

Continuous Manufacturing of Pharmaceuticals: Scale-up of a Hot Melt Extrusion Process



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Introduction

Over the last three decades industrial adaptability has allowed hot-melt extrusion (HME) to gain wide acceptance where it has established its place in the broad spectrum of manufacturing operations and pharmaceutical formulation development. HME has been demonstrated as a robust, novel technique to make solid dispersions in order to provide 1.) time-controlled, 2.) modified, 3.) extended, or 4.) targeted drug delivery, resulting in improved bioavailability as well as taste masking of bitter active pharmaceutical ingredients (APIs).

Hot melt extrusion applies heat and pressure to melt a polymer and force it through an extruder in a continuous process. The extruder generally consists of one or two rotating screws (either co-rotating or counter rotating) inside a stationary cylindrical barrel. Regardless of type and complexity of the function and process, the extruder must be capable of rotating the screws at a selected, predetermined speed, while compensating for the torque and shear generated from both the material being extruded and the screws being used.

Extruders come in various sizes, so an 11mm, 16mm, or 24mm extruder refers to the diameter of the twin screws being used in the respective instrument. In addition, throughput will vary depending on the size of the extruder. For example, a 16mm extruder might be applicable for a throughput rate of up to 5kg/h (**Figure 1**), ideal for small-scale production quantities of an API/excipient formulation.

But, when a formulation is developed at an R&D scale—such as on an 11mm extruder—making the jump to production-scale levels is not an easy proposition. One way to accomplish this successfully is by developing a process design that takes many variables into consideration, including speed, torque, volume, and temperature. Here we describe a scientific approach to developing the scale-up of an HME process across geometrically similar twin-screw extruders.

The Process Design

To start a process design from scratch, consider the maximum screw speed of the extruder and the throughput of the system that can feed the extruder. If when starting a process you don't know much about the behavior of the system, begin with a moderate screw speed and moderate throughput rate. Increase the screw speed slightly before increasing the throughput of the feeders. Depending on the size of equipment, give the system time to respond to the changes before setting up other parameters.

Once a desired screw speed is reached, increase the throughput again until the system reaches a process boundary (**Figure 2**). Because extrusion is a continuous manufacturing system, and the screw speed and throughput are variable, the process does not have to be stopped. Just changing the speed on the extruder screw or the speed of the feeder will allow you to obtain a desired result. Then allow the system some time to react and equilibrate again.

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Depending on your process, you will encounter a process boundary. This boundary can either be torque limited or volume limited, depending on the viscosity and the API/excipient formulation being used. The boundary provides an understanding of the relationship interdependencies of the process parameters.

Screw speed, throughput, and residence time become apparent once the process boundary for a given system is known (**Figure 3**). Residence time is the time a single particle is placed within the system until extruder output. There is a dependency between the screw speed and throughput and that influences residence time. As scale-up occurs,

the assumption is that within each of the different sizes of extruder (i.e., 11mm versus 24 mm), the residence time should be the same. Make sure that all of the particles going through the system have the same experience and residence time at the laboratory scale as they will have at the production scale.

Different screw speeds have little effect on residence time. This means a material throughput of e.g. 1kg/h can be processed at 200rpm/h and 600rpm/h screw speed. On the other hand, if throughput increases, there is more material in the system that

Figure 1: Thermo Scientific™ Pharma twin-screw extruders for HME.

