying the melting behavior of crystals in the heating run, to investigate whether a recrystallization occurs in the cooling run and derive suitable processing parameters for compounding and extrusion.

Moreover, frequency sweeps measured at different temperatures can be superimposed to a so called “Master Curve“ utilizing time temperature superposition (TTS).^{6,7} Master curves can be plotted for different relevant temperatures providing the respective relationship between viscosity curve and processing shear rates (Fig. 1) for process development/optimization and extruder dimensioning – depending on the temperature tolerance of the materials and the extruder characteristics like torque range and share rate range. Hence, the rheometer serves as a “Zero Level Extruder“ for pure components as well as for mixes with various components and concentrations of polymers, APIs, plasticizers and processing additives.⁸

Comparing the screening with a rheometer and with a small extruder, the rheometer on the one hand has a much higher throughput because of its much smaller sample volume (1 mL or less) and much shorter time for loading/

feeding and cleaning. On the other hand, the energy input in a rheometer in oscillatory testing is due to thermal energy while in an extruder the energy input is provided mainly mechanically by the screws.

Master curves are also capable of providing rheological input for process simulation calculations.⁵ Process simulation can help identifying appropriate extruder setups as well as setting parameters and hence reduce material consumption and labor intensive development time (trial and error would be the alternative approach). Process simulation is a well established method in designing molds and flow channels, where it reduces development time as well as costs significantly.

Figure 1 shows the viscosity curve of a technical polymer (LLDPE) at 220 °C as well as typical shear rate ranges for processing technologies (black) and a typical viscosity range for compounding and extrusion (grey). The viscosity data were acquired using oscillatory rheometry (blue; Thermo Scientific™ HAAKE™ MARS™) and extrusion capillary rheometry with a torque rheometer (Thermo Scientific™ HAAKE™ PolyLab™) equipped with a slit capillary die (red) or a rod capillary die (green). According to the empirical Cox-Merz Relation, the oscillatory complex dynamic viscosity as a function of angular frequency (blue) and the complex viscosity as a function of shear rate (red and green) can be superimposed for unfilled polymer melts and polymer solutions, as shown in Fig. 1. This is the reason why data measured in oscillation can be used to predict the processability in compounding and extrusion.⁷

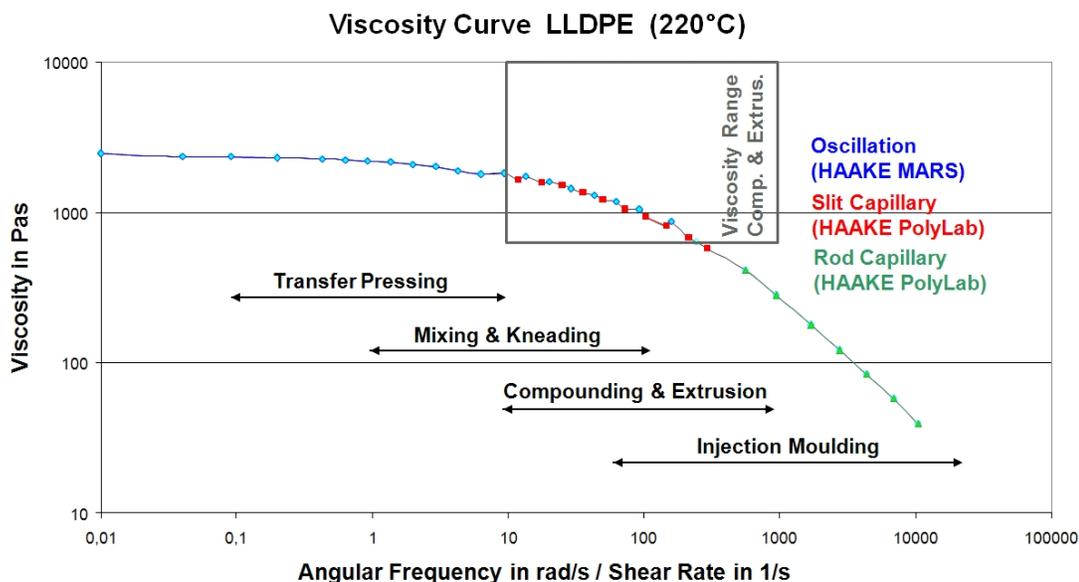


Figure 1: Viscosity curve of LLDPE and typical shear rate ranges in rheometry as well as in polymer processing.

Materials

An essential requirement for HME investigations is that all kind of samples from all processing steps, i.e. powder, extrudate and injection molded samples, can be characterized — pure components and mixes as well.⁵

For our investigations, we selected as model systems Soluplus® (BASF, approved for pharmaceutical applications,³ Figure 2) as polymer and Ibuprofen (BASF, ACROS) as well as Theophylline (BASF) as APIs.



