Investigating decisive parameters to achieve molecular dispersion via hot-melt extrusion

Dr. Margarethe Richter, Thermo Fisher Scientific, Karlsruhe, Germany

Introduction

Hot-melt extrusion is a process that can be used for a wide range of pharmaceuticals. It can be used for immediate release as well as sustained-release formulations and several applications like tablets, lozenges, or implants.

With the hot-melt extrusion process, a drug is embedded in a polymeric carrier, and a solid dispersion will be achieved. This solid dispersion can be either the drug dispersed into the polymer in the crystalline or amorphous state or even molecularly dispersed. When the drug is molecularly dispersed in the carrier, this solid solution may result in an increase in solubility, dissolution rate, and, ultimately, increase the bioavailability.

During the hot-melt extrusion process, the active pharmaceutical ingredient (API) and the excipients are fed into the extruder. All components will be sheared, heated, plastified, mixed and dispersed, and finally shaped by pressing it through a die opening.[1,2,3]

The purpose of this work was to monitor the impact of extrusion parameters on dispersion and distribution quality characterized by the values mean residence time (t_{mean}) and interquartile range (IQR). The residence time can also be used to avoid out-of-specification material (OOS).

A high dispersion mixing is needed to achieve a solid solution, but extensive mixing could potentially lead to degradation. A weakly soluble crystalline API and an amorphous polymer are transferred into a solid solution by introducing thermal and mechanical energy. For a given screw configuration, increasing exposure time to shear results in an increase in melt temperature, which may lead to degradation and a higher degree of dispersion.

This approach will show how one could optimize the degree of dispersion by minimizing the risk of degradation.

Materials and methods

For this approach, Kollidon® VA64 was extruded on a co-rotating twin-screw compounder, Thermo Scientific™ Pharma 16 Extruder, in different process settings following a design-of-experiments plan. Varied were throughput, screw speed, screw setup, and compounding temperature level.

Residence time distribution was measured, and the mean residence time and the interquartile range were calculated from it. As another important parameter, the specific mechanical energy input was measured.

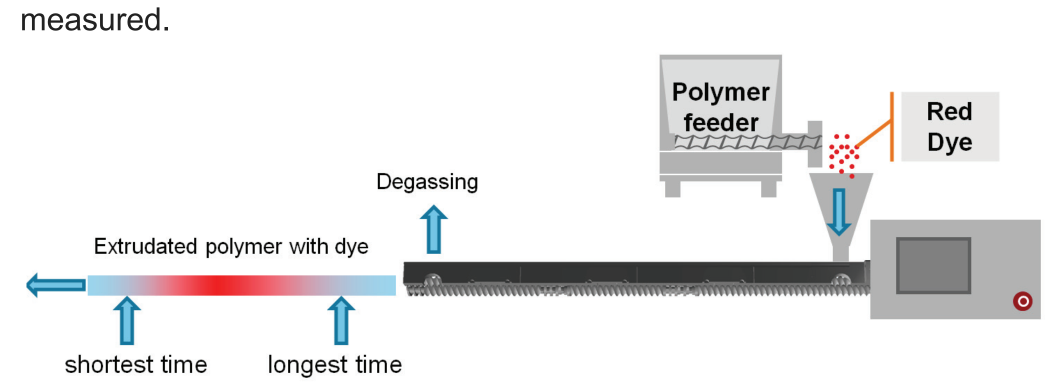

Figure 1. Setup of screws and barrel used for the scale-up experiments on the Pharma 16. At the feeding section, the Kollidon® VA64 is added, and the pigment is added at a given time, T0. The degassing section at the left-hand side is an atmospheric degassing to allow water vapor to evaporate out of the polymer.

Material

Kollidon® VA64 is used as a polymeric carrier. It is a poly-vinyl pyrrolidone-vinyl acetate copolymer (BASF SE, Ludwigshafen, Germany).

Hot-melt extrusion process

A Pharma 16 (Thermo Fisher Scientific, Karlsruhe, Germany) is used to conduct the experiments. It is a co-rotating twin screw extruder with a 16 mm screw diameter and a length of 40 L/D. Different parameters were used. The parameters are mentioned in the figures..

Measurement of the residence time

The pigment is added as a tracer to the hopper of the feeding section at a given time, T0. The color concentration is measured at the die over time as color intensity with a colorimeter every 0.2 sec (figure 1).

Calculation of t_{mean}

Mean residence time describes the 50% probability that a particle entered the process at T0 has left the process. It is calculated with the following equation:[4]

$$t_m = \frac{\int_0^\infty tE(t)}{\int_0^\infty E(t)dt} = \int_0^\infty tE(t)dt$$

Calculation of variance

Variance describes the degree of dispersion and is calculated as follows :

$$\sigma^2 = \int_0^\infty (t - t_m)^2 E(t)dt$$

The variance is often used as a measure for the axial mixing process in the extruder. But as the equation for calculation of variance includes a term squared, it amplifies especially noise in the measured signal yielding a relatively high standard deviation from measurement to measurement. The authors decided because of that to use the interquartile range as a measure of axial mixing instead. The interquartile range (IQR) is calculated as delta of the tracer intensity at 75-percentile and 25-percentile from the exit age distribution E(t) (figure 2).