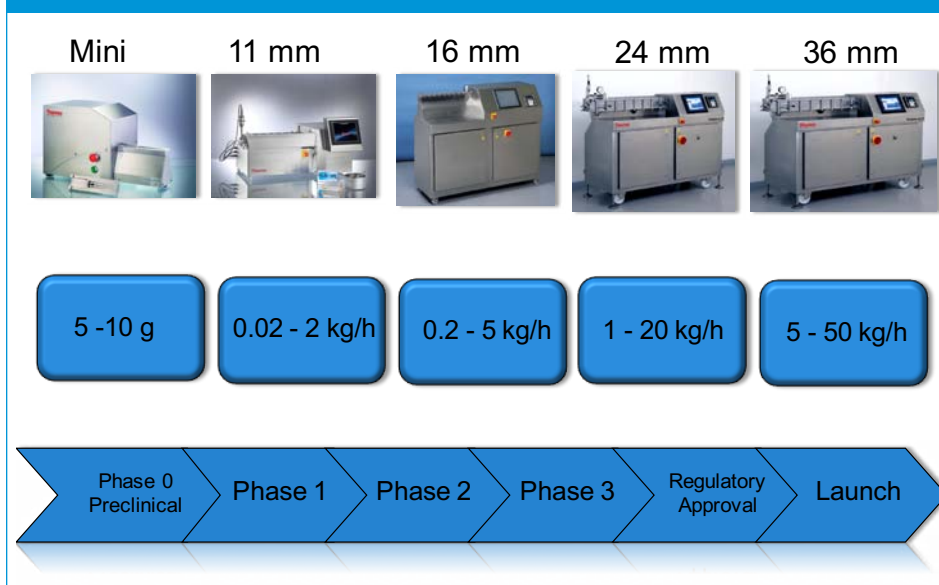
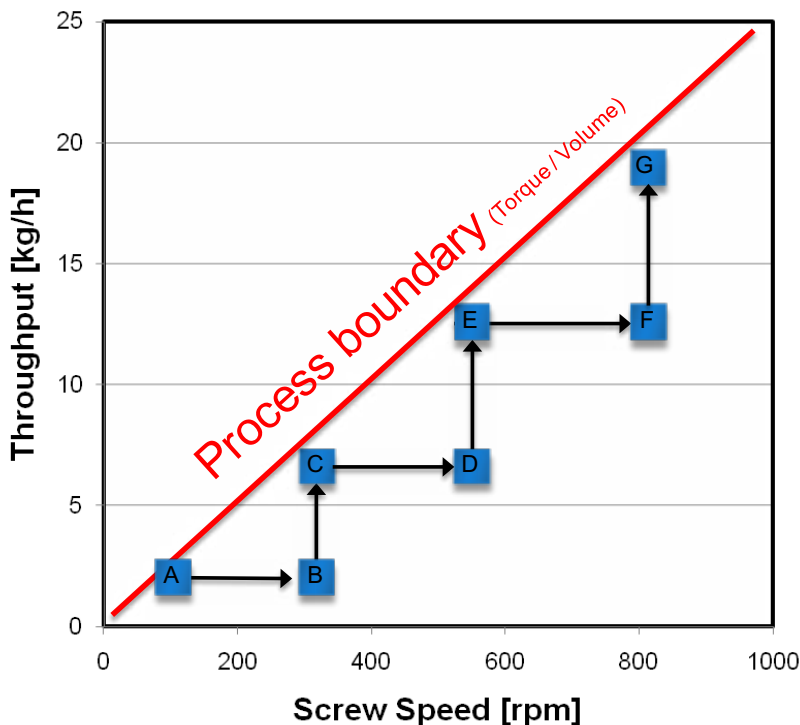


Figure 2: Compounding Trials – Set up your process.



- A Start up with low speed, low feed rate
- B Increase speed
- C Increase feed rate till process boundary (Torque/Volume) is reached
- D Increase speed, torque goes down
- Continue in steps till max values reached
- Process boundary, limited by torque or volume
- Position of process boundary dependent on
 - Temperature profile
 - Screw Configuration
 - etc.

can displace the old material. So, when adjusting the throughput feed rate, this has a significant impact on residence time.

In addition to residence-time dependency, the exposure to temperature is another important variable to consider when scaling up an HME process. Different screw speeds have a significant impact on melt temperature (**Figure 4**). The screw speed is a measure of the mechanical energy that goes into the system, so the faster the screw turns, the more mechanical energy is put into the system, and the hotter the average temperature of the melt becomes. On the other hand, if a screw speed is maintained and throughput is altered, there is little effect on the overall melt temperature.

By having the residence time and screw speed as the two most critical variables, there is a balance one has to find when optimizing a formulation. With the process boundary defined, the “Control Space” in the R&D process is able to be defined (**Figure 5**). This “parameter optimization zone” is the ability to produce the desired product quality in a continuous stage.

Affecting Residence Time

Residence time measurement can be done with a color tracer added to the formulation. There are different tracers available, just be sure that the tracer selected is detectable. The amount of tracer put into a stable system should not influence the process. In other words If the tracer detectability is so low that a high amount of tracer needs to be added, then this will disturb the entire process and result in an unsteady state.