Figure 2: BASF Soluplus® powder.³

Powder (ground)

With a spatula, a disc-shaped powder layer was formed (diameter 35 mm, thickness approx. 2 mm). Using the normal force control capability of the HAAKE MARS rheometer, a normal force of 30 N to 40 N was applied with the plate/plate measuring geometry, in order to interlock the particles, so that an amplitude sweep and a frequency sweep with the powder could be recorded at sample loading temperature. The amplitude sweep delivered the Linear Viscoelastic Range (LVR) with the powder and allowed to determine a suitable deformation amplitude range for the subsequent measurements — with too low oscillation amplitude the signal-to-noise ratio would have been insufficient, with too large amplitude the powder would have been conveyed out the sample gap.

The heating ramp revealed the softening and melting behavior of the powder sample (for example: Fig. 9). After the sample was molten, the sample gap was under filled and filling needed to be optimized by closing the gap further, then the heating run could be finished, followed by a cooling run (for example: Figure 11).

If heating curves are requested or the melting behavior of crystals needs to be investigated (Figs. 9, 10), extruded as well as injection molded samples can be ground and then treated as described above.

Extrudate (pellets, strand)

While powder can be loaded and measured at ambient temperature, extrudate sample loading requires melting of the extrudate pieces in order to obtain a proper mechanical coupling between measuring geometry and sample as well as proper filling of the measuring gap. Pellets or strand pieces were placed on the lower part of a plate/plate measuring geometry at a temperature above the sample's melting temperature (Figure 3). Then the upper geometry was lowered step by step while the sample was melting. Finally, the sample rim was trimmed (cylinder-shaped) with a trimming tool.⁹ Afterwards the sample gap was closed by 5% to 10% in order to obtain ideal gap filling (slightly barrel-shaped). Then amplitude and frequency sweeps of the melt and a cooling ramp were measured.



Figure 3: Extrudate pieces placed on the lower plate of the measuring geometry for melting and subsequent loading and trimming.

Cast (injection molded discs and bars)

Compared to extrudate pieces, injection molded discs can be loaded quicker and easier into a plate/plate measuring geometry at elevated temperatures and the completeness and reproducibility of gap filling (and therefore of the rheological data) is much better.

Injection molded solid bars can be measured in the glassy and rubbery state with DMTA solid sample clamps^{10,11} in the CTC oven (Figure 4) of the Thermo Scientific HAAKE MARS rheometer to investigate e.g. the impact of ingredients and processing parameters (like screw configuration, filling degree, residence time, temperature and shear rate) on the glass transition characteristics.¹³

Advantages of the self-centering and self-tightening spring-loaded DMTA solid sample clamps are faster loading (neither thickness measurement nor spacer adaption required), excellent reproducibility (self-centering) and no need to reopen the oven at lowest temperature for retightening of the solid sample clamps with the related issues of humidity precipitation and ice formation on sample clamp and measuring shaft (self-tightening).

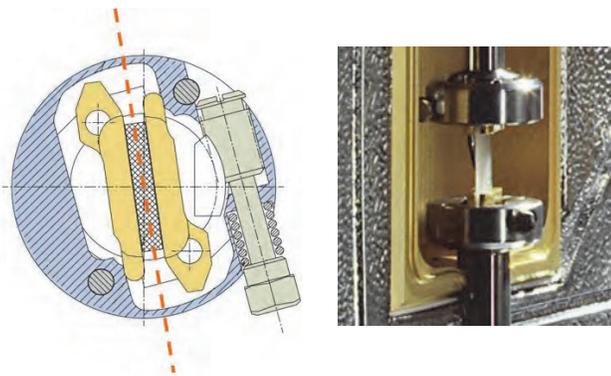


Figure 4: Self-centering and self-tightening spring-loaded DMTA solid sample clamps (drawing left) in a CTC oven and with an injection molded bar sample (right).

Methods

With the Thermo Scientific Material Characterization portfolio, a HME workflow can be easily investigated. The rheometer serves as a screening tool and as a “zero level extruder” and provides information regarding processing parameters and extruder dimensioning. For easy scale up, a family of 11 mm, 16 mm and 24 mm parallel twin screw extruders is available all of them having the same set of dimensionless quantities for smart scalability^{5,8}. Differential Scanning Calorimeters (DSC) and Thermo Gravimetric Analyzers (TGA) are part of the portfolio of our cooperation partner NETZSCH Analyzing & Testing.

The powder samples were fed into the Thermo Scientific™ HAAKE™ MiniLab for compounding and (after switchover via the pneumatically actuated bypass valve) for extrusion of a strand. The HAAKE MiniLab can be used with counter-rotating conical twin screws for conveying or with corotating conical twin screws for mixing — deployed here. A part of the back flow channel is a (relatively wide) slit capillary die with two pressure sensors (Figure 5), facilitating viscosity measurements in the shear rate range from 1 to 100 1/s.

The extruded sample material from the HAAKE MiniLab was directly transferred into the temperature-controlled sample container of the Thermo Scientific™ HAAKE™ MiniJet mini injection molding machine, which was used for the injection molding of sample discs and DMTA sample bars (Figure 6).



Figure 5: HAAKE MiniLab can be used with counter-rotating or corotating conical twin screws (center), has a bypass valve (right), a back flow channel with a slit capillary with two pressure sensors for viscosity measurement (top) and an extrusion channel (bottom right).



Figure 6: HAAKE MiniJet molds with injection molded samples of different shape and size.

