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MATERIAL CHARACTERIZATION INSTRUMENTS, KOREA

Innovative rheological and extrusion solutions for drug development

Application compendium

ThermoFisher SCIENTIFIC

Innovative rheological and extrusion solutions for drug development

When developing new drugs, shortening time-to-market, reducing waste of expensive APIs and minimizing overall development costs provide a distinct competitive advantage for pharmaceutical manufacturers. This compendium shows an approach to use different techniques in combination to achieve the best possible formulation for a new drug molecule.

Understand formulation properties:

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.

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. The preferred characteristics are often depending of the crystallinity state of the API in the formulation. Simultaneous rheology and polarization microscopy allows studying the melting behavior of crystals in the heating run, to investigate whether a re-crystallization occurs in the cooling run and derive suitable processing parameters for compounding and extrusion.

Hot Melt Extrusion (HME) for challenging formulations:

Hot melt extrusion (HME) has been used in the plastics and food industries since the 1930s. In the 1980s HME was recognized as a promising technology for enhancing the solubility and bioavailability of poorly soluble APIs. These challenging APIs are often enhanced when they are molecularly dispersed in a polymeric carrier using twin-screw extruders, making HME a valuable technology for the pharmaceutical industry.

Promising drug molecules that cannot otherwise be solubilized, will benefit from HME. The resulting polymer melt is suitable for direct shaping into pellets, spheres, implant, powders, films or patches. Due to the highly viscous nature of the extrudate, various solid drug delivery forms have been established over the last 25 years using HME such as:

- Controlled release medications
- Patches and films to deliver APIs
- Co-extrudates and implants
- Abuse deterrent formulations

Switch from batch to continuous manufacturing:

Agglomeration of powder mixtures is an important step in the manufacturing process of tablets, which represent over 50% of the most widely used oral dosage forms in use today. Twin-screw granulation (TSG) offers a significant advantage over traditional granulation methods: the possibility of continuous manufacturing. Therefore, TSG has established itself as a popular continuous manufacturing technology for consistent, repeatable high-quality production of both standard and complex dosage forms. For a continuous process to be successful it is most important to gain a sound understanding of process parameters and their influence on product quality as well as crucial parameters for scale-up.

APPLICATION NOTE

No. V262

Investigation of pharmaceutical hot-melts via simultaneous rheometry and polarization microscopy

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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 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.

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 re-crystallization 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 re-crystallization 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.

Fig. 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].

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], Fig. 2) as polymer and Ibuprofen (BASF, ACROS) as well as Theophylline (BASF) as APIs.

Powder (grinded)

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 underfilled 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: Fig. 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 grinded and then treated as described above.

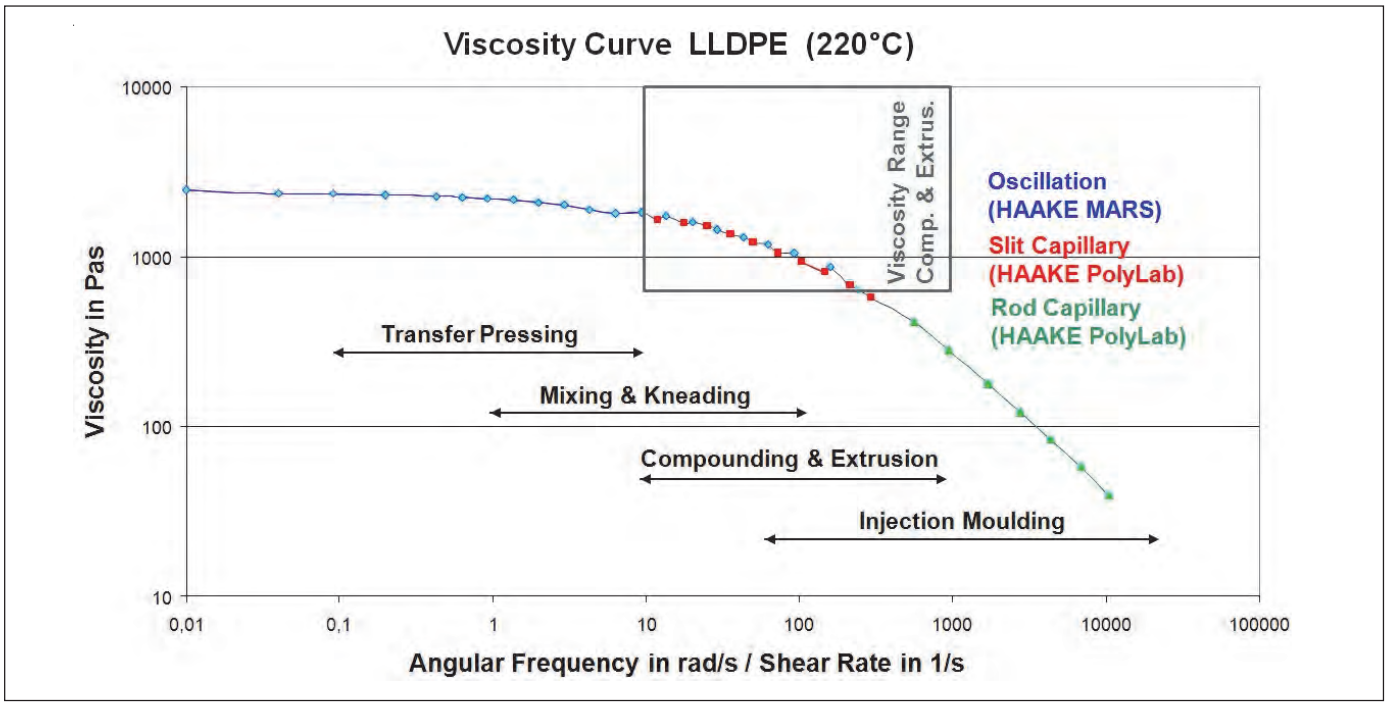

Fig. 1: Viscosity curve of LLDPE and typical shear rate ranges in rheometry as well as in polymer processing.

Fig. 2: BASF Soluplus® powder [3].

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 (Fig. 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.

Fig. 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 (Fig. 4) of the Thermo Scientific HAAKE MARS rheometer to investigate e.g. the impact of ingredients and processing parameters (like screw confi-guration, 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 re-open the oven at lowest temperature for re-tightening of the solid sample clamps with the related issues of humidity precipitation and ice formation on sample clamp and measuring shaft (self-tightening).

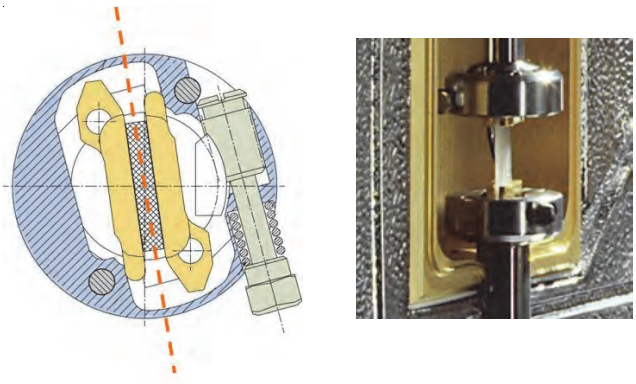

Fig. 4: Self-centering and self-tightening spring-loaded DMTA solid sample clamps (drawing left) in a CTC oven and with an injection molded bar sample (right).

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 pro-cessing 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 co-operation partner NETZSCH Analyzing & Testing.

The powder samples were fed into the Thermo Scientific™ HAAKE™ MiniLab for compounding and (after switch-over via the pneumatically actuated bypass valve) for extrusion of a strand. The Thermo Scientific™ 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 (relatively wide) slit capillary die with two pressure sensors (Fig. 5), facilitating viscosity measure-ments in the shear rate range from 1 to 100 1/s.

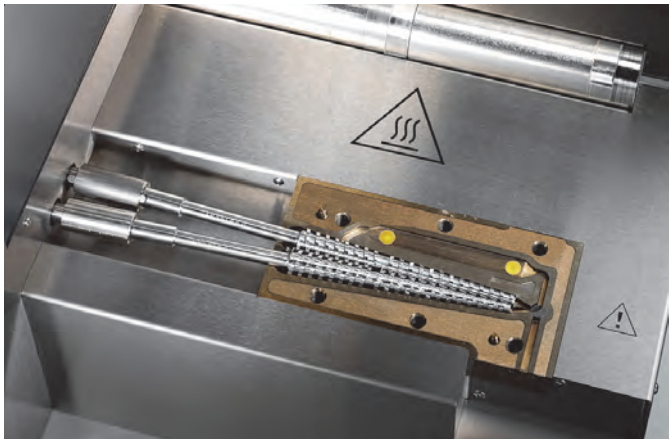

Fig. 5: HAAKE MiniLab can be used with counter-rotating or co-rotating conical twin screws (center), has a bypass valve (right), a backflow channel with a slit capillary with two pressure sensors for viscosity measurement (top) and an extrusion channel (bottom right).

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

Fig. 5: 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 TM-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 (Fig. 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 pre-sented 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.

Fig. 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.