As shown in **Figure 6**, a small amount of color tracer (Kollipat® IR, BASF) was added, and the tracer concentration was recorded over time. The peak at the upper right shows the mean residence time in relation to tracer concentration. A digital camera system was used to optically measure residence time. Software was developed and used to detect changes in tracer concentration that could then be plotted against time,

Figure 3: Residence time dependency.

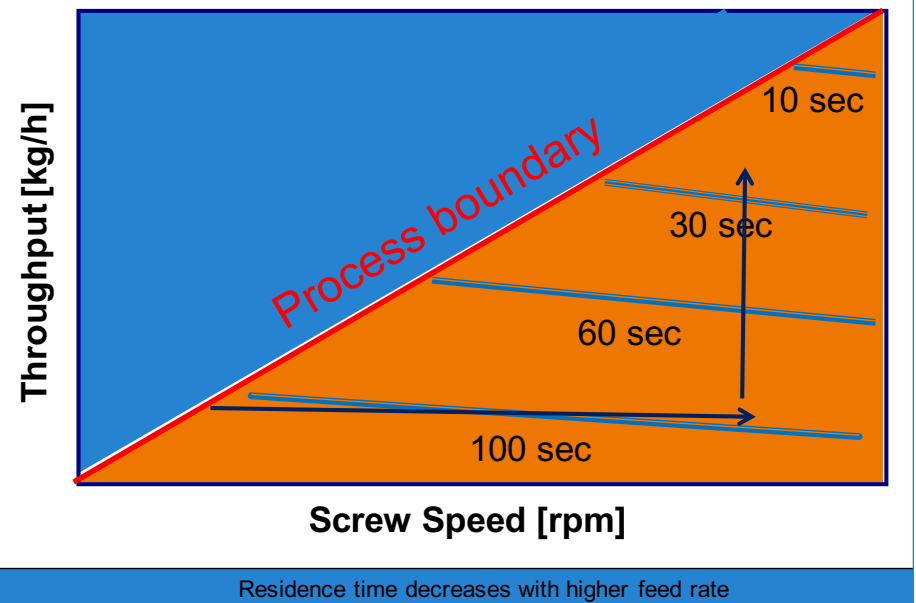
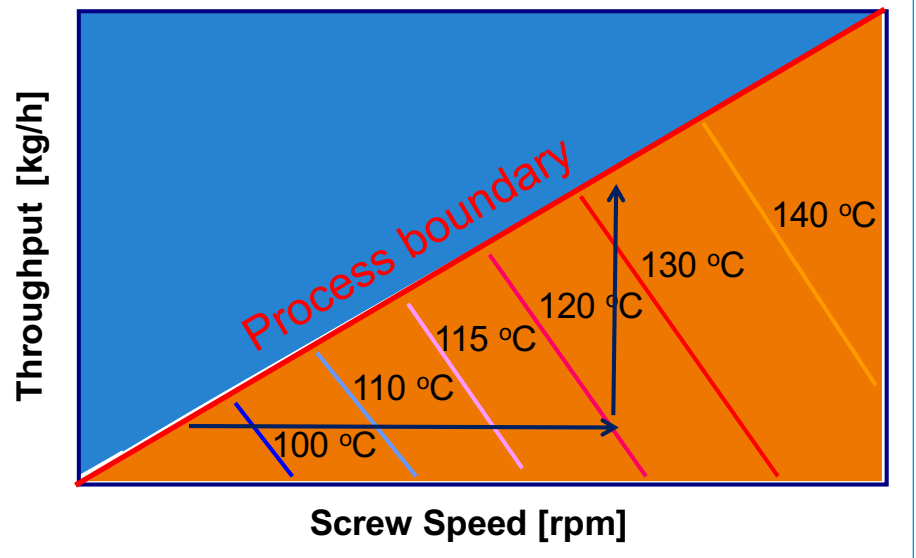


Figure 4: Melt temperature dependency.



as seen at the lower right of Figure 6.

While the amount of tracer should not influence the process, a few milligrams could have a tremendous effect on residence time. A lower throughput means a lower filling level, so the material stays longer in the system.

Screw configuration can also influence the residence time. Mixing elements and reverse mixing elements can help to keep the material longer in the system and, therefore, increase the residence time.