For rheometry, the HAAKE MARS rheometer was used with a temperature controlled polarization microscope (Thermo Scientific™ HAAKE RheoScope™ module with electrical hood™ EL-H, cold light source, lens 5 x or 20 x) and a 20 mm plate rotor or a 35 mm plate rotor with polished surface for enhanced quality of the microscopic images. The resolution with the 20 x lens was 1 μm, the temperature range up to 300 °C. For powerful and well-controlled counter-cooling, a refrigerated circulator was used — the bath temperature adjusted 10 K to 20 K below the minimum measuring temperature. The bath fluid’s flow rate was controlled via continuously adjustable valves in the HAAKE MARS rheometer. At subambient temperatures, the lens was kept clear by flushing it with a small flow rate of dry purge gas.

Two polarization filters can be moved into the ingoing and outgoing optical paths (Figure 7) and one of the both filters can be rotated to cross the polarization filters for contrast enhancement and for discrimination of crystalline or birefringent structures.

Polarization filter (on/off, angle adjustment), lens (radial and focus adjustment) as well as camera control (contrast, brightness, gamma, (auto)integration time) are all set and controlled via the Thermo Scientific™ HAAKE™ RheoWin™ software, which allows furthermore to save and load different sets of settings also within a measuring job: E.g. at first images of the melt without polarization filters can be recorded at elevated temperatures to discriminate different kind of particles and then, during the cooling run, images with crossed polarization filters to capture crystal growth. Changing the lens is also possible while the sample is in place.

The glass transition temperatures were determined by means of Differential Scanning Calorimetry (DSC). For the presented measurements, the NETZSCH DSC 204 F1 Phoenix® was used with autosampler and with Aluminum

crucibles with pierced lids. With this method, the powder samples could be easily prepared and investigated as well as the injection molded samples.

Figure 8 shows a cross section through the measuring cell. The heat flux sensor is incorporated in the cylindrical silver furnace. With its homogeneously heated disc-sensor system, this set-up provides stable and reproducible baselines. Different cooling equipment is available so that a temperature range from -180 °C to 700 °C can be covered.

Results

Ibuprofen – enantiomer and racemate

Pure Ibuprofen powder was loaded at room temperature into a 35 mm plate/plate measuring geometry and pressed with a normal force of several 10 N. After an amplitude sweep, a heating run was measured with 1 K/min. The thermal expansion of the measuring set-up was

compensated automatically by using the ThermoGap functionality provided by the HAAKE RheoWin software.

When Ibuprofen melts, its complex dynamic viscosity $|\eta^*|$ and its storage modulus G' change both dramatically over approx. 7 orders of magnitude — which has of course a major impact on the processability (Figure 9). The melting temperature is strongly affected by the chirality of the Ibuprofen. The cross-over temperature, where the storage modulus G' equals the loss modulus G'' and the phase angle δ equals 45° was evaluated. The racemate (BASF) melts at 77 °C whereas the enantiomer (ACROS) melts at 52 °C. The racemate is a mixture of two types of enantiomers and reveals a change in the slope of the normal force vs. temperature curve $F_n(T)$ at that temperature at which the first enantiomer's melting is completed. Two tangents were fitted to the two slope regimes and the intersection point of the tangent was determined (57 °C).

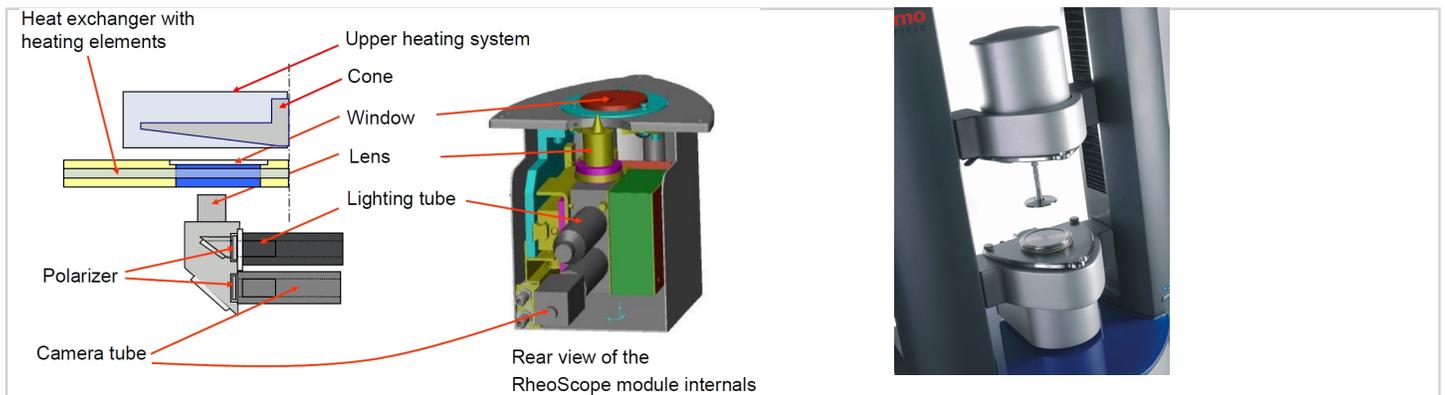


Figure 7: HAAKE RheoScope module: Schematic drawing (left: side view, center: rear view) and mounted in the HAAKE MARS rheometer (right).