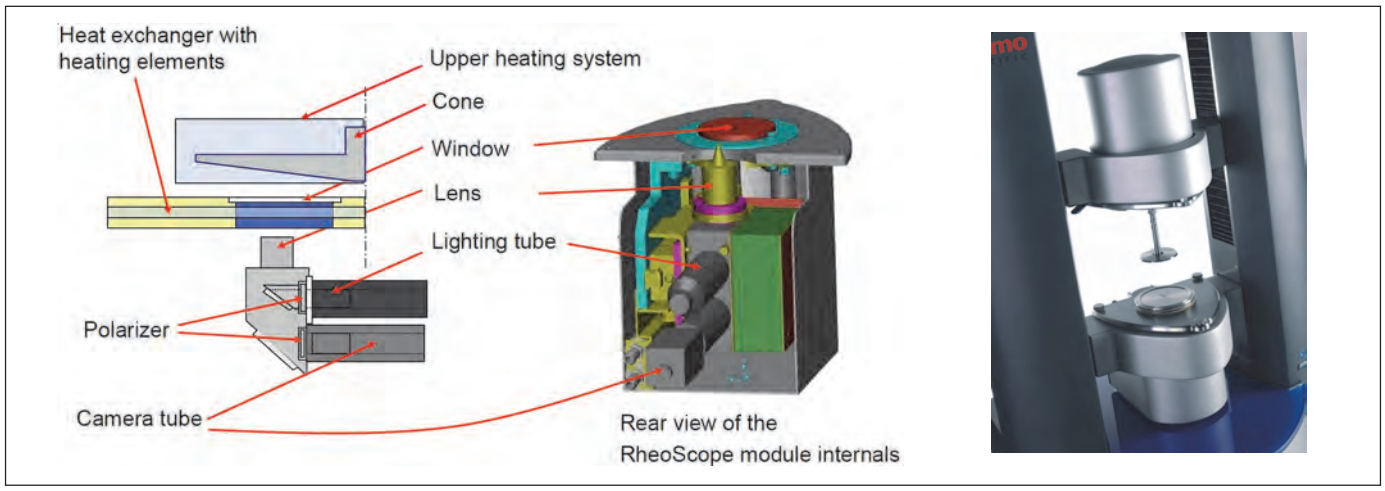

Fig. 7: HAAKE RheoScope module: Schematic drawing (left: side view, center: rear view) and mounted in the HAAKE MARS rheometer (right).

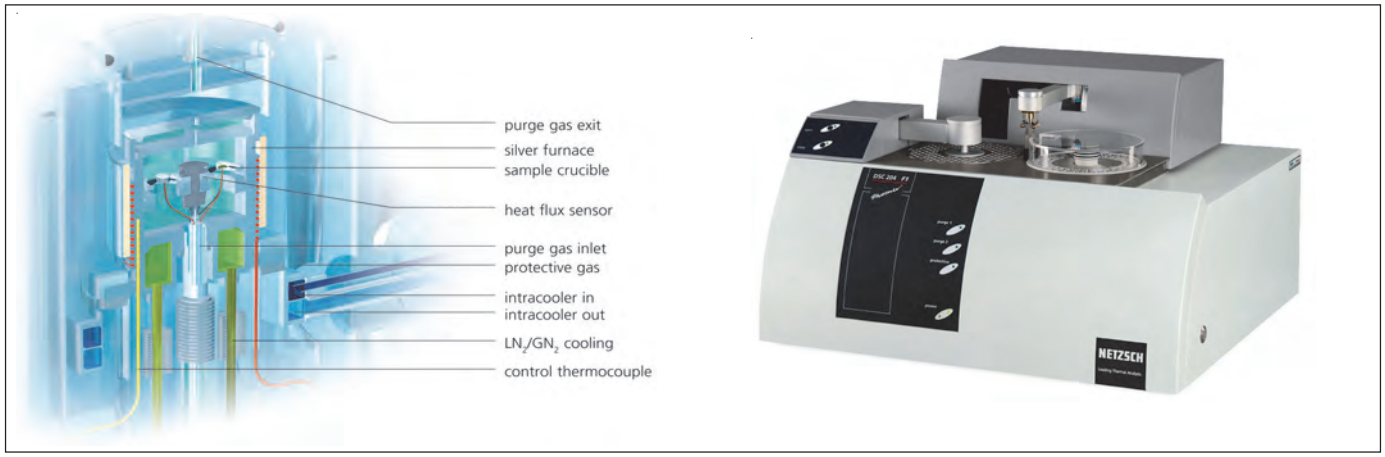

Fig. 8: NETZSCH DSC 204 F1 Phoenix® (right) and cross section through its DSC cell (left).

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 |η*| 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. 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).

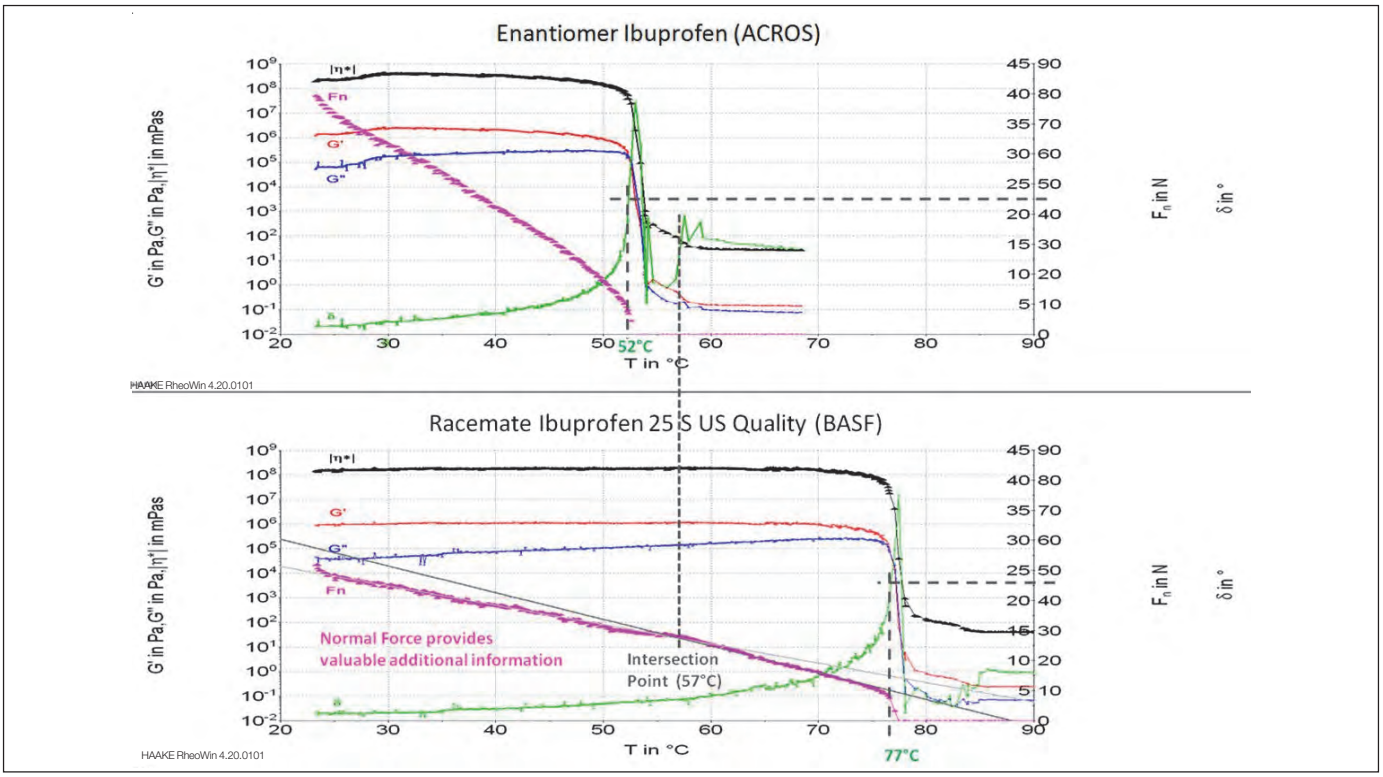

Fig. 9: Heating runs (1 K/min) with Ibuprofen powder (top: enantiomer, bottom: racemate), chirality indicated symbolically top left (measuring amplitude: 0.1% with powder, first 10% then 30% with fluid, measuring mode: CD-AS [14]).

