Investigating process parameter mechanism for successful scale-up of a hot-melt extrusion process

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Introduction

Hot-melt extrusion (HME) is a suitable process to produce a wide range of pharmaceutical dosage forms, like tablets, capsules, lozenges, or implants. HME can be used for immediate-release as well as for sustained-release formulations. Similar to freeze drying or spray drying, the melt extrusion process is used to achieve solid dispersions, meaning the drug is embedded in a polymeric carrier. In this solid dispersion, the drug can be dispersed into the crystalline or amorphous state, or it can be dispersed on a molecular level in the polymer. In the case of a drug that is molecularly dispersed within the carrier, the solid solution may result in increased solubility, dissolution rate, and also the drug's bioavailability. Because a growing number of poorly soluble drugs are coming from high-throughput screening of drug development departments into the formulation development laboratories, the hot-melt extrusion process is rapidly gaining interest. Since HME is still a relatively new process for the pharmaceutical industry, it is more often used for formulation development than in the production environment. To properly manage such a continuous melt extrusion process within the production environment, it is absolutely necessary to understand the influence of the variable process parameters on the resulting process and the final product.[1, 2]

The purpose of this work was to get a deeper understanding of the influence of process parameters on the residence time distribution of the material within the extruder and the specific mechanical energy consumption (SMEC), with an additional goal of determining the possibilities of upscaling this process from a laboratory scale to a production line extruder. To save development time and material, the predictability of the scale-up step was determined with a design-of-experiments (DoE) approach: The polymeric carrier Soluplus® was extruded using three different sizes of corotating twin-screw compounders, with different process settings following a DoE plan. The residence time distribution was measured with a tracer in each setup, and the specific mechanical energy consumption was calculated. In addition to these special process parameters, all standard parameters (e.g., the temperature of the melt at the extruder die, the pressure at the die, and torque) were measured as well.

From the residence time distribution data, the mean residence time was calculated. Residence time distribution was obtained by measuring the concentration of a color pigment with a photometric and a colorimetric method.

The data of the three independent design-of-experiment studies were analyzed in an ANOVA. The resulting multidimensional regression models were used to calculate the design spaces, which were compared for their overlap across the different scales of the extruders.

Material and methods

Soluplus is used as a polymeric carrier. It is a polyvinyl caprolactampolyvinyl acetate—polyethylene glycol graft copolymer (BASF SE, Ludwigshafen, Germany) with an amphiphilic structure which was developed specifically for increasing the solubility of poorly soluble substances via the HME process.

Ferric trioxide is used as a tracer because of its intense red color.

Instrumentation

Three different sizes of parallel, corotating twin-screw extruders are used to simulate the scalability of the HME process:

- Thermo Scientific™ Pharma 11 Twin-Screw Extruder as a lab-scale extruder
- Pharma 16 Twin-Screw Extruder for medium scale
- Pharma 24 Twin-Screw Extruder (Thermo Fisher Scientific, Karlsruhe, Germany) for production scale

The index describes the screw diameter. All barrels have a length of 40 L/D.

The settings were varied to minimum, midpoint, and maximum values for the screw speed (100 rpm, 300 rpm, and 500 rpm), the temperature program (130 °C, 165 °C, and 200 °C), and the feed rate (shown in Table 1).

Table 1: Different feed rates used on a different twin-screw extruder sizes.

Throughput [kg/h]	min	mid	max
Pharma 11	0.17	1.33	2.40
Pharma 16	0.50	4.00	7.50
Pharma 24	1.13	6.60	12.0

The feed rate for the different extruder sizes is calculated in dependence on the equation of Schuler (Equation 1).[3]

$$\dot{m}_P = \left(\frac{D_P}{D_L}\right)^3 \cdot \dot{m}_L$$

Equation 1: Empirical equation of Schuler.

For all the experiments, the screw setup was kept constant with two mixing sections, as shown in Figure 1.

Figure 1: Set up of screws and barrel used for the scale-up experiments on the Pharma 11, Pharma 16, and Pharma 24. At the feeding section, the Soluplus is added, and the pigment is added at a given time T_0. The degassing section at the left-hand side is an atmospheric degassing to allow water vapor to evaporate out of the polymer.

Measurement of the residence time

The ferric trioxide pigment is added as a tracer to the hopper of the feeding section at a given time T_0. The color concentration is measured at the die over time.

Picture method: a picture of the strand is taken every 0.2 sec. In every picture, a defined strand size is detected regarding the amount of red pixels (Figure 2).

