W4343

Investigating decisive parameters to achieve molecular dispersion via hot melt extrusion

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Introduction

Hot melt extrusion is a process which can be used for a wide range of pharmaceuticals. It can be used for immediate release as well as for sustained release formulations and for 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 is 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 of 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 press 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 inter quartile 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 so also it may lead to degradation but also in higher degree of dispersion.
This approach will show how one could optimize the degree of dispersion with minimizing the risk of degradation.

Material and Methods

For this approach Kollidon® VA64 was extruded on a co-rotating twin-screw compounder, Pharma 16 Thermo Fisher 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 inter-quartile range were calculated from it. As another important parameter the specific mechanical energy input was measured.

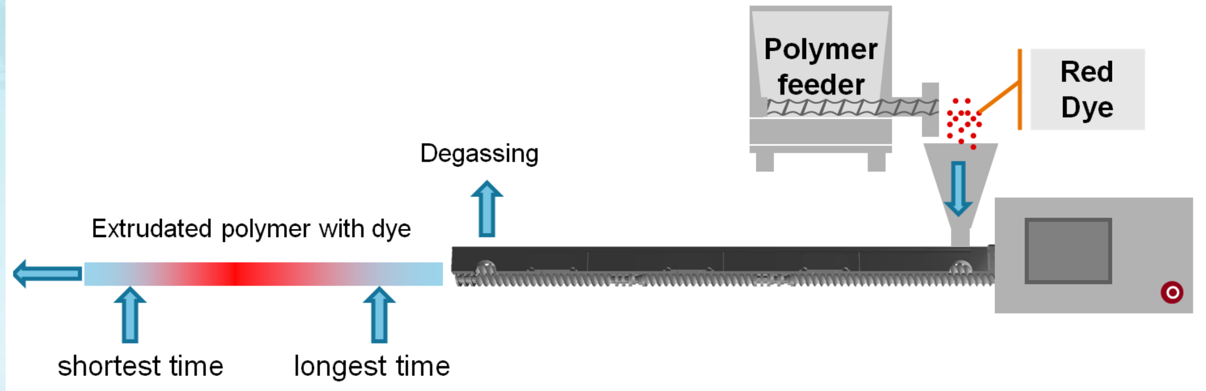

FIGURE 1: Set up of screws and barrel used for the scale up experiments on the Pharma 16. At the feeding section the Kollidon® VA64 is added as well as the pigment is added at a given time T0. The degassing section at the left hand side is an atmospheric degassing to allow water vapor to evaporate out 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 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 the 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 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 followed:

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

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 as term squared, it amplifies especially noise in the measured signal yielding in a relative high standard deviation from measurement to measurement. The authors decided because of that to use the inter quartile range as measure of axial mixing instead. The inter quartile 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).

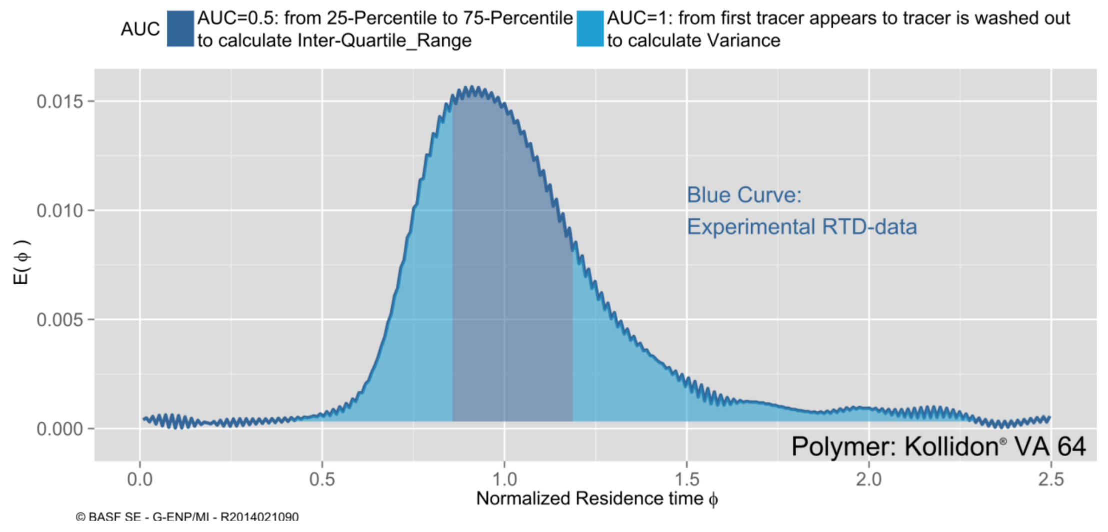

FIGURE 2: Residence time distribution of Kollidon® VA 64 in the Pharma 16 Extruder with a feed rate of 2 kg/h, a screw speed of 200 rpm and a barrel temperature ramp up to 260°C.

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 no mixing at all take place which is unlikely for an extrusion process. The data showed that the IQR in an extrusion process is larger 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, beside the screw setup, mainly influenced by the feed rate. In figure 3 a the tracer intensity versus the time is displayed. With increasing feed rate the residence time gets more narrow and the mean residence time in the extruder shorter. With low feed rate a wide residence time distribution is observed with a very long mean residence time.