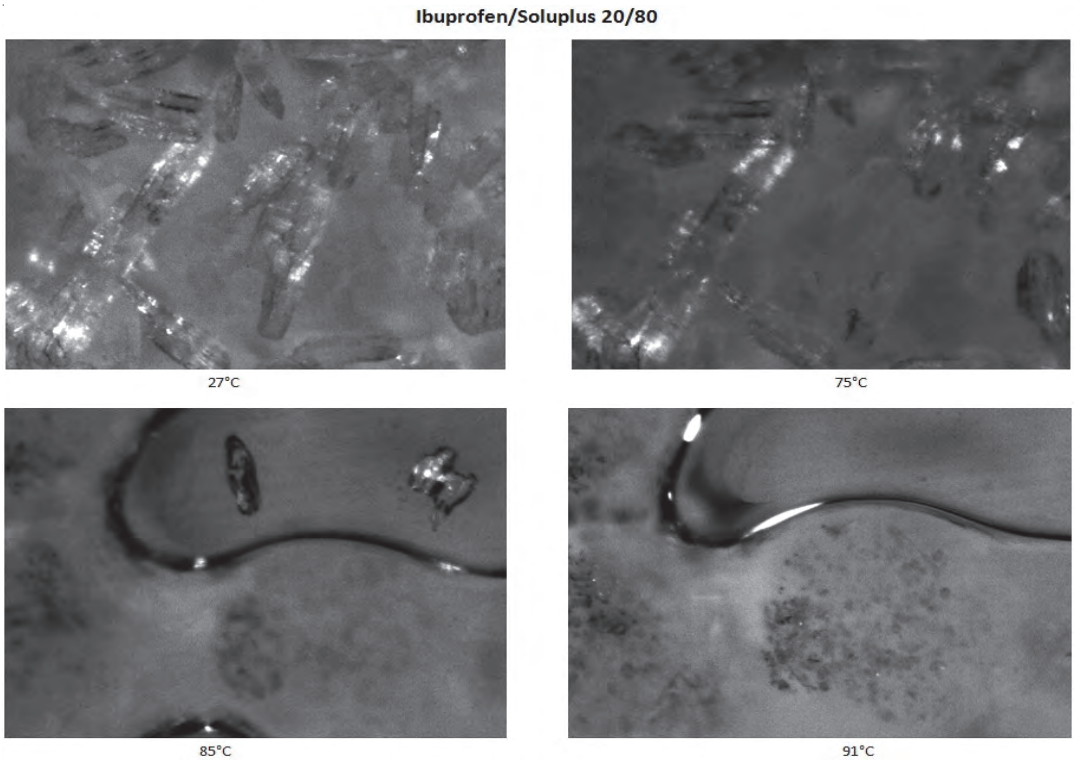

Fig. 10: Powder mix with 20% Ibuprofen and 80% Soluplus® at 27 °C (top left) and gradual melting of the API shown in images taken at 75 °C, 85 °C and 91 °C (lens 20 x).

Ibuprofen in Soluplus®

Polarization microscope images of crystalline Ibuprofen powder (racemate) mixed with Soluplus® powder are shown in Fig. 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 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. 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 Fig. 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 (Figs. 13, 14).

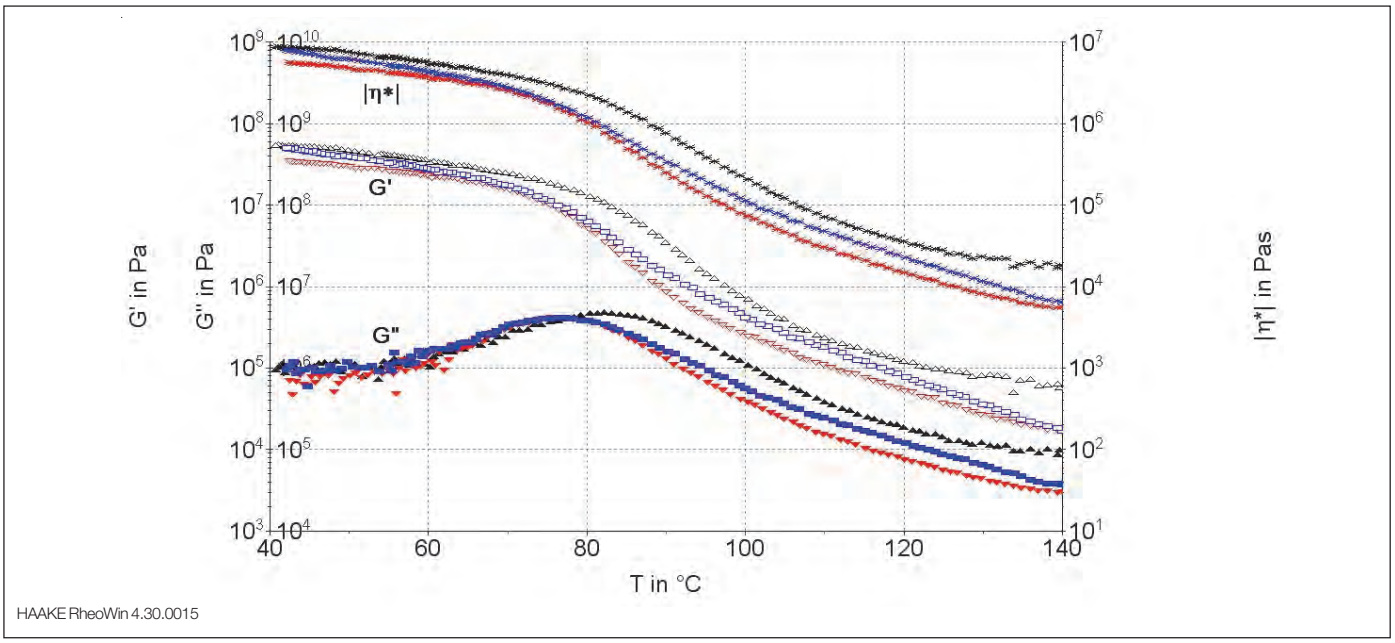

Fig. 11: ACooling run (-5 K/min) with 3 powder samples molten at 140 °C with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus® measured in plate/plate measuring geometry (measuring amplitude: 0.01 %, measuring mode: CD-AS [14]).

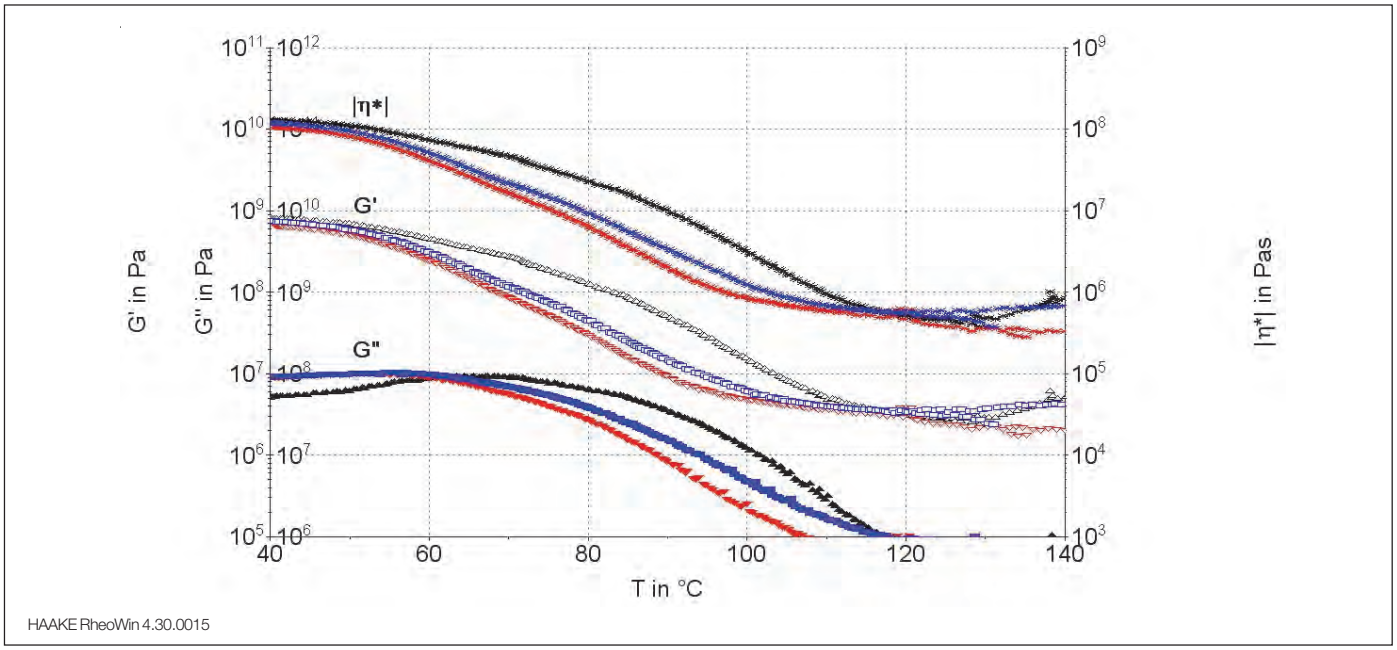

Fig. 12: DHeating run (5 K/min) with 3 injection molded rectangular bars with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus® measured with DMTA clamps (measuring amplitude: 0.01 %, measuring mode: CD-AS [14]).

Discussion

Absolute values of the storage modulus

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 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 Fig. 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 (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. 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 diagram [7].

In Fig. 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 Tg and the sample with 10 % Theophylline (red) the lowest Tg. It is also evident from the results, that a further increase of the Theophylline content (30%, blue) does not lead to a lower Tg than with the 10% sample.

The results for the injection molded samples are shown in Fig. 14. Here the same trend in the shift of Tg with the Theophylline concentration could be found. Furthermore, it is remarkable that for all three molded samples, Tg 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.