IR method: ExtruVis 2 is a colorimeter developed by A. Gryczke. It measures, in line, the concentration of the pigment in the melt at the die exit.

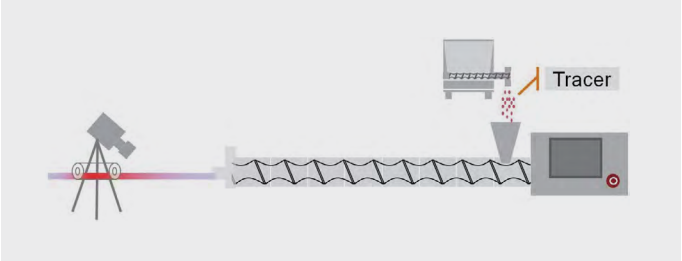

Figure 2: Residence time distribution measurement setup.

Software for data analysis

Visual X-Sel 11.0 (CRGRAPH, C.U. Ronniger, Germany) with a Design-of-Experiments (DoE) module is used for planning the experiments. For calculating the prediction, a module for multidimensional regression models is used. The optimization calculation was done with MS Excel 2010 (Microsoft).

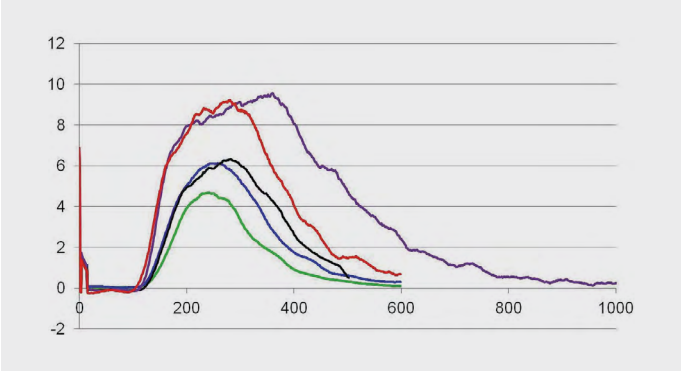

Figure 3: Influence of tracer concentration: green curve: 0.1 g, blue curve: 0.2 g, black curve: 0.3 g, red curve: 0.5 g, and purple curve 1.0 g of tracer were added to the Pharma 16 with constant parameter and constant feed rate.

Results

To have a successful scale-up, the material on the lab-scale extruder must undergo the same experience as it does on the bigger, production-scale extruder. Therefore, it is assumed that the residence time of the material within the extruder must be the same—to allow melting and mixing on the one hand, and to avoid degradation on the other.

When working with very low feed rates, it needs to be ascertained that there is no influence of the tracer itself on the process and, therefore, on the measurement of the residence time distribution. For example, if one considers the low feed rates of the lab-scale 11 mm extruder, with a feed rate of only 0,17 kg/h, that means that less than 50 mg is fed into the extruder every second. If the amount of tracer is too great, then the overall value for the feed rate will be elevated at that moment the tracer is added, and therefore all the other parameters that depend on the feed rate will also change. This hypothetical example shows how easy it is for the amount of the tracer to exert an influence. To determine the influence of the tracer concentration, the residence time distribution was measured with different amounts of tracer under the same process settings (Figure 3).

As is evident in the plot in Figure 3, with an increasing amount of tracer, the distribution gets broader, and the mean residence time shifts to higher values. Therefore, a very small amount of tracer should be used to get comparable results across experiments, and the effective tracer concentration should be held constant.

For the scale-up experiments, at first, the feed rate was only calculated by the equation of Schuler. As shown in Figure 4, the throughput was increased from 1 kg/h to 3 kg/h according to this equation when a change was made from an 11 mm screw diameter to an extruder with a 16 mm diameter.