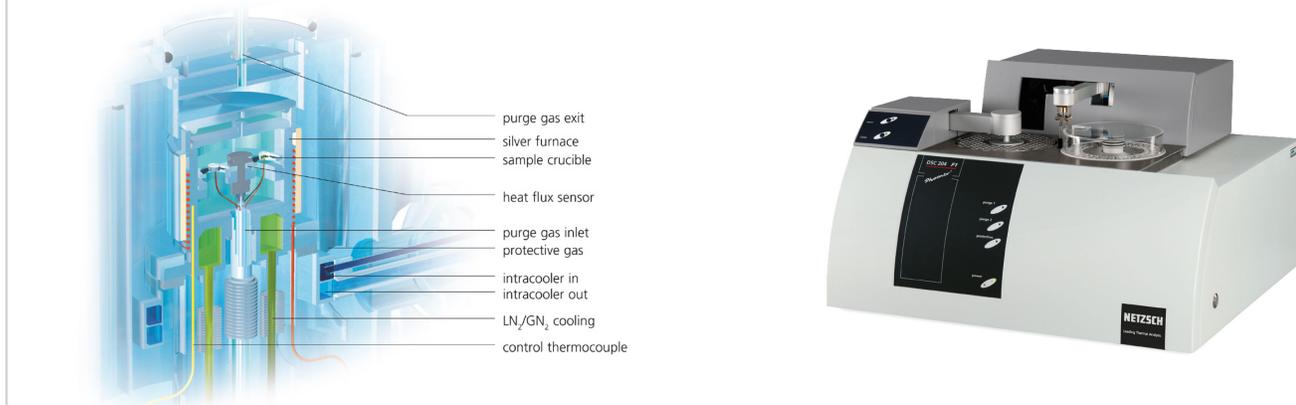


Figure 8: NETZSCH DSC 204 F1 Phoenix® (right) and cross section through its DSC cell (left).

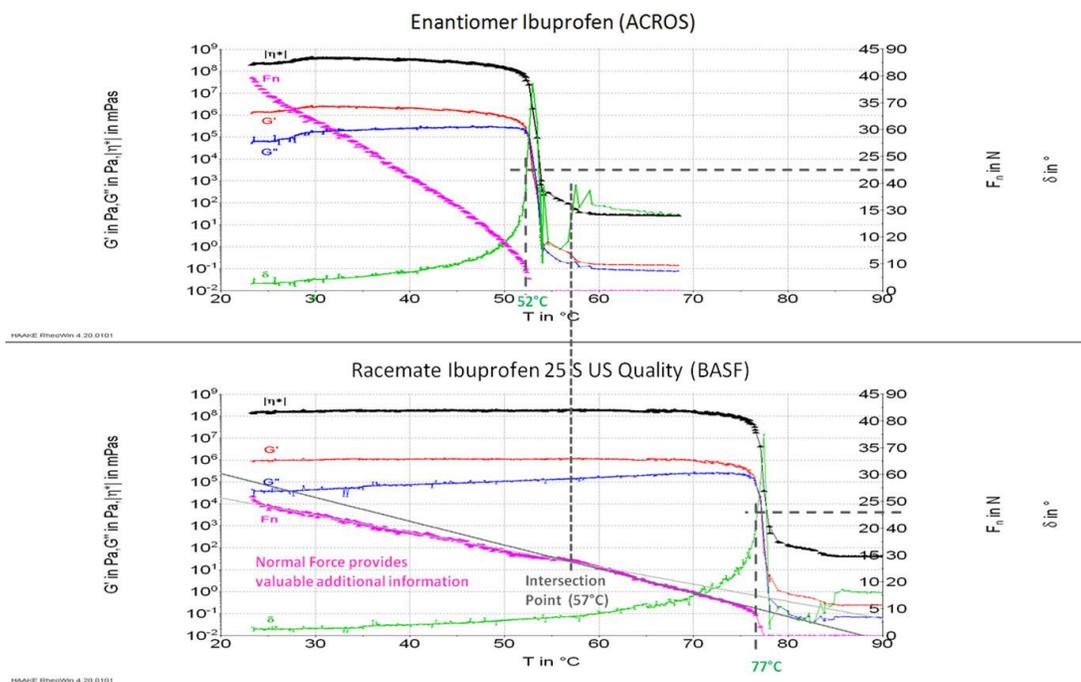


Figure 9: Heating runs (1 K/min) with Ibuprofen powder (top: enantiomer, bottom: racemate), chirality indicated symbolically top left (measuring amplitude: 0.1% with powder, first 10% then 30% with fluid, measuring mode: CD-AS¹⁴).