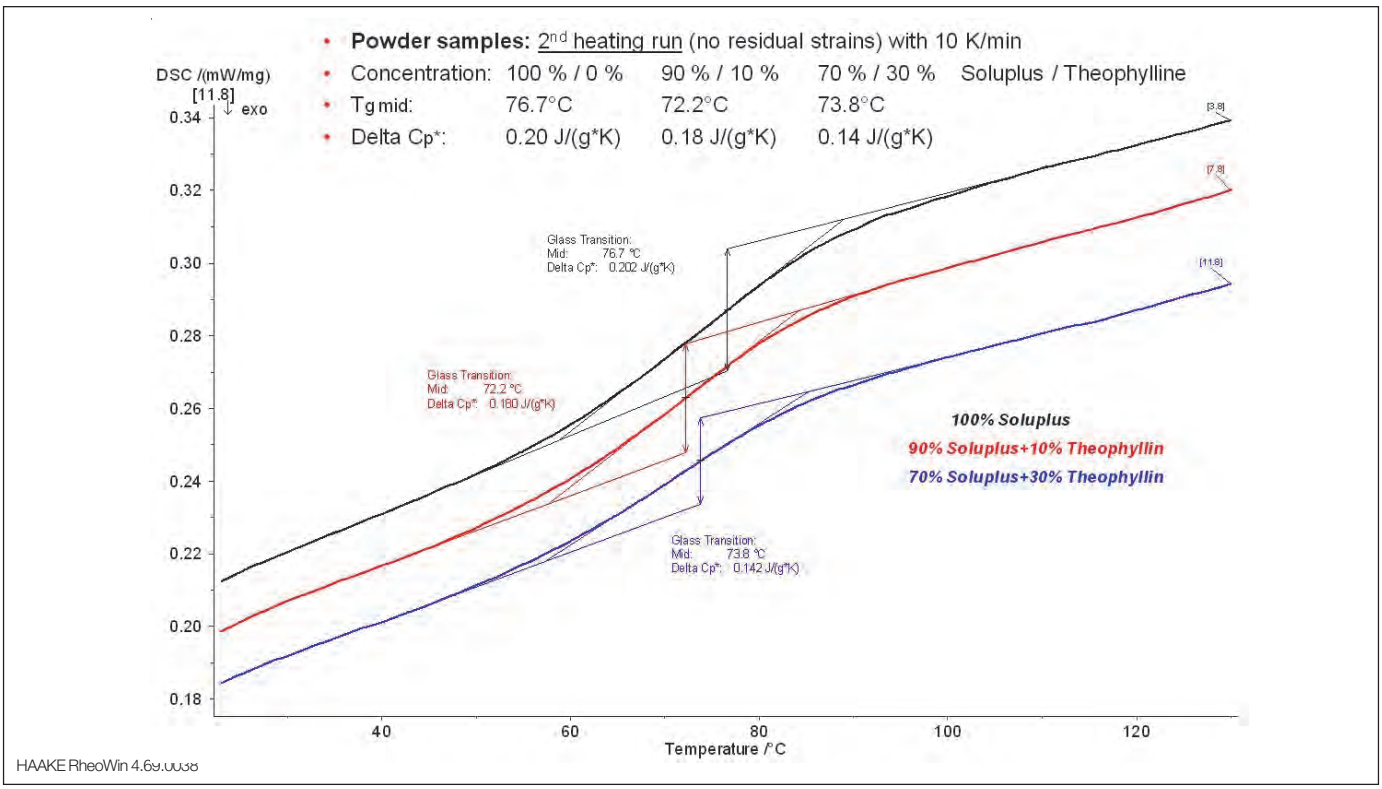

Fig. 13: DSC measurements – second heating run (10 K/min) with 3 powder samples with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus®.

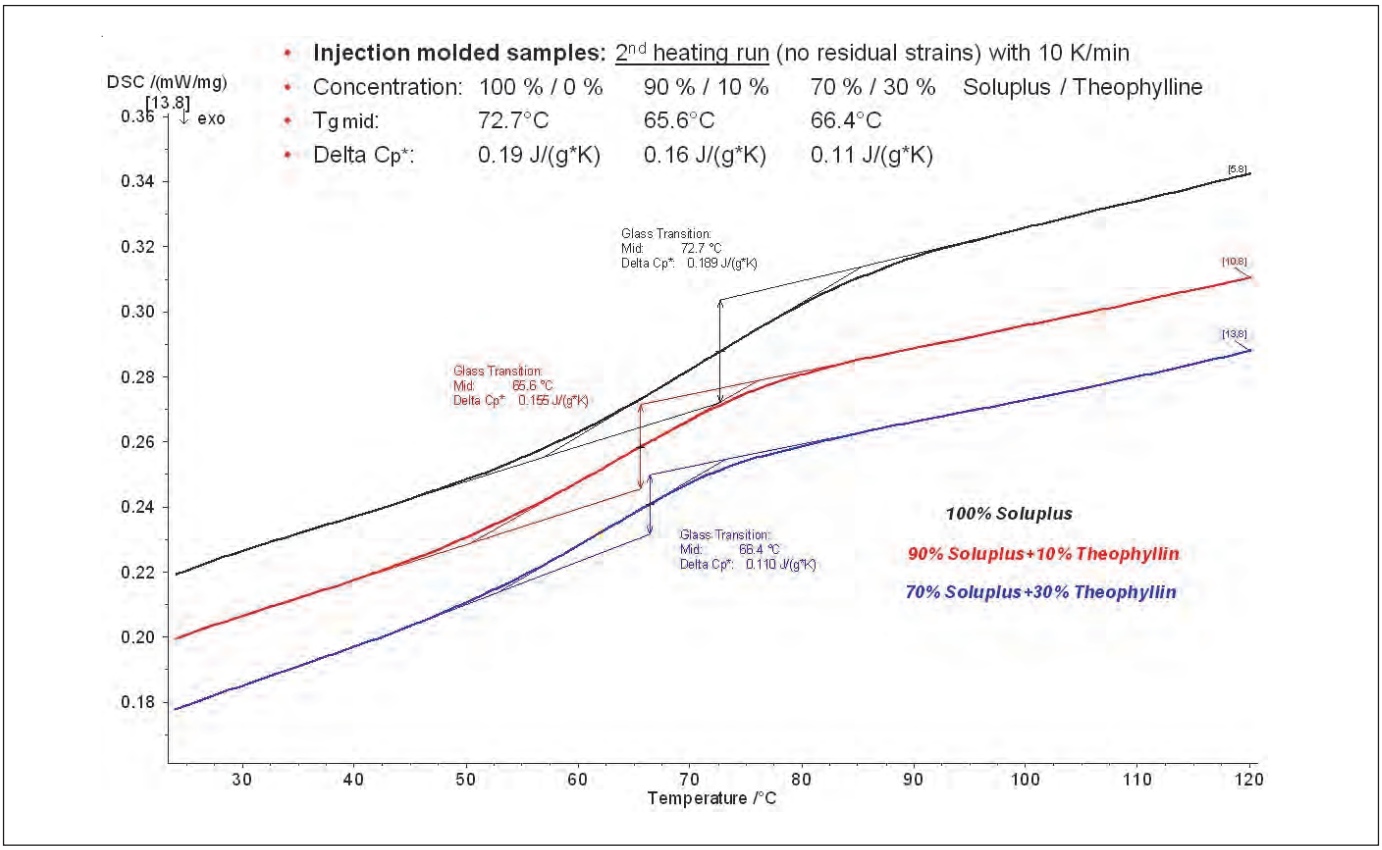

Fig. 14: EDSC measurements – second heating run (10 K/min) with 3 injection molded samples with different Theophylline concentrations (0% black, 10% red, 30% blue) in Soluplus®.

The evaluation of the DSC "mid step hight" (second heating run; no residual strains, Figs. 13, 14) and the maximum in the DTMA loss modulus curves G"(T) (measured with a frequency of 1 Hz, Figs. 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 (Fig. 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 (Figs. 1, 11, 12), which allow to study e.g. the impact of plasticizers and provide data for determination of molecular weight M_W and molecular weight distribution, processability prediction and modeling calculations [7].

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.

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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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APPLICATION NOTE

No. LR-73

Co-extrusion as an innovative method for pharmaceutics

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Key words
Hot melt extrusion, implants, oral solid dosage

Introduction

Hot melt extrusion is a process to produce a broad range of pharmaceutics. It can be used for oral applications, implants or patches. In oral solid dosage forms it can be either used to increase the bioavailability of poorly soluble active pharmaceutical ingredients (API) in immediate and sustained release formulations or even in combination of different release behaviors [1, 2].

To produce a combination of different release profiles and/or different drugs in fixed-dose combinations, it can be extruded in a multi-layer system. With co-extrusion, the production of an inner core and an outer shell will be realized in one single step. The most important parameter is a precise inner core and outer layer to achieve the desired drug content and release. For quality control Raman imaging microscopy is used.

Materials and methods

Hot Melt Extrusion Equipment

For co-extrusion one extruder is needed to produce each layer. For production of the inner core a co-rotating twin-screw extruder with a screw diameter of 16 mm was used (Thermo Scientific™ Pharma 16 Extruder). For the outer layer a lower throughput is needed, therefore, a co-rotating twin-screw extruder with a screw diameter of 11 mm (Thermo Scientific™ Process 11 Extruder) was used. The co-extrusion die was equipped with an insert of 4 mm for the total diameter. The thickness of the outer layer was controlled by the ratio of the mass flow of the inner and the outer phase. For co-extrusion the extruders are arranged in a 90° position, as shown in Figure 1, with the Process 11 Extruder orientated from the left to the right. Two gravimetric MiniTwin powder feeders were used (Brabender Technology, Duisburg, Germany) to achieve precise feed rates of the inner and the outer phase.

