

## Investigation of Pharmaceutical Hot-Melts via Simultaneous Rheometry and Polarization Microscopy

Jan Philip Plog<sup>1</sup>, Fritz Soergel<sup>1</sup>

<sup>1</sup> Thermo Fisher Scientific, Dieselstr. 4, 76227 Karlsruhe, Germany.

### ABSTRACT

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].

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 re-crystallization [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 re-crystallization of a solid dispersion.

In this contribution we want to show that the Thermo Scientific 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. Results will be presented that allow not only investigating pure polymers and pure APIs but also mixtures of those - also with plasticizers and additives and that reveal whether an amorphous solid dispersion or a crystalline solid dispersion is obtained during heating and whether it is stable during cooling or storage.

### MATERIALS AND METHODS

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]) as polymer and Ibuprofen (BASF, ACROS) as well as Theophylline (BASF) as APIs.

As for the methods used, with the Thermo Scientific Material Characterization portfolio, a HME workflow can be easily investigated. The HAAKE MARS 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) used are from 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 co-rotating conical twin screws for mixing – deployed here. A part of the backflow channel is a wide slit capillary die with two pressure sensors, facilitating viscosity measurements in the shear rate range from 1 to 100 1/s.

For rheometry, the HAAKE MARS rheometer was used with a temperature controlled polarization microscope (HAAKE RheoScope module with electrical upper temperature control, 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  $\mu\text{m}$ , 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 sub-ambient temperatures, the lens can be 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 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 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.

## RESULTS AND DISCUSSION

### Ibuprofen:

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 (Fig. 1). 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  $\delta$  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

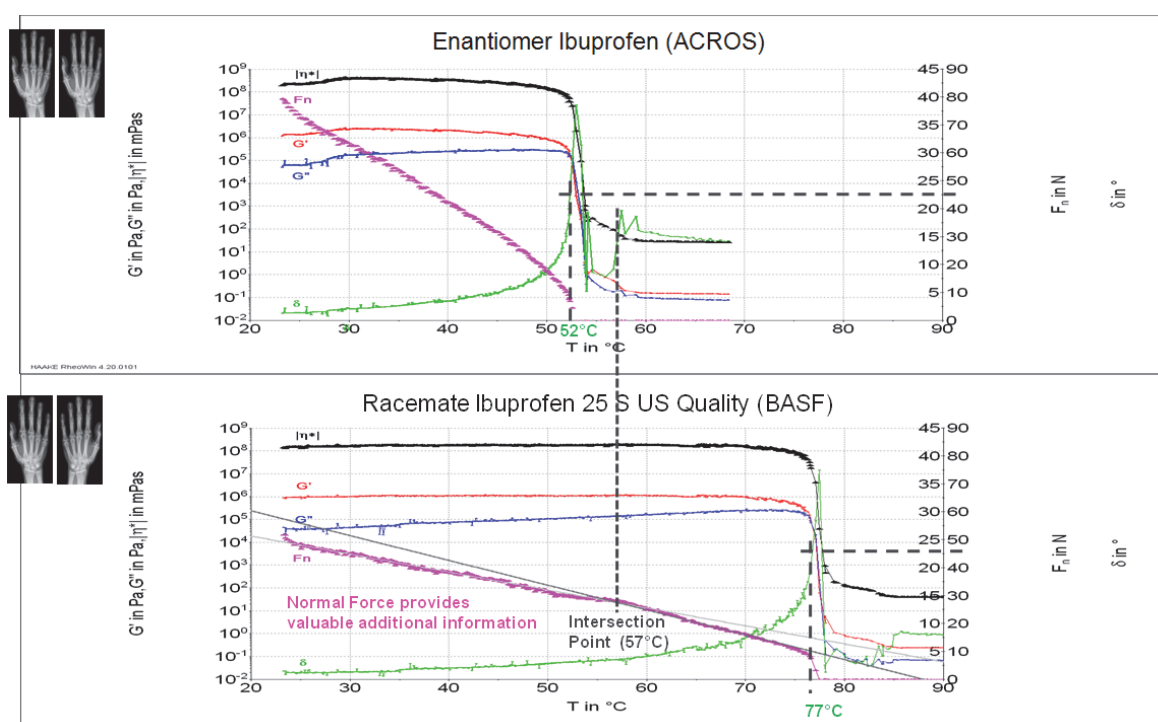


Figure 1. Heating runs (1 K/min) with Ibuprofen powder (top: enantiomer, bottom: racemate), chirality indicated symbolically top left (strain: 0.1 % with powder, first 10% then 30% with fluid)

### Ibuprofen in Soluplus®:

Polarization microscope images of crystalline Ibuprofen powder (racemate) mixed with Soluplus® powder are shown in Fig. 2. 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 Metrology [12]) can be employed.