Working with different extruder sizes means the residence time and the feed rate cannot be compared one to one. However,

having extruders with geometrically scalable screw and barrel ratios results in having comparable residence times relative to the feed rate. **Figure 7** shows the calculation of a feed

load and the plotted mean residence time. With comparable volume specific feed load, all of the Thermo Scientific™ Pharma Twin-Screw Extruders behave similarly in respect to residence time distribution. Each disturbance of a material feed load that goes into the systems has a significant effect on the mean residence time.

The Scientific Scale-Up Approach

Throughput, screw rotation rate, and barrel temperature need to match the extruder at both the R&D scale and at production scale. In addition, machine parameters must be constant and identical on both the R&D-scale and production-scale machines. This includes screw configuration, die geometry, and volume.

Figure 8 illustrates a case study of the scientific scale-up approach on the complete

Figure 5: Quality by Design – Twin-screw extrusion.

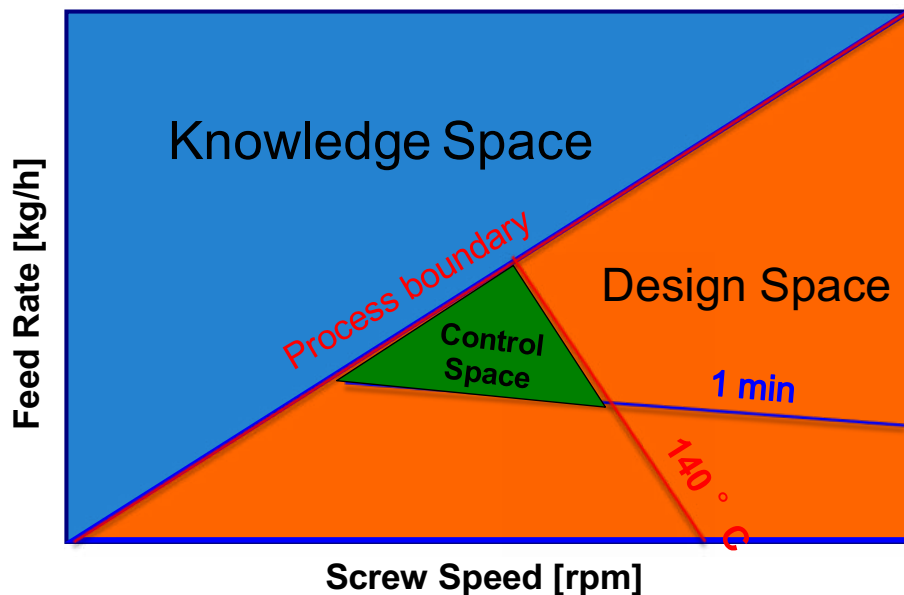
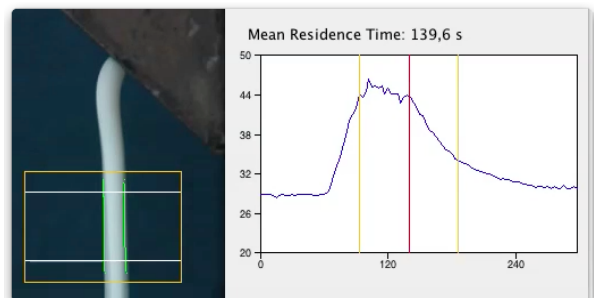
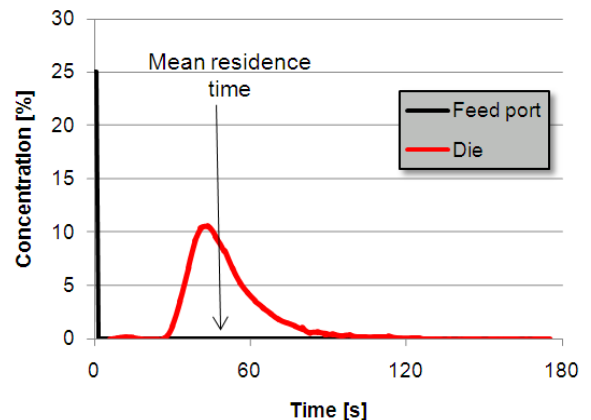


Figure 6: Residence time measurement.