Figure 1: Set-up of twin-screw extruders for co-extrusion.

Materials

In the inner layer, Itraconazol was used as a model drug (BASF, Ludwigshafen, Germany) with Lactose (GranuLac®, Meggle, Germany) and PVP/PVA Copolymer (Kollidon® VA 64, BASF, Ludwigshafen, Germany) as a carrier. The outer layer consistes of a cationic methacrylate copolymer (Eudragit® E, Evonik, Darmstadt, Germany) without API.

Thermal Analysis

To determine the solid state of the inner core dynamic scanning calorimetry (DSC) was used (DSC 204 F1 Phoenix; Netzsch-Gerätebau GmbH, Selb, Germany).

Raman Spectroscopy

For characterization of the co-extrudates Raman microscopy imaging is used (Thermo Scientific™ DXRxi Raman Imaging moicroscope, Thermo Fisher Scientific, Madison, USA). The Raman spectra were collected using a 532 nm laser with 10 mW power and a 10 µm step size. For imaging a 10x magnification is used. The exposure time was 0.0025 s and the number of exposures was 100. The reference spectra of the single components were measured.

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Results

Determination of the solid state

The crystalline Itraconazol should be transferred into a solid solution by the hot melt extrusion process to increase the solubility and therefore, consequently, the bioavailability. The result of the DSC measurement in Figure 2 shows only one glass transition of the sample of the inner core, which means that a solid solution was achieved.

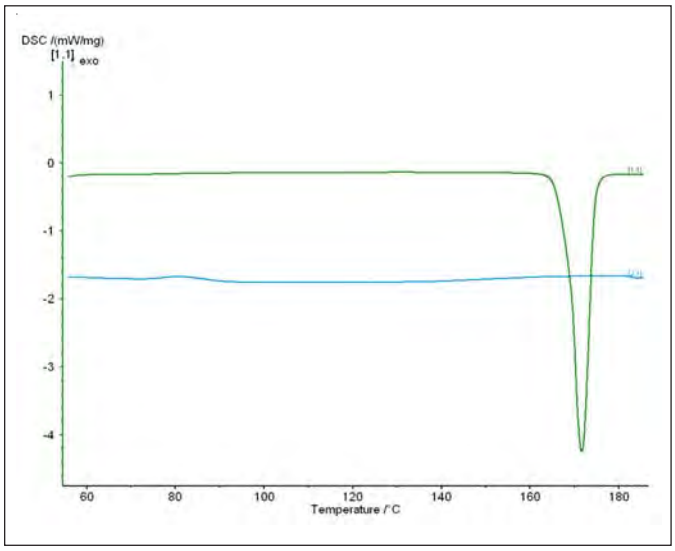


Figure 2: DSC scan of the crystalline Itraconazol (green) and the extruded product (blue).

Quality Control Measurements of the Two Layers

To determine the shell thickness and the quality of the shell Raman chemical imaging was used.

With Raman imaging microscopy, it is possible to visualize the thickness of the layers, making thickness measurements much easier to perform than light microscopy. Also any defects in the layers can be easily determined (Figure 3). This method is also used to determine if there is any migration of the Itraconazol from the inner core to the outer shell, which would result in a change in the Raman spectra of the outer shell.

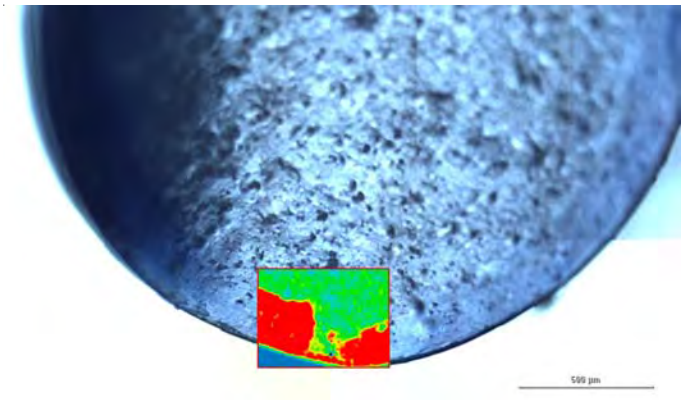


Figure 3: Cross section of a co-extrudate with a clear defect of the outer shell layer.

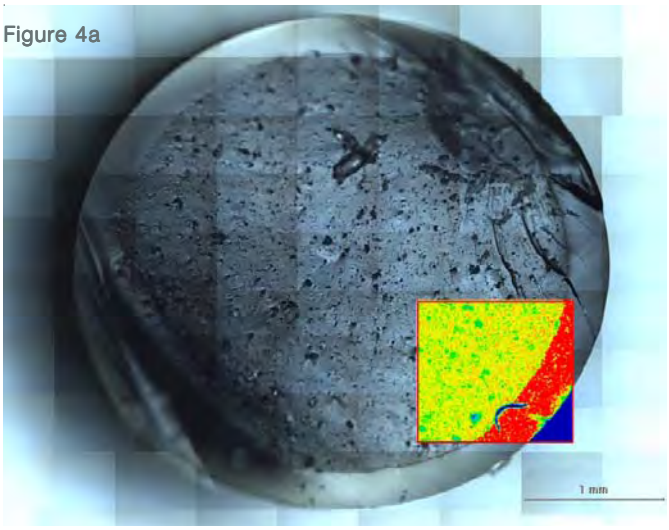
Impact of Extrusion Parameters on the Co-extrudate

During a stable process the appearance of the co-extrudate is very homogeneous, and the surface is without any defects. The Raman microscopy images given in Figure 4 clearly show that the shell has a very homogeneous thickness, and there is no migration of the Itraconazol into the outer layer.

The total diameter of the strand is defined by the die insert used. By varying feed rates different shell thicknesses are generated. With an increased feed rate for the inner core the outer shell becomes thinner. By doubling the feed rate of the inner core, the thickness of the outer layer will be half the thickness (Figure 4a and b).

Different process temperatures and, therefore, different viscosities of the different layers do not have an impact on the layer thickness. In the case of the co-extrudate shown in Figure 4c the process temperature of the extruder for the outer layer was increased 25 K compared to the co-extrudate process in Figure 4b, resulting in no change in outer layer thickness.

Figure 4a



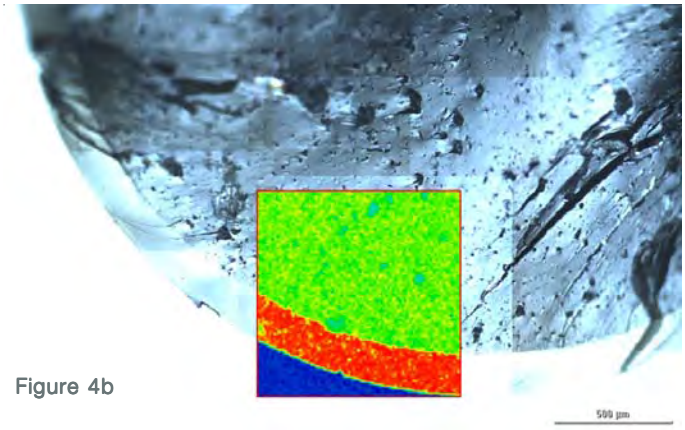


Figure 4b

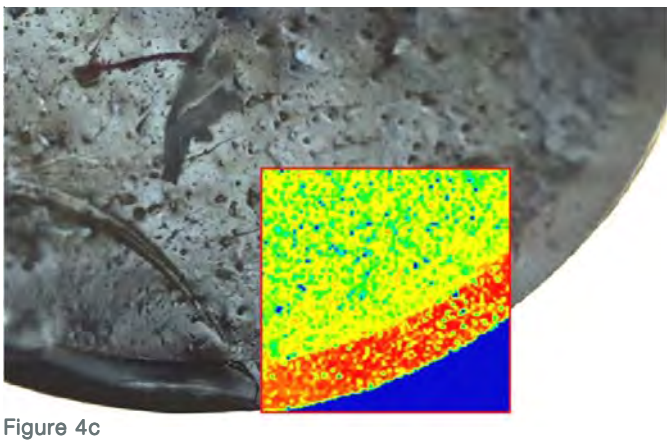


Figure 4c

Figures 4a-c: Cross section of co-extrudates, produced with different process parameters: from a to b the throughput of the inner core is doubled and as a result the thickness of the shell in b is only half the size; from b to c the process temperature of the extruder producing the outer shell was increased by 25 K, and the layer thickness stays the same.

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Conclusion

Hot melt extrusion can be used to produce multi-layer systems by co-extrusion to produce pharmaceutical dosage forms with different dissolution behavior for one API or for fixed-dose combinations of different APIs.

The outer shell thickness is very homogenous and can be varied easily by varying the throughput.

Raman microscopy imaging is an ideal tool to determine the shell layer thickness and to visualize any chemical and physical defects of the outer shell.

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LR-73 0520

APPLICATION NOTE

Hot-melt extrusion of orally disintegrating films

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Key words
Orally disintegrating films, ODF, pharmaceutical technology, hot-melt extrusion, HME

Executive summary
Orally disintegrating films (ODFs) are an appealing dosage form because they allow safe, easy and exact dose administration of an active pharmaceutical ingredient (API). Additional benefits of ODF forms include improved bio-availability of the drug and avoidance of the first pass effect.