Ibuprofen/Soluplus 20/80

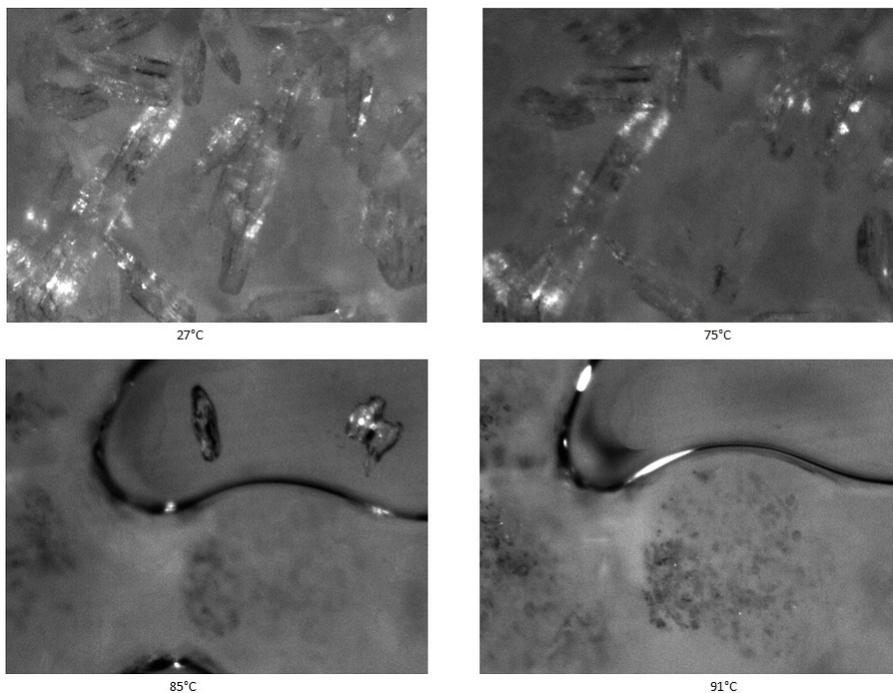


Figure 10: Powder mix with 20% Ibuprofen and 80% Soluplus[®] at 27 °C (top left) and gradual melting of the API shown in images taken at 75 °C, 85 °C and 91 °C (lens 20 x).

Ibuprofen in Soluplus[®]

Polarization microscope images of crystalline Ibuprofen powder (racemate) mixed with Soluplus[®] powder are shown in Figure 10. The images were obtained with crossed polarization filters revealing size, morphology and spatial distribution of crystals and their melting with increasing temperature. For the analysis of particle size or particle size distribution, an image analysis software (e.g. SPIP by Image Metrology¹²) can be employed.

In a subsequent cooling run, no recrystallization of the Ibuprofen occurred. Thereafter, the samples would usually be subjected to long-term stability testing according to currently valid ICH guidelines. Typical parameters for such tests are 25 °C and 60% relative humidity (RH) for standard stability testing and 40 °C and 75% RH for accelerated aging.⁵ Evaluation is made typically (e.g. after 1, 2, 4 and 8 weeks and 3, 6, 12 and 24 months).

Soluplus® — pure and with 10% or 30% Theophylline

Theophylline has a very high melting point (270 °C), which allows studying the impact of this API on the glass transition of the polymer Soluplus®. Figure 11 shows cooling ramp results with 3 powder samples, which had been heated up to 140 °C for sample loading and trimming in a plate/plate measuring geometry. From these 3 powder samples, additionally, injection molded samples (potential residual strains) were made with the HAAKE MiniLab and HAAKE MiniJet and measured with DMTA solid sample clamps in the CTC oven with a heating ramp, see Figure 12.

In both measurements, the pure Soluplus® sample (black) shows a higher glass transition temperature than the samples containing 10% (red) or 30% (blue) Theophylline. Theophylline has obviously a plasticizer effect, which shifts the glass transition of Soluplus® to lower temperatures. Interestingly, the 10% sample shows this effect to a higher extent than the 30% sample. DSC measurements confirm these findings (Figures 13, 14).