In a subsequent cooling run, no re-crystallization 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 ageing [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®. Fig. 3 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 Fig. 4.

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 (Figs. 5 and 6).

The storage modulus  $G'$  of an un-filled and non-crystalline polymer is typically slightly above  $10^9$  Pa in the glassy state and  $10^6$  Pa in the rubbery polymer melt. 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 are really consistent. The glassy state plateau would be fully reached at temperatures lower than the measured ones.

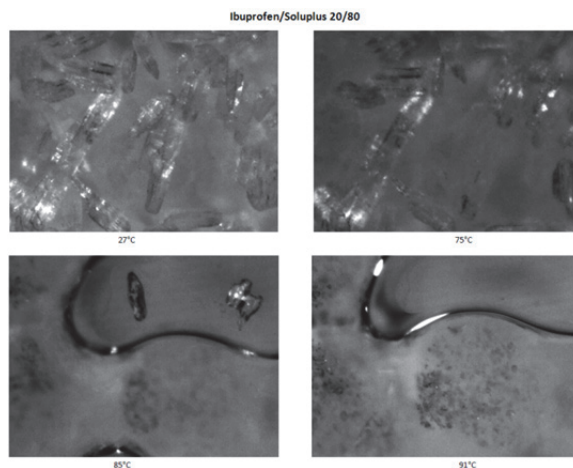


Figure 2. Powder mix with 20% Ibuprofen and 80% Soluplus® at 27°C (top left) and gradual melting of the API shown in images taken at 75°C, 85°C and 91°C (lens 20 x).

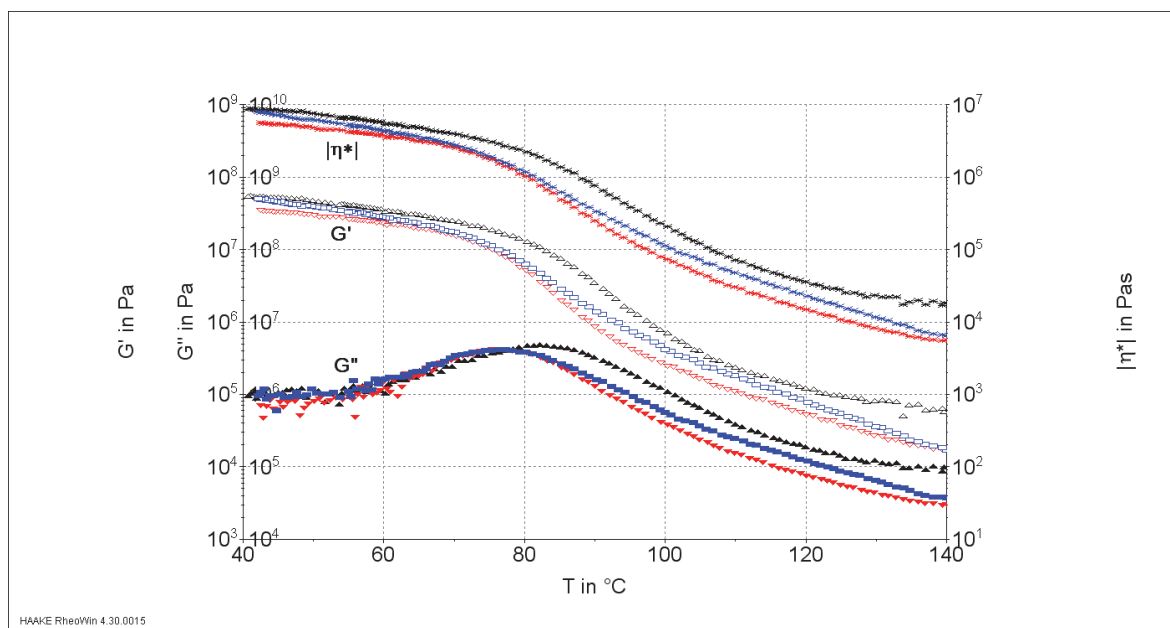


Figure 3. Cooling run (-5 K/min) with 3 powder samples molten at 140°C with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus® measured in plate/plate measuring geometry (strain: 0.01 %).