There are several possible manufacturing techniques for ODFs. Of those, hot-melt extrusion is recommended as a continuous, well-reproducible process that operates without the addition of solvents.

With Thermo Scientific™ pharmaceutical extruders and down-stream equipment, high quality ODFs can be produced on a lab scale or at production scale.

Manufacturing methods for ODF
Typical manufacturing methods for ODFs include solvent casting and hot-melt extrusion (HME) [1]. Solvent casting is a very common method for first studies and excipient screening. It is well-suited for thermolabile APIs but requires the handling of a solvent and can create problems during scale-up. HME offers a better alternative. In comparison to solvent casting, HME is a solvent-free, environmentally friendly technology. It is highly reproducible, and it shows better content uniformity with fewer processing steps and decreased production costs [2]. Furthermore, API and excipients are mixed on a molecular level with HME, resulting in a more uniform dispersion of the API in the ODF which increases the bioavailability of the drug. Scale-up in HME has been well established [4], and it can be easily done with Thermo Scientific extruders. With a suitable range of excipients, HME is the method of choice for innovative ODF formulation [2].

Figure 1: Benchtop system including a Pharma 11 Twin-Screw Extruder for production of ODFs.

Hot-melt extrusion
With a long history in plastics and food processing, HME is a well-known and established manufacturing technique with a growing popularity in the pharmaceutical industry. Pharmaceutical formulations for HME include combinations of API, polymers and mostly plasticizers or other excipients. Here's how HME works. The polymer is melted in a twin-screw extruder, all ingredients are mixed and kneaded, and thus, intense compounding takes place. The die, which is placed at the end of the twin-screw extruder, defines the shape of the extrudate. The melt is squeezed through the die hole. Down-stream equipment, such as a conveyor, pelletizer or take-off system and cutters, provides further continuous processing. Using HME granules, tablets with a modified drug release profile can be produced as well as transdermal, transmucosal or subcutaneous drug delivery systems [3].

For the production of ODFs, a sheet-die is used to define the width and thickness of the film. As most pharmaceutical polymers are quite brittle, the choice of plasticizing excipients is crucial. The extruded film should be flexible and stretchable. Using a take-off and wind-up system, the

extruded film is pulled at a constant speed to achieve a homogenous thickness. A typical benchtop system (see Figure 1) consists of a gravimetric twin-screw feeder that is feeding the pre-blended material into a Thermo Scientific™ Pharma 11 Twin-Screw Extruder. The extruded film is constantly pulled by the sheet take-off. At the end, the film is wound up on a roll (see Figure 2). With this system, thin films can be produced at a constant thickness of 100 µm. The thickness of the film can be changed by adjusting the slit of the sheet die as well as the pulling speed and throughput.

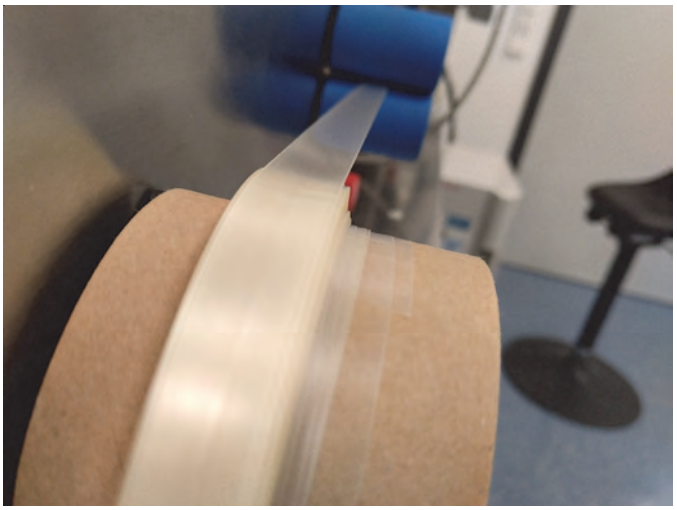

Figure 2: ODF being wound up on a roll.

Further information

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LR-85 0219

WHITE PAPER

Continuous twin-screw granulation – What to consider in process design, development and scale-up

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Abstract
Twin-screw granulation (TSG) offers a significant advantage over traditional granulation methods: the possibility of continuous manufacturing. Due to the recognized advantages of continuous manufacturing, twin-screw granulation has drawn increased attention in recent years. This whitepaper summarizes the most important process parameters and their influence on product quality as well as crucial parameters for scale-up based on a recent study. The results show that it is possible to tailor particle size distribution of the granules, which enables scientists in pharmaceutical technology to influence final product quality right from the start. This whitepaper also provides a summary of useful recommendations to address typical errors in designing, developing and scaling-up TSG. Consequently, TSG leads to faster process development and reliable scale-up from lab to production scale.

Keywords
Twin-screw granulation, continuous manufacturing, continuous processing, scale-up, process parameters, granule quality

Abbreviations and nomenclature

API	Active pharmaceutical ingredient
CM	Continuous manufacturing
DoE	Design of experiment
D	Screw diameter (mm)
$d_{v,50}$	Mass median diameter (µm)
HME	Hot melt extrusion
L/S	Liquid-to-solid ratio (%)
MRT	Mean residence time (s)
PAT	Process analytical technology
PSD	Particle size distribution
R&D	Research and development
RTD	Residence time distribution
ρ_G	Granule density (g cm^{-3})
SA	Sieve analysis
TSG	Twin-screw granulation

Introduction
Continuous manufacturing of pharmaceuticals has grown more popular in recent years [1]–[6]. There are several advantages of continuous processes over traditional batch processes:

1. The “batch size“ is not a fixed value in CM. Therefore, especially in the R&D phase of a drug, the amount of product can be reduced to the minimum needed for analysis and clinical trials. Furthermore, once the steady state has been reached, the product stream out of the extruder can be sampled and analyzed without needing to finalize the complete batch. This leads to fast conclusions as well as adaption and optimization of process parameters. Consequently, DoEs and relevant tests as well as small scale production take less time and less material in the R&D phase. Users of continuous processes report that up to 80% of time and material can be saved in comparison to a batch process. That makes CM quite valuable, especially when the API is only available in small quantities.
2. Once a continuous manufacturing line is set up, it can be operated in a very flexible way. Production volumes can be adapted to meet varying market demand, less storage space is needed for intermediate products and less product is wasted because the amount can be tailored by process run time instead of the size of the equipment.
3. In CM a constant process means constant product quality. Handling errors can be reduced more easily than with batch processes and thus quality improves. Process analytical technology can also help to control process stability and ensure product quality. Essentially, with CM only a limited amount of material is being handled at a time, rather than an entire batch. So if there is a problem with the process, the limited amount of current material can easily be discarded and the process continues without interruption.

Based on the advantages above, many industries have already converted most of their processes to continuous manufacturing lines, e.g., polymer and food industries. While pharmaceutical manufacturers are considering CM now, some of their processes are already inherently continuous, e.g., roller compaction, tableting and HME. HME is one of the most important techniques to produce solid dispersions for solid oral dosage forms, and several commercial drug products are currently produced with this technology [7].

Based on HME, TSG has been developed as a continuous technique for granulation. The principle is shown in Figure 1. A solid powder is automatically fed into the twin-screw extruder. This can be done in a so-called split feed: feeding API and excipients separately or as a powder blend. A pump adds the liquid binder separately. Within the barrel, the material is mixed, kneaded and tempered to a target temperature (cooling or heating). Agglomeration takes place during this process. In contrast to extrusion, there is no die at the end of the barrel and, thus, there is no pressure and no final compaction of the material. The granules exit the barrel through an open discharge and are transferred to the next process step (e.g., drying). There are several process parameters that can be changed independently: the liquid-to-solid ratio, the total throughput of material that is fed into the barrel, the screw speed of the extruder, the screw configuration and the temperature of the granulation process. All of these influence the granule quality and hence the final tablet hardness and the release profile of the API.

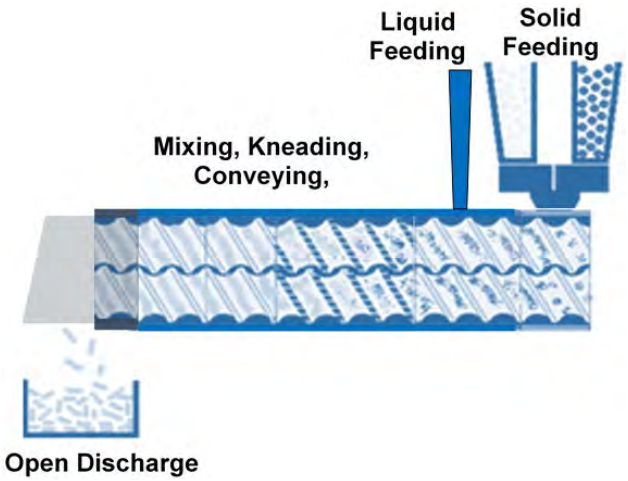

Fig. 1: Schematic of a TSG process.

Fig. 2: Pharma 11 benchtop twin-screw extruder (left); Pharma 16 production scale twin-screw extruder (right).