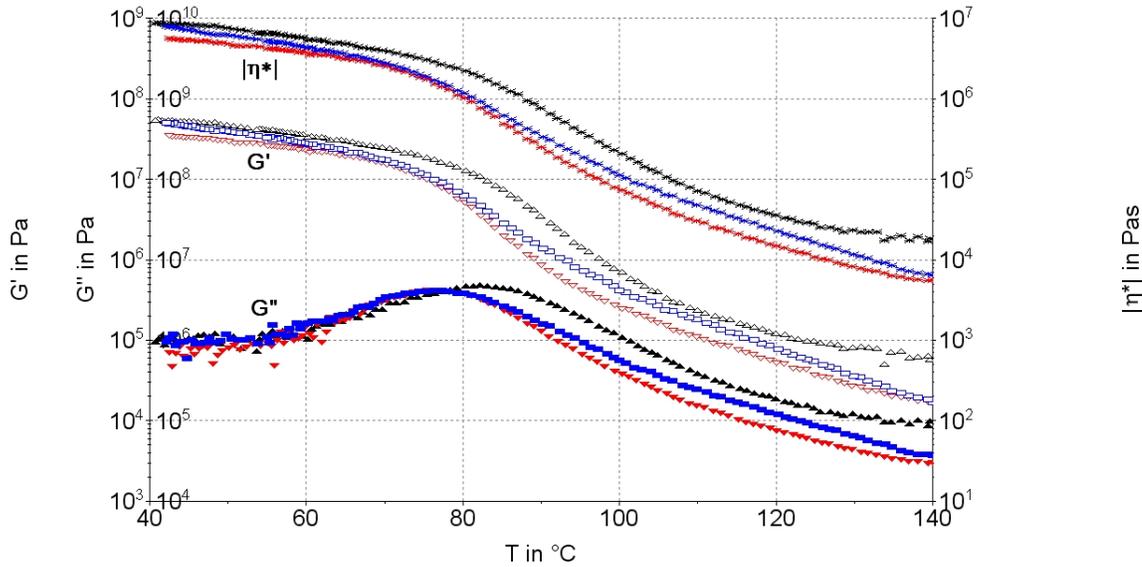


Figure 11: A cooling run (-5 K/min) with 3 powder samples molten at 140 °C with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus® measured in plate/plate measuring geometry (measuring amplitude: 0.01 %, measuring mode: CD-AS¹⁴).

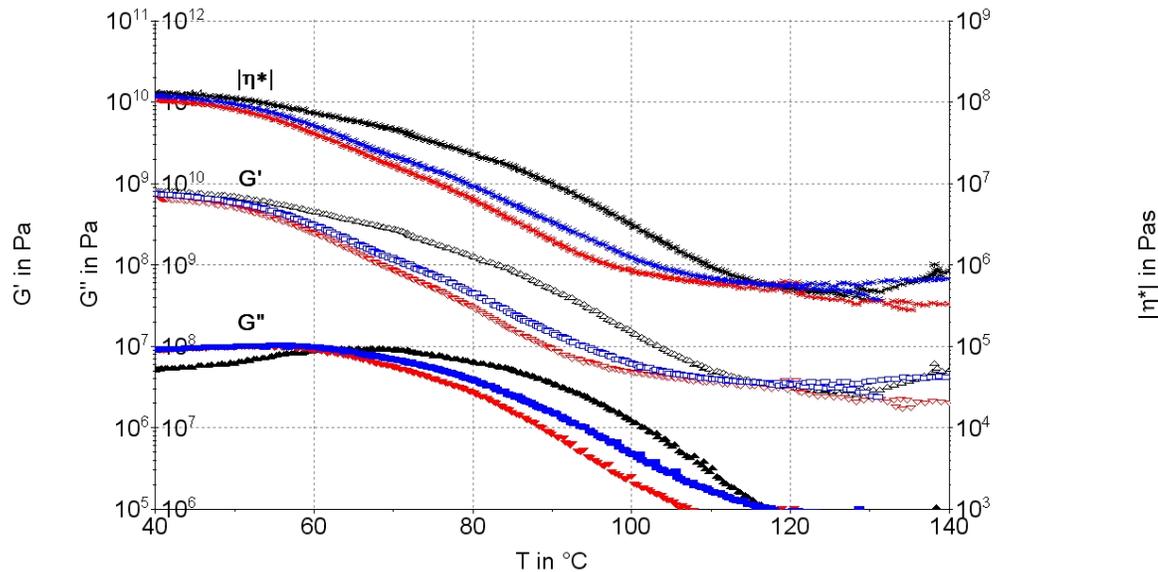


Figure 12: D heating run (5 K/min) with 3 injection molded rectangular bars with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus® measured with DMTA clamps (measuring amplitude: 0.01 %, measuring mode: CD-AS¹⁴).

Discussion

Absolute values of the storage modulus

The storage modulus G' of an unfilled and non-crystalline polymer is typically slightly above 109 Pa in the glassy state and 106 Pa in the rubbery state. Filler particles or crystals increase the G' value in the rubbery state considerably. To increase G' in the glassy state slight, high-impact filler particles or fibers (e.g. nanotubes) were required.

For the measurements with the DMTA clamps, torsional deformation is applied. As long as small amplitudes are used, a pure shear deformation of the sample bar is generated (only large amplitudes would lead to a superposition of shear deformation and of elongational deformation). The DMTA measurements with injection molded solid bars (shown in Figure 12) are really consistent. The glassy state plateau would be fully reached at temperatures lower than the measured ones.

Cooling runs with molten powder or extrudate particles in a plate/plate measuring geometry deliver on the one hand correct temperatures for the maxima in G'' (for the regarding cooling rate) but do on the other hand usually not reach the correct value for G' in the glassy state with 20 mm diameter (or bigger) because the measured deformation is then partly related to the glassy sample and partly to the torsional deformation of the measuring geometry (Figure 11). Therefore, using DTMA solid sample clamps is mandatory for a correct determination of G' in the glassy state.

Powder samples, however, may have further effects on the G' data: Figure 9 shows that there is no full coupling between the measuring geometry and the powder sample at the beginning of the heating run (up to 29 °C). Above 29 °C, the temperature-induced softening brings about full coupling. But still, the powder in the measuring gap has plenty of hollows leading to considerably lower G' values. The hollows disappear when the powder sample is melting – which of course leads to a significant under filling of the measuring geometry and the measuring gap needs to be closed manually in order to obtain proper filling and correct G' data with the molten sample.