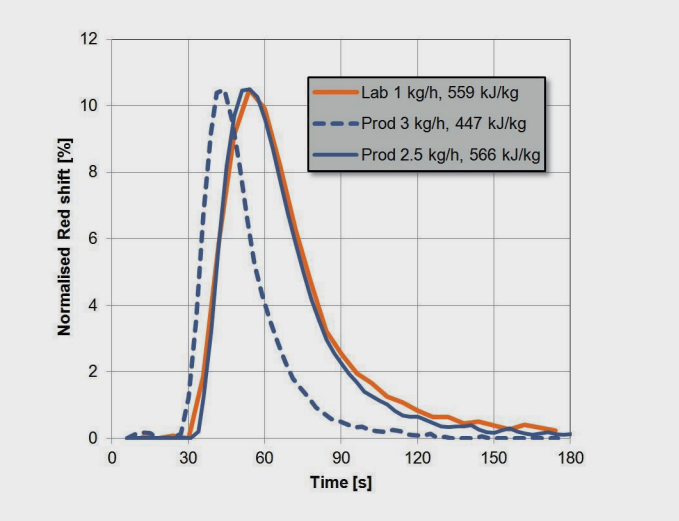

Figure 4: Influence of feed rate and SMEC on the residence time distribution; orange curve: Lab scale extruder (11 mm); blue curves: middle size extruder (16 mm); continuous line: feed rate calculated by Schuler; dotted line: feed rate adjusted regarding SMEC.

When increasing the feed rate in accordance with Schuler's equation, the residence time distribution on the next scale extruder is very similar. Nevertheless, the distribution is narrower than the lab scale extruder distribution and slightly shorter. It was found that the residence time distribution matches perfectly when matching the specific mechanical energy consumption (SMEC).[4]

The SMEC is calculated by the torque, the screw speed, and the feed rate, as shown in Equation 2. While the screw speed and throughput are parameters that can be set individually, the torque is a resulting value. Therefore, the SMEC needs to be adjusted by adjusting the feed rate.

$$\text{SMEC} = \frac{\tau \cdot n}{\dot{m}} \left[\frac{kJ}{kg} \right]$$

τ = torque (Nm)
n = screw speed (rpm)
$\dot{m}$ = throughput (kg/h)

Equation 2: Calculation of the specific mechanical energy consumption (SMEC).

The knowledge space of the used extruder sizes was explored in the next step with a DoE. Then an ANOVA (analysis of variance) was performed, and the design space was described via multiple regression. Using this method, the design space of all the other sizes could be calculated.

The regression model was used to calculate the design space from the 11 mm lab scale to the 24 mm production scale. The regression model was matched regarding residence time, melt temperature, and SMEC. The results are shown in Figure 5.

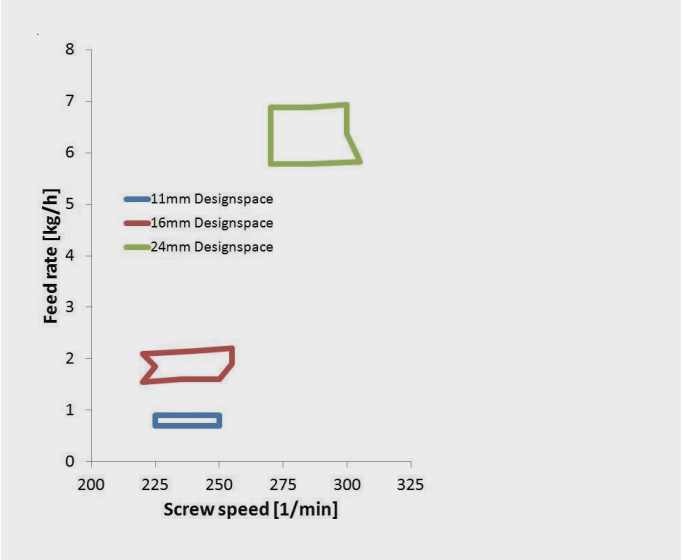

Figure 5: The design space of different sizes twin-screw extruder, calculated from the 11 mm scale extruder via regression mode.

For the scale-up from the design window of the Pharma 11 to that of the Pharma 16, only the feed rate needs to be adjusted to the bigger size. In case the scale-up is to a 24 mm system, the feed rate needs to be adjusted, of course, but the screw speed needs to be increased as well.

What might be shown here is a possible limitation of the scale-up process. When increasing the screw diameter of the extruder equipment, the surface area will increase by the power of two. When the feed rate increases, then this volume will increase by the power of three. So, with increasing extruder screw size, the ratio of the surface area—which allows the introduction of heating or cooling energy to the system—to the volume of the material gets smaller. This is why additional energy needs to be added via an increase in the screw speed.Also, the design space windows grow with increasing scale-up steps.

Another effect demonstrated in this study is the correlation of the SMEC with the degree of filling of the extruder (Figures 6a, 6b, and 6c).

The equation of the SMEC can explain all these effects. With increasing feed rate and therefore increasing volume-specific feed load (VSFL), there is a decreasing mechanical energy input because more materials share the mechanical energy supplied by the system. Another point that is also very important is that with increasing barrel temperatures, the SMEC is decreasing. With increasing barrel temperature, the viscosity of the material will decrease. Therefore also, the torque will decrease. And compared to Equation 2, with decreasing torque, the SMEC will also decrease.