Several publications describe and analyze this process, showing its efficiency and potential for various drugs [1], [3], [8]–[14]. This white paper summarizes the influence of the most important process parameters

In general, there are two ways to increase the amount of material produced via CM. First, the process can be run for a longer time (at maximum throughput) and second, especially if time is a limiting factor, larger equipment can be used. The second possibility requires scale-up from an R&D scale to a production scale, for example. Osorio *et al.* analyzed different scales of TSG processes resulting in a limited comparability of the granules [15]. While the scale-up approach is very straightforward, it's still critical to understand the key parameters involved in scale-up. This white paper shows a scalable process for a placebo formulation to help demonstrate the influence of key parameters.

Material and methods

In the study described in this white paper, granulation was performed on three different scales:

1. 11 mm with the Thermo Scientific™ Pharma 11 Benchtop Extruder (Figure 2, left)
2. 16 mm with the Thermo Scientific™ Pharma 16 extruder (Figure 2, right)
3. 24 mm with the Thermo Scientific™ TSE 24 MC Twin-screw Extruder.

The screw elements of these different instruments have a diameter (D) of 11 mm, 16 mm and 24 mm respectively and are shown in Figure 3. The extruders are geometrically comparable in terms of the similarity principle [16]. This means that all sizes exhibit the same ratio of the inner to outer diameter and the same screw clearance ratio. Therefore, results obtained in one scale can be directly compared with other scales. In TSG mode, all screw lengths are 40 ¾ times the respective screw diameter.

For this study, a placebo formulation consisting of a dry blend of 62.8% lactose, 32% corn starch, 5%PVP 30 and 0.2% talcum. To feed the solid pre-blend into the barrel, a gravimetric twin-screw feeder was used for each scale. Water as liquid binder was fed into the barrel by a peristaltic pump. The granules were analyzed in-line using the Eyecon$_2$™ Particle Analyzer (Innopharma

Technology) and at-line with a Retsch® sieve analysis (SA) after drying. On all scales, a full factorial DoE was performed changing the process parameters independently. The residence time distribution was measured on the Pharma 16 extruder using a UV-sensor and washing powder as tracer.

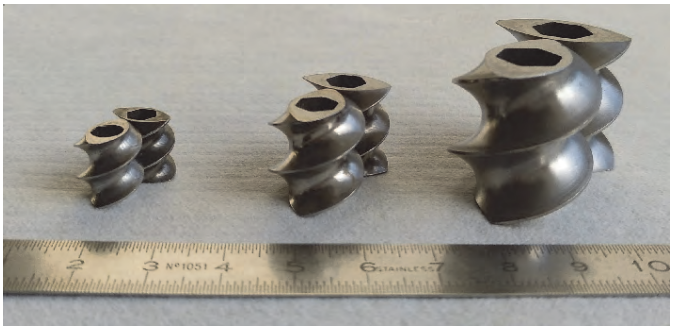

Fig. 3: The three scales in this study: 11 mm, 16 mm and 24 mm sized twin-screws.

Results and discussion

The influence of TSG process parameters on the granule attributes (i.e. mass median diameter $d_{v,50}$, PSD and the granule density ρ_G) is summarized in Table 1. If the liquid-to-solid ratio is increased, the particles have a higher density and are larger (i.e., there are more oversize and less fine particles). This effect is the same as in other granulation methods and has been described before [2], [17], [18].

A more interesting effect can be observed if the filling level of the screw is changed. This is mainly influenced by the total throughput and screw speed. An increase in throughput, for example, results in an increase of the filling level within the screws. Thus, stronger kneading and compaction is performed. In general, lower screw speeds and higher throughputs increase the filling level resulting in larger particles (see Figure 4). Based on this effect, the granules can be tailored more easily and quickly to the desired size. To obtain larger granules, for example, a higher throughput or a lower screw speed should be chosen. Furthermore, this effect should be considered for scale-out, i.e., reaching a higher throughput on the same scale should always incorporate an increase in screw speed.

Table 1: Influence of TSG process parameters on granule attributes.

Increase of...	Effect on		
Process parameter	$d_{V,50}$	PSD	ρ_G
...liquid-to-solid ratio	+	0	+
...throughput	+	+	+
...screw speed	-	-	-
...intensity of mixing (screw configuration)	+	0	+
...temperature	+	+	+

Note that the strength of the screw speed effect depends highly on the formulation and amount of binder (water). Figure 5 shows two curves of the mean particle size of the placebo formulation changing with the throughput. For a liquid-to-solid ratio of 25% there is a strong dependency of the particle size on the throughput. An increase from 1 kg/h to 1.5 kg/h almost doubles the particle size. For a lower L/S, however, the particle size is almost independent from the throughput. Only at a throughput of above 3 kg/h does the mass median diameter of the granules increase significantly. These results are discussed in more detail in a dedicated lab report [19].

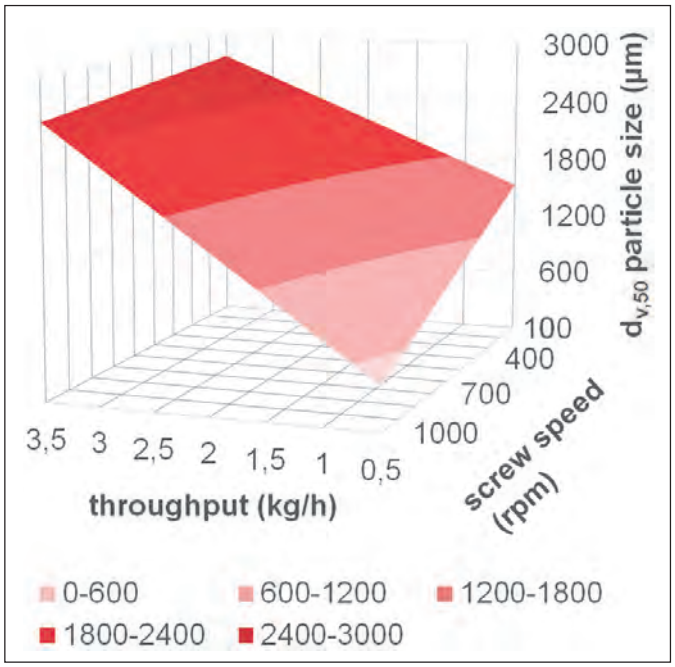

Fig. 4: Surface plot of the mean particle size ($d_{v,50}$) over throughput and screw speed. The data shown is an approximation of determined size data in this study.

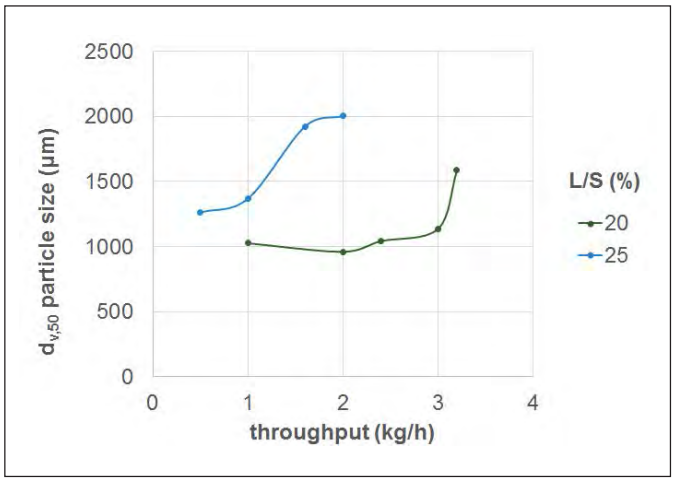

Fig. 5: Influence of throughput and L/S on the mass median diameter (d_{v50}) of the granules (Pharma 11 extruder, 500 rpm).

Consequently, the independent process parameters influence dependent parameters, e.g., the filling level of the screws. Thus, it is tempting to use this parameter (as a dimensionless number) to scale-up this process [15]. But another dependent parameter needs to be taken into account: the residence time distribution of the material inside the barrel. Figure 6 shows the mean residence time of the material within the Pharma 16 extruder. MRT is defined as the time when 50% of the tracer leaves the barrel. It has been determined mathematically at 50% of the area below the tracer intensity curve. As can be seen in Figure 6, MRT decreases with increasing screw speed for most throughputs. But at a very low throughput and high screw speed, a sharp increase of mean residence time is obtained. This is due to the low filling level of the screws resulting in a poor conveying behavior. That means a minimum filling level has to be reached to achieve an efficient process. An increase of particle size due to this mechanism has also been reported by Kumar *et al.* [20] and Seem *et al.* [1].