Comparison of DTMA and DSC results

The glass transition, i.e. the loss of molecular mobility during cooling, makes itself apparent in dynamic mechanical properties as well as in specific volume, enthalpy, entropy, specific heat, refractive index etc. The glass transition data obtained with different methods are interlinked over the activation diagram⁷.

In Figure 13, the DSC curves for the second heating run on the powder samples with different concentrations of Theophylline in Soluplus® are shown: The samples were heated up with a constant heating rate of 10 K/min under nitrogen atmosphere. As the samples lost moisture (which was verified with TGA measurements) always the curve of the second heating run was evaluated.

The glass transition can be seen very clearly in these measurements as a change in the specific heat capacity, i.e. as a step in the DSC heat flow curve. Pure Soluplus® (black) shows the highest T_g and the sample with 10 % Theophylline (red) the lowest T_g . It is also evident from the results, that a further increase of the Theophylline content (30%, blue) does not lead to a lower T_g than with the 10% sample.

The results for the injection molded samples are shown in Figure 14. Here the same trend in the shift of T_g with the Theophylline concentration could be found. Furthermore, it is remarkable that for all three molded samples, T_g is shifted to lower temperatures compared to the powder samples. This effect is most likely due to the processing of the material in HAAKE MiniLab and MiniJet altering the thermal history of the samples – which can be detected by means of Thermal Analysis.

The evaluation of the DSC “mid step hight“ (second heating run; no residual strains, Figures 13, 14) and the maximum in the DTMA loss modulus curves $G''(T)$ (measured with a frequency of 1 Hz, Figures 11, 12) are delivering similar results for the glass transition temperature. Strictly speaking, an extrapolation from higher heating/cooling rates (DSC: 50, 20, 10 K/min, DTMA: 5, 2, 1 K/min) to 0 K/min would deliver the correct results – only then the hysteresis between heating and cooling runs would disappear (if then still a hysteresis would appear, it would be related e.g. to undercooling).

However, there are several differences between the DSC and DMTA method, which need to be taken into consideration – also for hot melt characterization. DSC is a static method while DMTA is a dynamic method. A risk is that without mechanical deformation, DSC samples may turn into an undercooled melt due to a lack of crystallization seeds.

The glass transition temperature can be detected with both methods very precisely. The impact of side chains and lower temperature glass transitions as well as anisotropy (e.g. direction of production or fiber direction in reinforced materials) can usually not be detected with DSC, but DMTA has a high sensitivity for these effects.

Advantages of DSC measurements are that they only require a small sample quantity, can be run in series with an autosampler, with high heating and cooling rates and are therefore used as an essential screening tool for HME formulation development, providing glass transition, melting, crystallization temperatures as well as melting and crystallization enthalpies.

Rheometry/DMTA measurements, on the other side, are closer to what happens in an extruder (Figure 1). In addition to temperature-dependent measurements (glass transition, softening, melting and crystallization temperature), they can provide amplitude- and time-dependent as well as frequency- dependent measurements (Figures. 1, 11, 12), which allow to study e.g. the impact of plasticizers and provide data for determination of molecular weight MW and molecular weight distribution, processability prediction and modeling calculations⁷.

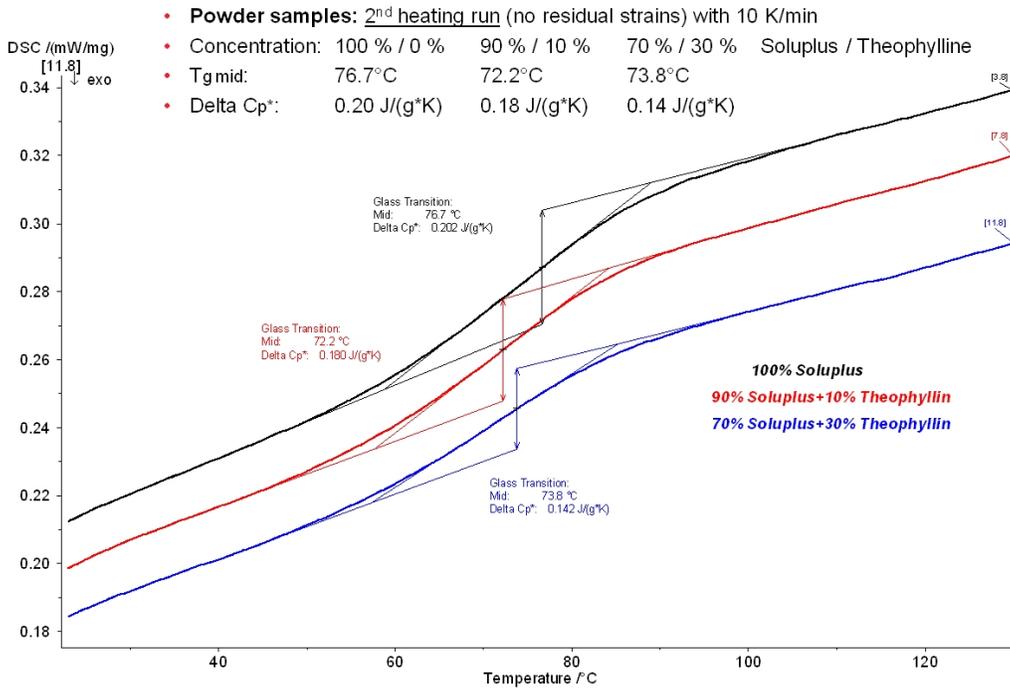


Figure 13: DSC measurements — second heating run (10 K/min) with 3 powder samples with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus®.