- Tracer selection
 - Detectable
 - Does not influence the process
- Traditional
 - At t_0 tracer is added
 - Record tracer concentration at exit
 - Result: Residence time distribution
 - Mean residence time (calculated)
 - Width of distribution
- Our new approach
 - Digital camera takes pictures (and records time),
 - Software detects strand and
 - calculates tracer color ratio (concentration)
 - Plots concentration vs. time



Thermo Scientific Pharma extruder family. Pure Soluplus® polymer (BASF) was put in the different scale extruders: 11mm, 16mm, and 24mm. All are parallel twin-screw extruders with co-rotating screws, with the barrel length to diameter ratio (L/D) of 40. Input variables (feed rate, screw speed, and process temperature) were tested, and the system response was recorded. Twenty-five experiments were performed for each extruder. **Figure 9** shows relevant parameters from the knowledge space that provide stable extrusion conditions for the different sized extruders.

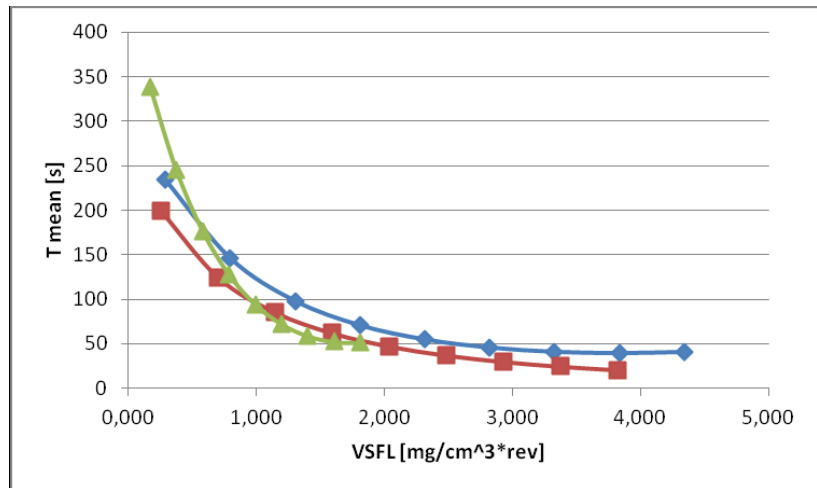
A scientific scale-up approach has two different aims. First is scaling up for optimal heat transfer. This is when melt temperature is the most sensitive parameter. Then there is scaling up for optimal mixing. There needs to be a balance between the amount of heat and the mixing level (**Figure 10**) to make a high quality drug product.

Apply the One Step Scale-Up

One aim is to have a higher throughput and higher feed rate in the scaled-up process than in the R&D process. Going back to the case study, the feed rate for the 11mm extruder (the R&D extruder) and the feed rate for the larger extruder were calculated to determine the scale-up for mixing and heat transfer. The result is the optimal production feed rate.

Figure 11 shows the scale-up for the feed rate from the 11mm to the 16mm extruder. A non-linear regression model provides an understanding about the relationship between

Figure 7: Pharma Extruder Sizes: Residence time dependent on degree of filling.



Pharma 11 in blue, Pharma 16 in red and TSE 24 in green

Figure 8: Case Study: Pharma extruder parameter testing - size comparison.

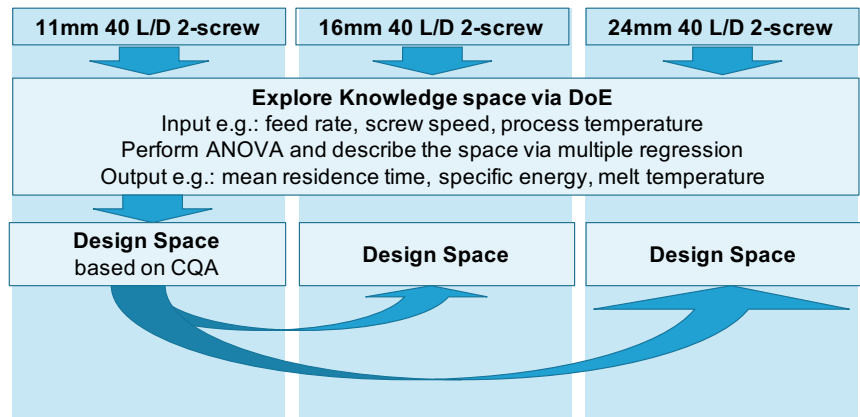
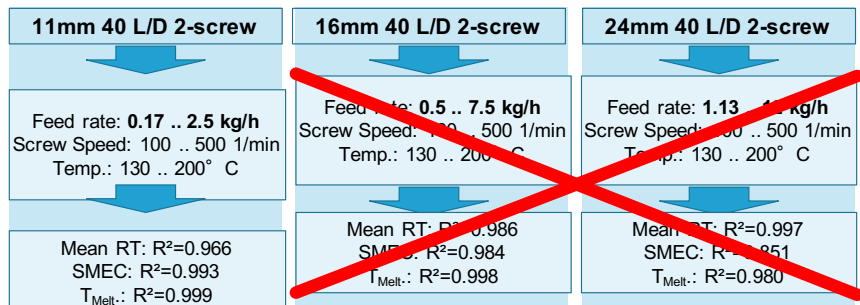