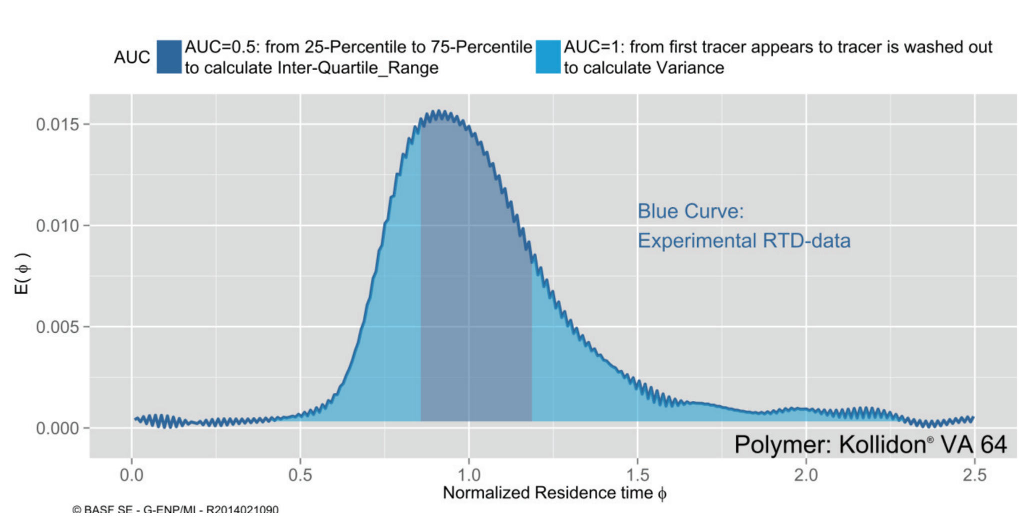

Figure 2. Residence time distribution of Kollidon® VA 64 in the Pharma 16 Extruder with a feed rate of 2 kg/h, a screw speed of 200 rpm and a barrel temperature ramp up to 260° C.

A further advantage of using the IQR is the fixed borderlines of IQR = 1 means ideal mixing, and IQR = 0 means plug flow. In case of plug flow, there would be no mixing at all taking place which is unlikely for an extrusion process. The data showed that the IQR in an extrusion process is larger than 0.2 to achieve an acceptable mixing.

Results

Even though the dye is introduced as one sharp dosage (equally a pulse), it is widely distributed in the extruded polymer strand. That distribution in the strand displays the residence time distribution of the particles within the extruder.

The mean residence time is, besides the screw setup, mainly influenced by the feed rate. In figure 3, the tracer intensity versus the time is displayed. With increasing feed rate, the residence time gets narrower and the mean residence time in the extruder shorter. With a low feed rate, a wide residence time distribution is observed with a very long mean residence time.

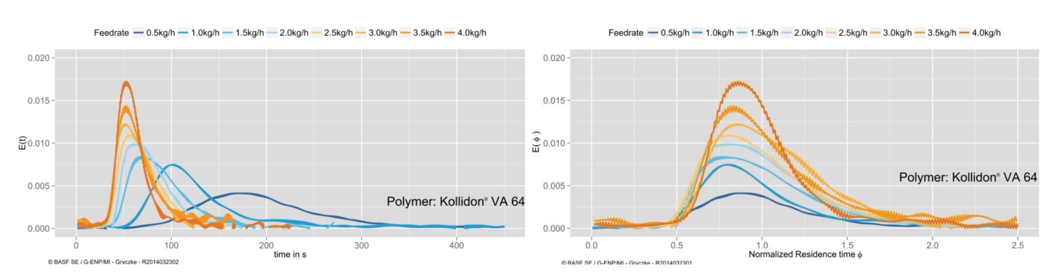

Figure 3. a and b: Residence time distribution of Kollidon® VA 64 in the Pharma 16 Extruder with different feed rates, a screw speed of 200 rpm, and a barrel temperature ramp up to 260° C.

The narrower residence time distribution does not allow the conclusion of a reduced mixing in the extrusion process. The interquartile range as a mixing measure has to be calculated on the exit age function when plotted versus normalized time phi (ϕ). ϕ is calculated as t/t_{mean}. To visualize that, in figure 3 b, the tracer concentration is given versus the normalized residence time. If E(ϕ) is plotted versus phi, the distributions obtained from different experiments can be analyzed for comparison, such as the IQR.

The mean residence time of the material within the extruder is impacted by the feed rate (figure 4), but the IQR is not dependent on the feed rate (figure 5).