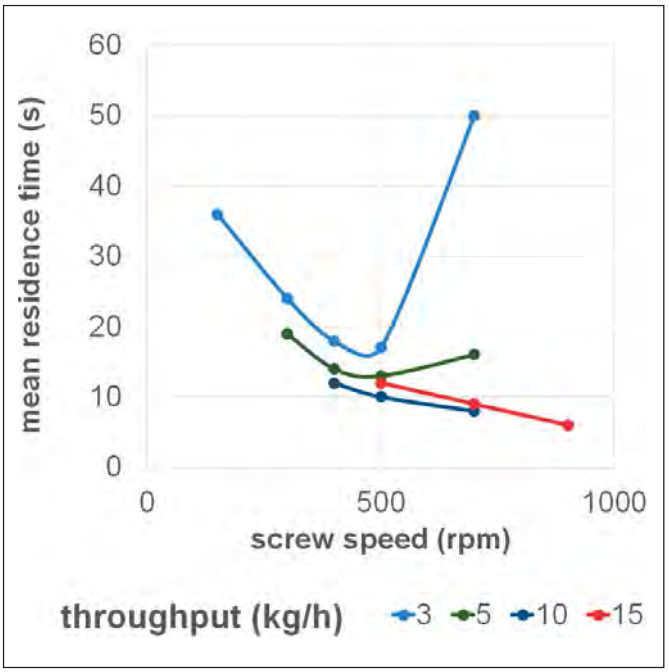

Fig. 6: Mean residence time during granulation on the Pharma 16 extruder.

Figure 7 summarizes the influence of throughput and screw speed on the mass median diameter of the granules made with the TSE 24. For a relatively high throughput (e.g., 40 kg/h) the mean particle size decreases with increasing screw speed as described before. But for a relatively small throughput (e.g., 5 kg/h) the opposite happens; the granules become larger with increasing screw speed. This is due to the strong decrease in filling level and thus poor conveying behavior resulting in a wide RTD and a long MRT.

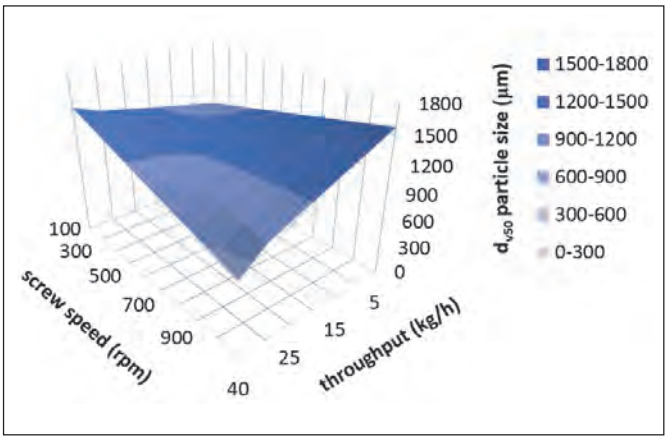

Fig. 7: Influence of throughput and screw speed on the mass median diameter ($d_{v,50}$) of the granules (TSE 24). The data shown is an approximation of determined size data in this study.

The final determination is that there are two main parameters that influence granule growth: compaction force depending on the filling level inside the screws and residence time within the extruder. Considering these effects and keeping all other parameters constant, the TSG process can be scaled-up successfully. To demonstrate this on different scales, Figure 8 shows the accumulated particle size of dry granules obtained on the Pharma 11 Extruder and the Pharma 16 Extruder.

Typical errors in TSG

Based on the findings in this study and several publications, there are three typical errors to avoid in designing, developing, running or scaling-up TSG processes.

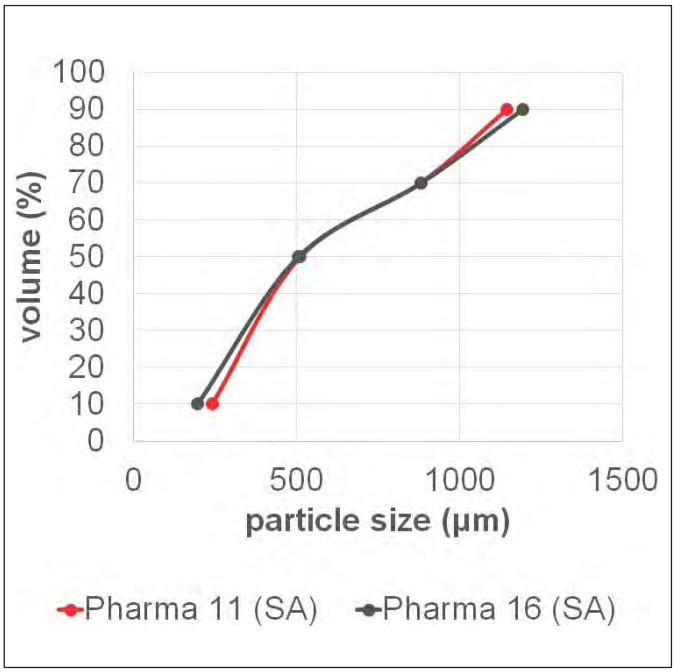

Fig. 8: Particle size distribution from sieve analysis of granulates obtained on two different scales.

1. **Working with a fixed screw configuration. It really limits design space.** Although not discussed in the present paper indepth, the screw configuration highly influences the granule quality [10], [18]. As shown by Meng *et al.* the influence of TSG process parameters on the granule quality can be quite limited if the screw is not changed [14]. A screw consisting of only soft mixing and kneading characteristics, for example, conveys the material very efficiently and thus MRT is very low. This can lead to very poor granulation behavior for most process parameters. Therefore, the screw configuration needs to be adapted to the formulation.
2. **Inaccurate feeding of the solid or liquid materials into the extruder. It leads to an inhomogeneous product.** A twin-screw extruder has only limited back-mixing capability. This means that all material is conveyed as it enters the barrel. If this feed is not constant, the complete granulation process is not constant. This can result in a very wide or multimodal residence time distribution or granules with various densities. This effect has been well described by Meier *et al.* [12]. Peristaltic pumps in particular tend to show a „dropping mode“ for very low feed rates. Working with multiple liquid injections, peristaltic pumps with two pump heads or with gravimetric pumps instead can solve this problem.
3. **Neglect of cooling power needed at different scales. Particle size increases with higher temperatures caused by insufficient cooling.** When scaling up a process, the amount of heat generated depends mainly on the mass or volume within the barrel (~D^3). The heat transfer for cooling, on the other hand, is limited mainly by the surface area (~D^2). Figure 9 shows the ratio of heat transfer area to volume plotted vs. the screw diameter. For small screw diameters, this ratio is very high resulting in an efficient cooling of the granulation process. But the ratio sharply decreases for larger screw diameters. This shows the importance of designing an adiabatic process or, if not possible, reducing the heat generation to a minimum, i.e., set the screw speed and the intensity of kneading zones in the screw configuration as high as necessary but as low as possible.

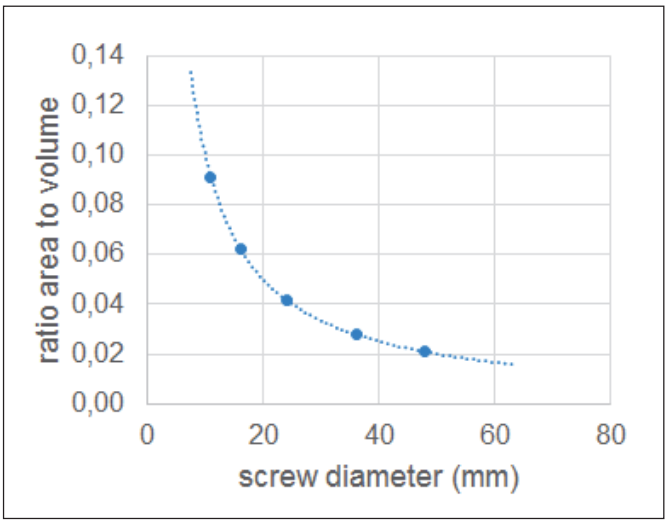

Fig. 9: Ratio of heat transfer area to volume over screw diameter.

Paying special attention to the issues mentioned above can help to successfully implement continuous TSG in all phases of pharmaceutical manufacturing.

Conclusion

This white paper summarizes the most relevant parameters and provides a recommendation for process development and scale-up of a continuous twin-screw granulation process. The summary explains how the particle size distribution can be tailored to reach the desired product quality and API release profile on an R&D scale and a production scale (see Figure 10).

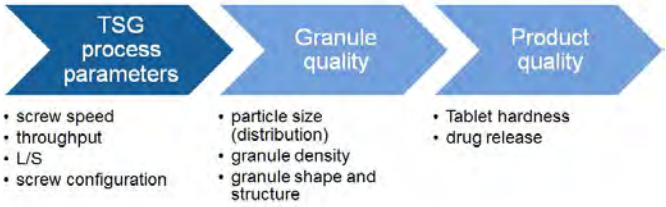

Fig. 10: Schematic from tailor-made granules to optimal tablets.

The exemplary results show the importance of process understanding in continuous twin-screw granulation. All process parameters (total throughput, liquid-to-solid ratio, screw speed and barrel temperature) as well as the screw configuration can significantly alter the granule quality. As a result, granule attributes can be tailored by changing the process parameters.

Extreme regimes, e.g., a very low filling level of the screws, a wide residence time distribution or a high L/S, can lead to non-linear dependencies with a strong influence on particle size and particle density. A scale-up in these regimes can be problematic as demonstrated in the results of Osorio *et al.* [5]. Therefore, the relevant process parameters need to be determined for each formulation before scale-up. Filling level and residence time within the barrel need to be considered. Special attention needs to be drawn to determine the design space where the influence of process parameters is manageable. Scale-up can then be easily done with the resulting information. The granule quality produced on a small scale is predictive of granule quality generated at larger scales. This concept can be also seen in continuous wet granulation including the drying process (Glatt® MODCOS xs-line, s-line and m-line).

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