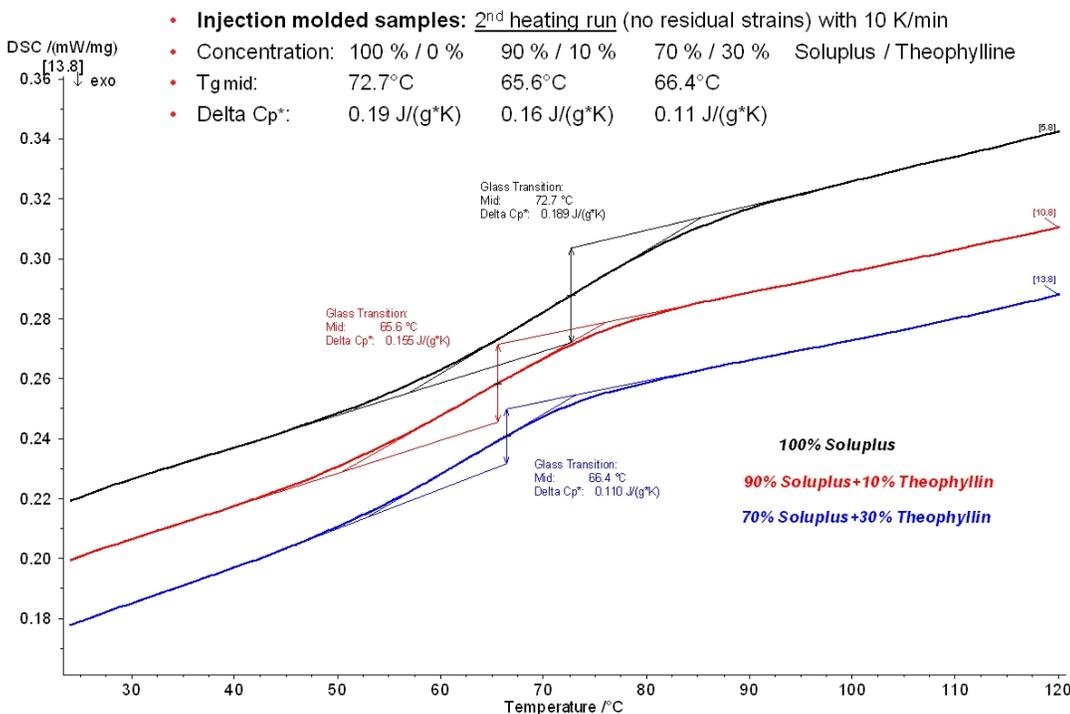


Figure 14: EDSC measurements — second heating run (10 K/min) with 3 injection molded samples with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus®.

Conclusion

The HAAKE MARS equipped with the HAAKE RheoScope module delivers a consistent set of simultaneously acquired rheological data and polarization microscopy images for purposeful hot melt formulation development and process development/optimization as well as for modeling calculation input. This combined method allows investigating pure polymers, pure APIs and mixtures of those – also with plasticizers and additives and reveals whether an amorphous solid dispersion or a crystalline solid dispersion is obtained during heating and whether it is stable during cooling or storage.

Rheometry married together with microscopy, providing well defined heating and cooling rates. is a highly efficient screening tool delivering parameters which are traditionally collected with several methods parallel to each other using different equipment (examples in brackets): Crystal concentration, morphology and distribution and their melting behavior (hot stage microscope), temperatures of softening, melting or thermal decomposition (Kofler Bench, DSC or TGA) as well as information about the glass transition (DSC). Compared to information acquired with different equipment, simultaneously collected information requires less sample, has a better correlation and higher reproducibility and is more efficient, consuming less lab space and is more cost-conscious. For a fast screening of a large number of formulations, however, always a DSC with autosampler will be employed.

Rheometry is a dynamic mechanical method and therefore close to compounding and extrusion and delivers with its temperature curves and master curves on the one hand processing parameters (softening, melting and degradation temperature as well as angular frequency/shear rate range) and on the other hand input, which is required for extruder dimensioning and modeling calculations. Therefore, rheometry serves as a “zero level extruder“. Compared to a small extruder regarding sample volume and time required for feeding, compounding and extrusion as well as cleaning, the rheometer allows a much faster screening of different combinations and concentrations of polymers,

APIs, plasticizers and additives for process development. With the most promising formulations, compounding and extrusion is then tested and optimized with a small extruder, because the energy input in a rheometer in oscillatory testing is due to thermal energy whereas in an extruder the energy input is mainly due to the mechanical energy provided by the screws.

With a family of easy scalable 11 mm, 16 mm and 24 mm twin-screw extruders (with the same set of dimensionless quantities), the subsequent scale-up can be achieved most time- and cost-efficient and reduces the time to market considerably.

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