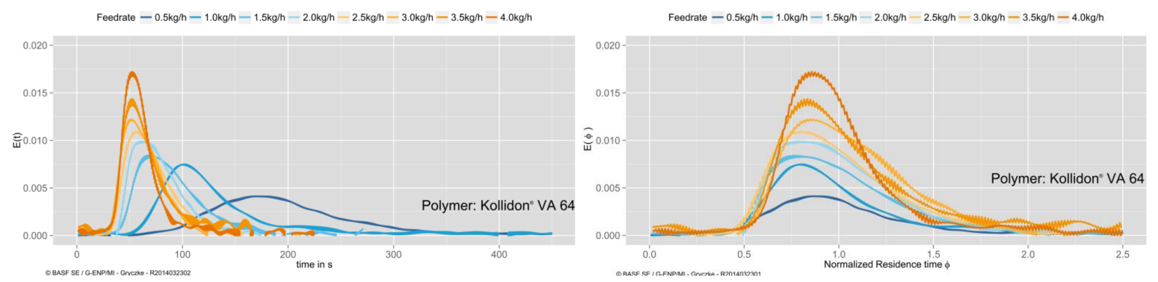

FIGURE 3 a and b: Residence time distribution of Kollidon® VA 64 in the Pharma 16 Extruder with different feed rates, a screw speed of 200 rpm and a barrel temperature ramp up to 260°C.

The more narrow residence time distribution does not allow the conclusion of a reduced mixing in the extrusion process. The inter-quartile range as measure of mixing 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. Only 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).

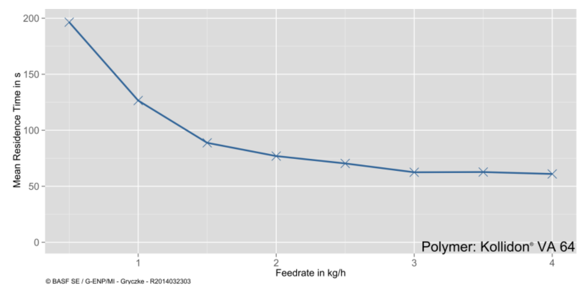

FIGURE 4: Mean residence time distribution vs. feed rate of Kollidon® VA 64 in the Pharma 16 Extruder with different feed rates, a screw speed of 200 rpm and a barrel temperature ramp up to 260°C.

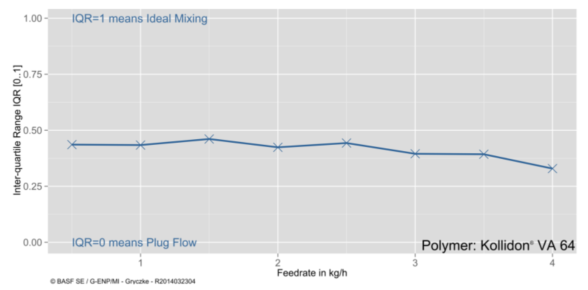

FIGURE 5: IQR from residence time distribution vs. feed rate of Kollidon® VA 64 in the Pharma 16 Extruder with different feed rates, a screw speed of 200 rpm and a barrel temperature ramp up to 260°C.

Beside the mean residence time and the inter-quartile range calculated both from the residence time distribution the flow rate is a theoretical consideration which can be used to understand the mixing in the extruder better. The flow rate is a measure for a fluid element how often it passes in 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:

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

In which D is the screw diameter, n the screw speed, δ the clearance between flight tip and the barrel, l_s the length of the considered section, z 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 rate are calculated and plotted.

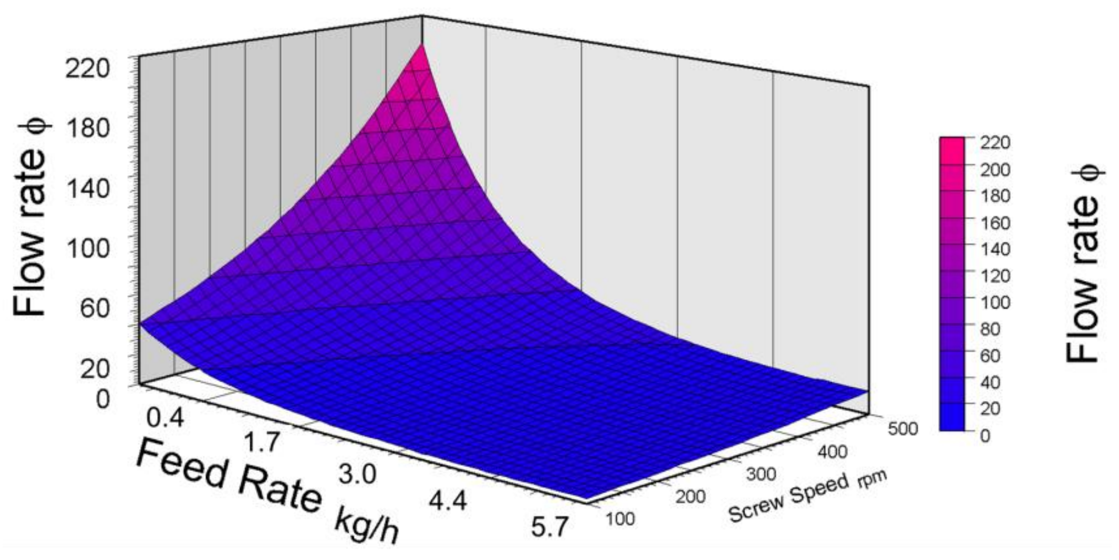

FIGURE 6: Visual X-sel 11-software produced charts of the impact of screw speed and feed rate on the flow rate

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 need to be adopted [5].

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**
- **Inter quartile range is preferred over variance as parameter for measuring axial mixing**
- **The axial mixing is not influenced by feed rate, screw speed or temperature, but 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 to have 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 close together to investigate the dependency and influences of process parameters in Hot Melt Extrusion Processes. Also the link between Rheology and HME is investigated.

Especially to understand the process and the way to scale up HME processes are focus of this work