Figure 9: Exploring the knowledge space: Identify optimal parameters for scale-up.



the extruders' process parameters (small left graph). The scale-up goal was to maintain the specific mechanical energy (SMEC) and the mean residence time constant (t_{mean}) between the two extruders. The 11mm extruder had a feed rate tested from 0.25 kg/h up to 2.5 kg/h. As Figure 11 shows process conditions are profitable and transferable from the Pharma 11 extruder to the Pharma 16 extruder when the feed rate is 1.25 kg/h and above (green section on the right graph). With a throughput

lower than 1.25 kg/h (red and yellow sections on right graph) process parameters are scalable, but they would not result in an economically viable process. The higher the throughput, the more stable and more economical the process scale-up becomes (**Figure 12**).

There is a one-step scale-up possibility as seen in **Figure 13**. This is a scale-up procedure of an 11mm extruder to a 16mm extruder, without testing the 16mm system first,

as it had been done for the previous experiment. Conclusions are made in terms of the resulting t_{mean} and SMEC for the Pharma 11 extruder. Feed rate can then be fine tuned to get the same quality as in the R&D process.

Summary

Extrusion is an elegant process for continuous manufacturing of pharmaceuticals.

Geometric similarity between the extruders used for R&D and production scale matters.

Understand the dependencies of process variables for a scientific approach to drug delivery scale-up.

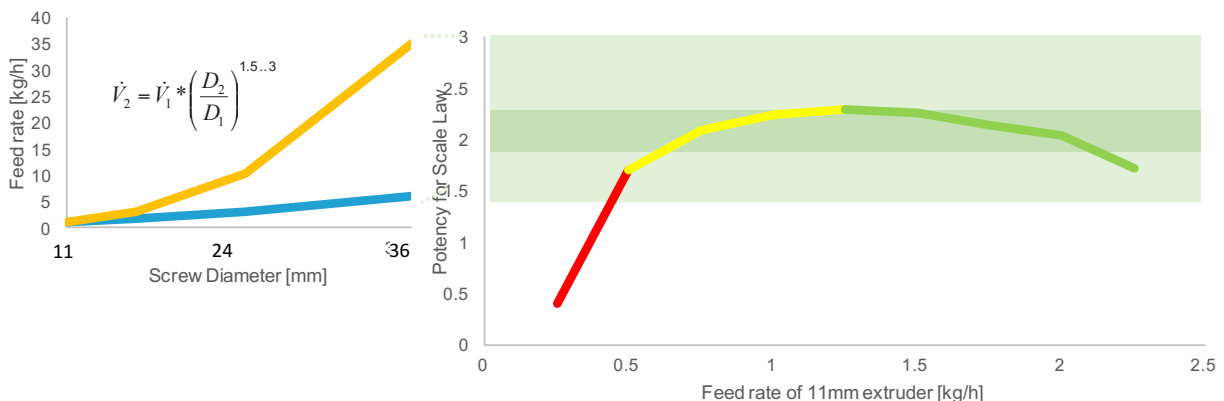
Figure 10: Scale-Up theory.