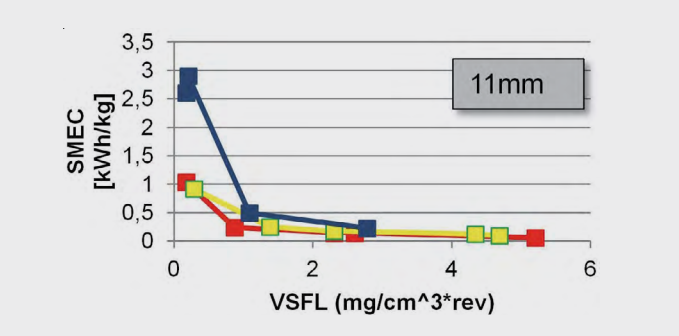

Figure 6a: Overview of the correlation between the VSFL and the SMEC, the 11 mm extruder.

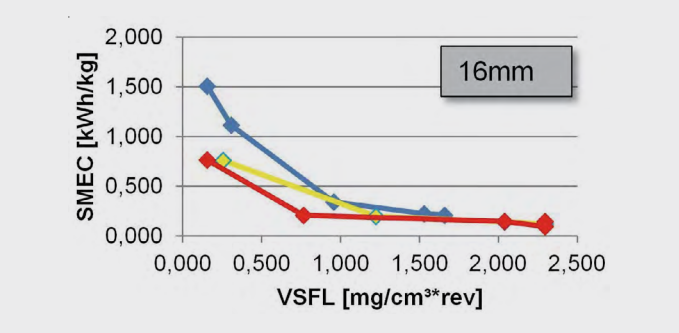

Figure 6b: Overview of the correlation between the VSFL and the SMEC, the 16 mm extruder.

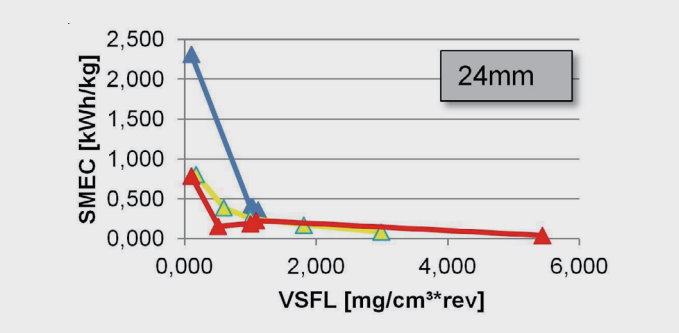

Figure 6c: Overview of the correlation between the VSFL and the SMEC, the 24 mm extruder. The different colors are linked to different barrel temperatures: blue curve: 130 °C, yellow: 165 °C and 200 °C is shown in red.

Conclusion

For each of the three extruder scales, a design space could be calculated based on the residence time distribution and the specific mechanical energy consumption.

It could be shown that the residence time distribution and the specific mechanical energy consumption are crucial parameters for a successful scale-up of a pharmaceutical melt extrusion process.

It could also be shown the amount of tracer influences the residence time distribution measurement.

Acknowledgments

This work was performed in collaboration with the BASF. In this collaboration, the BASF and Thermo Fisher Scientific are working closely together to investigate the dependency and influences of process parameters in the hot-melt extrusion processes. The teams are also investigating the link between rheology and HME. The focus of this work is to increase understanding and determine the optimal way to scale up HME processes.

Reference

1. Breitenbach, J.: Melt extrusion, from process to drug delivery technology, European Journal of Pharmaceutics and Biopharmaceutics, 2002
2. Douroumis, D.: Hot melt Extrusion—Pharmaceutical applications, Willey 2012
3. Bogun, M.: Untersuchungen zur kontinuierlichen Herstellung von Kautschukmischungen basierend auf Rubber/Filler-Composites am Doppelschneckenextruder, Thesis Hallee Germany, 2005
4. Kohlgrüber, K.: Der gleichläufige Doppelschneckenextruder, Carl Hanser Verlag, 2007

Figure 7: Pharma 11 Twin-Screw Extruder with 11 mm screw diameter

Figure 8: Pharma 16 Twin-Screw Extruder with 16 mm screw diameter

Figure 9: Pharma 24 Twin-Screw Extruder with 24 mm screw diameter

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