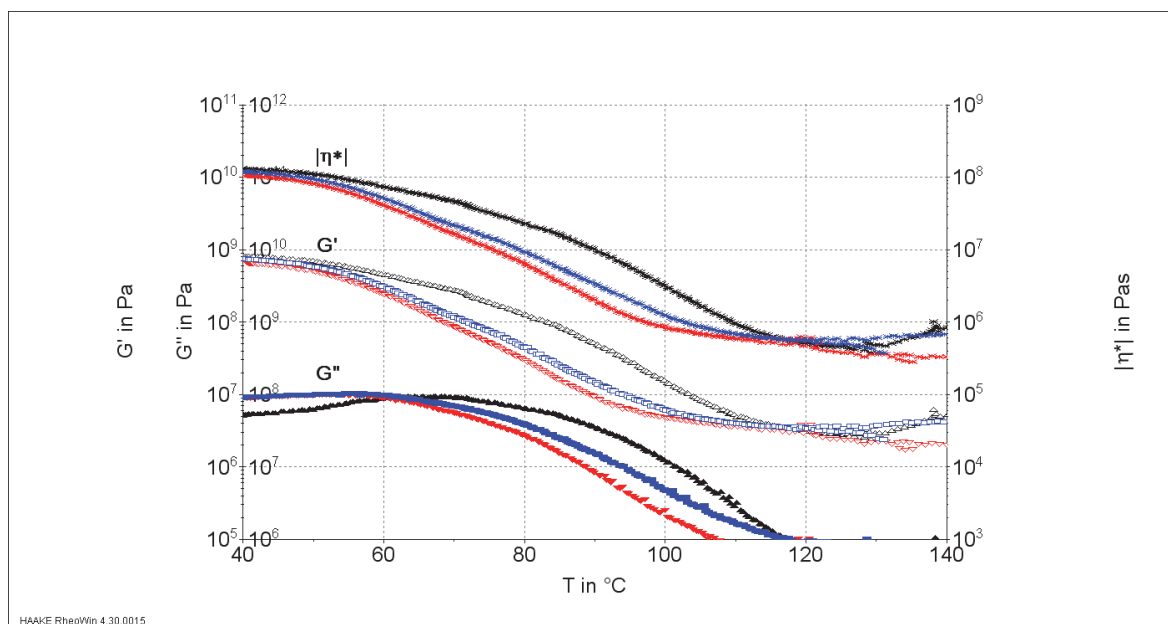


Figure 4. Heating run (5 K/min) with 3 injection molded rectangular bars with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus® measured with DMTA clamps (strain: 0.01 %).

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 (Fig. 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: Fig. 3 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 DCS 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 diagram [7].

In Fig. 5, 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.