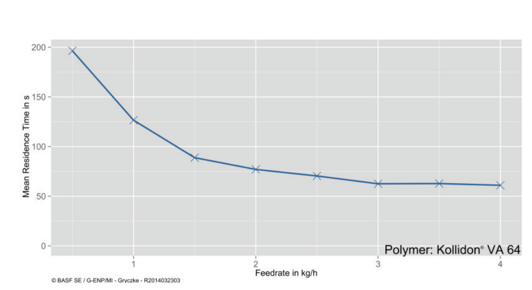

Figure 4. Mean residence time distribution vs. feed rate of Kollidon® VA 64 in the Pharma 16 Extruder with different feed rates, a screw speed of 200 rpm, and a barrel temperature ramp up to 260° C.

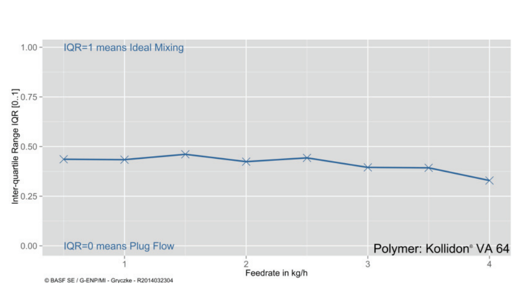

Figure 5. IQR from residence time distribution vs. feed rate of Kollidon® VA 64 in the Pharma 16 Extruder with different feed rates, a screw speed of 200 rpm, and a barrel temperature ramp up to 260° C.

Besides the mean residence time and the interquartile range calculated from the residence time distribution, the flow rate is a theoretical consideration that can be used to understand extruder mixing better. The flow rate is a measure of a fluid element and how often it passes on average over a screw flight tip for a considered section length of the process.[5]

The following equation gives the flow rates feasible for standard conveying elements on a screw:

$$\phi = \frac{0.5(\pi * D * n) * \delta * l_s * z * z_w}{\dot{m}}$$

D is the screw diameter, n is the screw speed, δ is the clearance between the flight tip and the barrel, l_s is the length of the considered section, z is the number of flights per extruder screw, and z_w is the number of shafts in the extruder. The above equation is valid if the density of the extruded material is considered to be 1g/cm³.[5]

For the 16mm twin screw extruder used for the study, the flow rate for different screw speeds and feed rates are calculated and plotted.

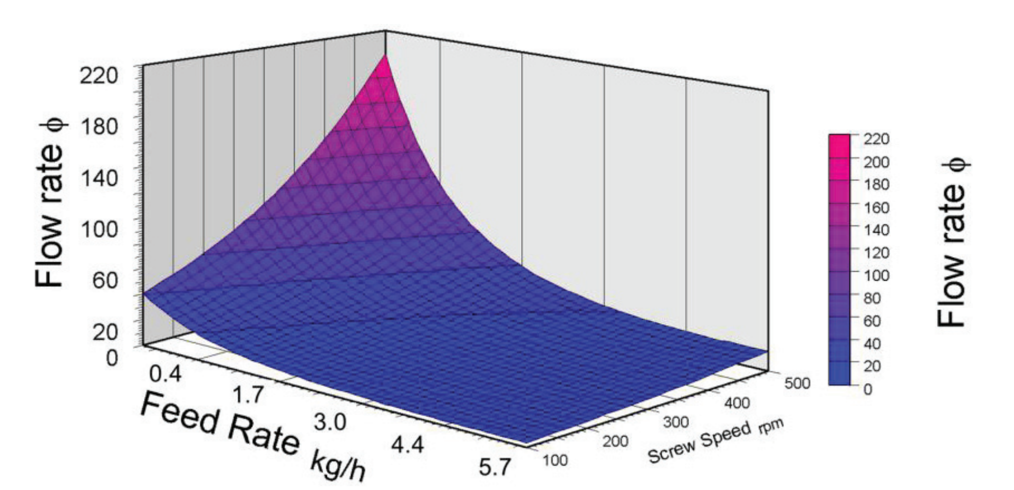

Figure 6. Visual X-sel 11-software produced charts of the impact of screw speed and feed rate on the flow rate.

The above figure shows that it is mainly the screw speed influencing the flow rate. This is in agreement with experimental findings. For special mixing and dispersing elements, the above-given equation needs to be adopted.[6]

Conclusion

- Residence time distribution is a key instrument to study and optimize mixing behavior
- Mean residence time is a measure of mixing history: long residence time means large mixing history
- Interquartile range is preferred over variance as a parameter for measuring axial mixing
- The axial mixing is not influenced by feed rate, screw speed, or temperature, but is expected to be influenced by screw geometry
- The mean residence time is mainly influenced by the feed rate: higher feed rate yield in shorter residence time
- Degree of dispersion is a function of axial mixing and exposure time (residence time) and is hence influenced by feed rate and screw geometry

Outlook

- Screw speed is suspected of having a minor impact on the degree of dispersion due to shear thinning behavior of polymer
- Further studies need to be conducted to determine the impact on active pharmaceutical ingredient
- Study to impact the balance between the degree of dispersion and the degradation profile of active

References

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Acknowledgements

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 Hot-Melt Extrusion Processes. Also, the link between Rheology and HME is investigated, and this work focuses on the process and how to scale up HME processes.