| | Common Factors | Scale for Heat Transfer | Scale for Mixing |
|-----------------------|---|--|--|
| Screw Speed | $N_2 = N_1 * \left(\frac{D_2}{D_1}\right)^{0.5}$ | $N_2 = N_1 * \left(\frac{D_2}{D_1}\right)^{1.0}$ | $N_2 = N_1 * \left(\frac{D_2}{D_1}\right)^0$ |
| Feed rate | $\dot{V}_2 = \dot{V}_1 * \left(\frac{D_2}{D_1}\right)^2$ | $\dot{V}_2 = \dot{V}_1 * \left(\frac{D_2}{D_1}\right)^{1.5}$ | $\dot{V}_2 = \dot{V}_1 * \left(\frac{D_2}{D_1}\right)^3$ |
| Residence Time | $t_2 = t_1 * \left(\frac{D_2}{D_1}\right)^{0.5}$ | $t_2 = t_1 * \left(\frac{D_2}{D_1}\right)^1$ | $t_2 = t_1 * \left(\frac{D_2}{D_1}\right)^0$ |
| Specific Energy | $\hat{z}_2 = \hat{z}_1 * \left(\frac{D_2}{D_1}\right)^{0.5}$ | $\hat{z}_2 = \hat{z}_1 * \left(\frac{D_2}{D_1}\right)^0$ | $\hat{z}_2 = \hat{z}_1 * \left(\frac{D_2}{D_1}\right)^0$ |
| Plasticating Capacity | $\dot{M}_{p2} = \dot{M}_{p1} * \left(\frac{D_2}{D_1}\right)^{1.75}$ | $\dot{M}_{p2} = \dot{M}_{p1} * \left(\frac{D_2}{D_1}\right)^{1.5}$ | $\dot{M}_{p2} = \dot{M}_{p1} * \left(\frac{D_2}{D_1}\right)^2$ |

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Figure 11: Feed rate workspace: Parameter scale-up from Pharma 11 to Pharma 16 extruder.

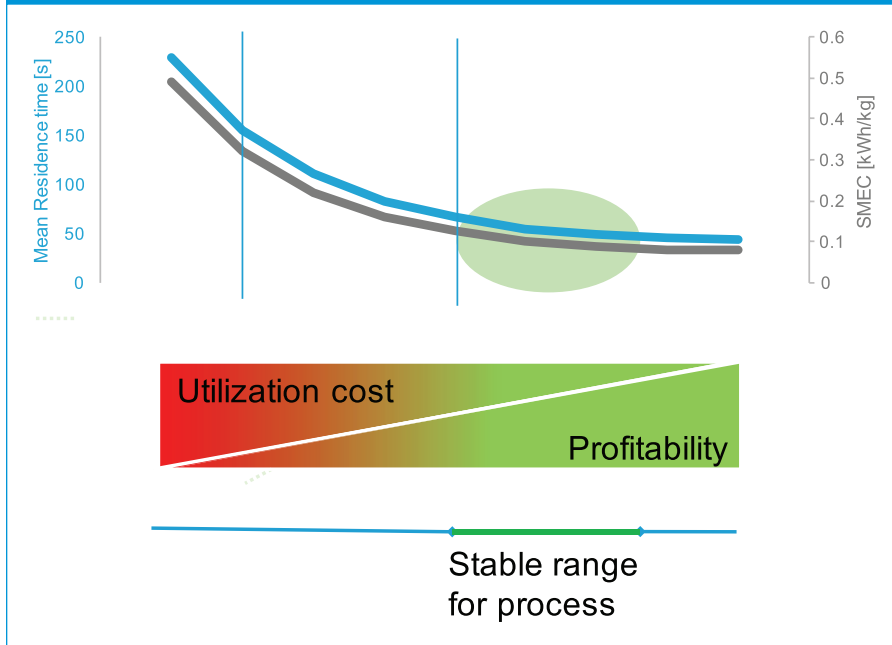
1. Feed rate range scaled from 11mm to 16mm extruder using DoE (non-linear) regression model
2. Target parameter for scale-up to keep constant: SMEC and t_{mean}
3. Scale-law potency is conditioned on above assumptions



Drive at the adiabatic point and use the extruder screws to deliver the necessary energy to the system. Don't rely too much on external heating and cooling except at the starting phase of the process.

After performing extensive research on DoE for each Pharma extruder and showing that the results matched the predicted outcomes of the scale-up equations, we are now able to justify eliminating DoE and apply a one-step scale-up approach to process parameters when increasing HME throughput for drug production.

Figure 12: Recommended working point.



Reference

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Figure 13: Optimization without DoE.