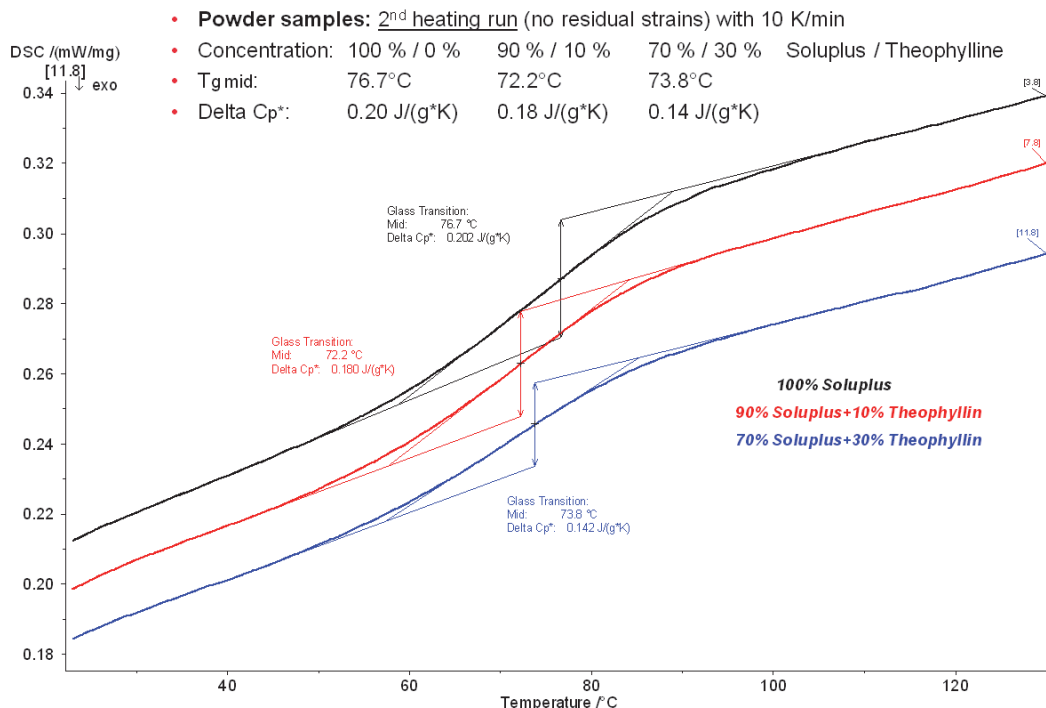


Figure 5. DSC measurements – second heating run (10 K/min) with 3 powder samples with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus®.

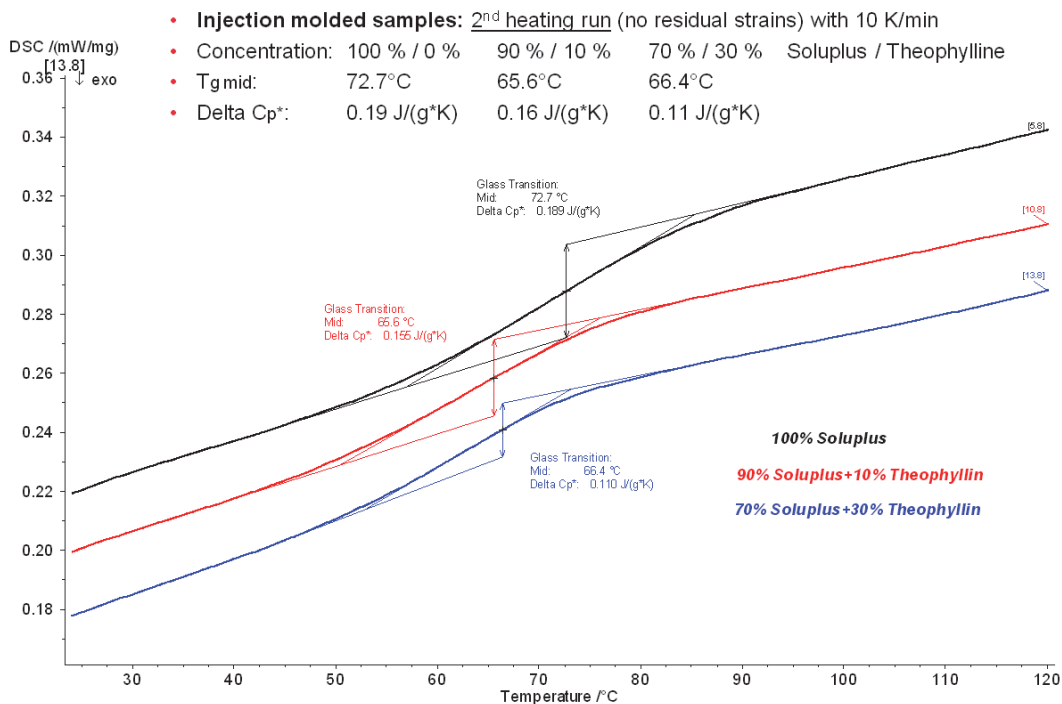


Figure 6. DSC measurements – second heating run (10 K/min) with 3 injection molded samples with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus®.

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<sub>g</sub> and the sample with 10 % Theophylline (red) the lowest T<sub>g</sub>. It is also evident from the results, that a further increase of the Theophylline content (30%, blue) does not lead to a lower T<sub>g</sub> than with the 10% sample.

The results for the injection molded samples are shown in Fig. 6. Here the same trend in the shift of T<sub>g</sub> with the Theophylline concentration could be found. Furthermore, it is remarkable that for all three molded samples, T<sub>g</sub> 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 high" (second heating run; no residual strains, Figs. 5, 6) and the maximum in the DTMA loss modulus curves G''(T) (measured with a frequency of 1 Hz, Figs. 3, 4) 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 under cooling).

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, 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. In addition to temperature-dependent measurements (glass, softening, melting and crystallization temperature), they can provide amplitude- and time-dependent as well as frequency-dependent measurements, which allow to study e.g. the impact of plasticizers and provide data for determination of molecular weight M<sub>w</sub> and molecular weight distribution, processability prediction and modeling calculations [7].

## CONCLUSIONS

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 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/share 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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