I’d like to talk about the way we at GSK go about scaling up our pharmaceutical intermediates.
Batch crystallization scale-up

- Gather data
- Develop model
- Rational design based on predictive rules

RIGHT FIRST TIME

To scale up a batch crystallization, we have to several things. First, we go over the existing data and study it thoroughly. Then we develop a model so we know exactly what we want and how we are going to do the scale-up. Finally, we develop a rational crystallization process based on predictive rules so we get the process right the first time. Pharmaceuticals are expensive products. A single batch failing costs the company an enormous amount of money.
How do we go about doing this? First of all, we gather data. We look at particle size, ripening, aging, habit changes, solubility, etc. Then we develop our model based on the knowledge of supersaturation and solubility. We develop a seeding protocol and then we look at how we are going to control the crystallization. Finally, we do the rational scale-up calculations.
Rational crystallization scale-up

- Vessel characteristics
  - heat transfer
  - mixing (computational fluid dynamics CFD)
  - mass transfer
- Thermodynamics (solubility)
- Kinetics (growth, nucleation, attrition)
- Process modelling, simulation and optimisation
- Validation

For the rational scale-up, we first need vessel characteristics. We look at heat transfer, mixing, CFD, mass transfer, and various other engineering parameters. We look at the thermodynamics (solubility, metastable zone, etc.) and the kinetics. Then, using these parameters, we model the process on predictive scale-up rules. (Unfortunately, the rules for predictive scale-up have not yet been developed. This is something GSK is involved in with several universities around the world). Lastly, we define the final process.

The vessel characteristics are universal. Once we’ve characterized the vessel, we know what happens when we stir a mixture. This is applicable to a whole range of compounds. What is more specific is the thermodynamics and kinetics of a compound. In this presentation I would like to talk about the measurement of the growth kinetics. This is key data for process modeling and rational scale up.
There are several methods of measuring kinetics, but it is generally accepted in the industry that kinetics are best measured at steady state.

What do I mean by steady state? Steady state means the number of particles entering a given size range must equal the number of particles leaving the same size range. Steady state is achieved by doing a continuous crystallization using a mixed suspension mixed product removal (MSMPR) crystallizer. The stirring in the crystallization vessel must be efficient, which is the reason for using a draft tube. The use of a draft tube promotes laminar flow within the crystallizer.

We feed in a solution of material and, at the same time, draw off crystallized product. The feed rate and the product removal rate must be the same so the volume of the magma stays the same. Once the crystallization has reached steady state, we measure the particle size distribution of the material. Traditionally, this is done by sampling and isolating the product and then measuring the particle size distribution using a Coulter Counter, laser light scattering, or by sieve analysis.

Obviously, it would be extremely useful if we could put in a probe and measure particle size distribution on line. That would avoid sampling errors and any problems with changes during washing, drying, and dispersion.
If we look at a narrow range of the particle size distribution, particles are going to grow into a size range and then subsequently grow out of it. At the same time, we are going to get particles entering that one size range by flow and also particles leaving that size range by flow. The equation for this is the population balance equation, which has been developed by Randolph and Larson.

\[ Vn_1G_1 + Q_1n_1\Delta L = Vn_2G_2 + Qn_2\Delta L \]

- \( G \) = growth rate
- \( Q \) = flow rate
- \( n \) = population density
- \( L \) = size
Calculation of kinetics

\[ Vn_tG_1 + Q_t\bar{n}_t\Delta L = Vn_xG_2 + Qn_x\Delta L \]

Assuming no particles in feed, ie \( n_f = 0 \) and growth is independent of size

Then as \( V/Q = \tau \) (residence time) the result becomes

\[ n = n^0 \exp \left( -\frac{L}{G\tau} \right) \]

\[ \text{Ln} n^0 \]

\[ \text{Ln} (n) \]

\[ \frac{1}{G\tau} \]

\[ L (m) \]

\[ B^0 = n^0 G \]

\[ G = \text{growth rate} \]
\[ Q = \text{flow rate} \]
\[ n = \text{population density} \]
\[ L = \text{size} \]

\( \tau \) = residence time

\[ B^0 = \text{nucleation rate} \]

In the population balance equation we make several assumptions. First of all, that there are no particles in the feed. This is a reasonable assumption because we add a clear solution. Second, for this to work properly, growth should be independent of size. This means that larger particles will grow at the same rate as smaller particles. Again, this is a reasonable assumption to make. After re-arrangement and integration, this gives us the classic population balance equation.

If we plot the log of the population density versus the size of our size range, we should get a straight line. Knowing the residence time \( \tau \) (t), we can calculate growth rate from the slope of the line. The intercept will give us \( n^0 \). Growth rate multiplied by \( n^0 \) will give us the nucleation rate B.

I have to add a word of caution about the nucleation rate. If there were no attrition within the vessel, \( Gn^0 \) would give us the primary nucleation rate. But because of the dynamic nature of the crystallization inside the MSMPR, we will get primarily secondary nucleation. In this case, we probably have a mixture of both primary and secondary nucleation.

Population density is the number of particles per unit volume of the crystallization slurry. Normally, from any size measurement, the value we get is not little \( n \), but big \( N \). Big N is just a count and we have to convert to little \( n \). This is done relatively simply using this series of equations. All of this can be found in Allan Myerson’s book on industrial crystallization noted here.
The first thing we did was look at a model to test the system. Citric acid is an easy crystallization to do. It is well documented, we know the kinetics, and the crystals themselves are usually fairly discrete. They approximate to spheres so we felt we didn’t need to put in a shape factor. We measured the growth kinetics using FBRM on line.
The results we got were very encouraging. We got a straight line, with a little bit of curvature, which is very common with this technique. We then took the straight-line portion of the curve and extrapolated it to the intercept to get n°. From the slope of that line, we calculated the growth rate. How does this compare to the literature values?
The growth rate is always going to be very dependent on the relative supersaturation. If our relative supersaturation is zero, crystals will not grow and the growth rate will be zero. Conversely, if we have a very high supersaturation, the driving force for crystal growth is high. The relationship between relative supersaturation and growth rate is linear.

Here we plot growth rate versus relative supersaturation. The green value is the measured growth rate that we got from MSMPR and FBRM. The other two are literature values. You can see there is a straight-line relationship, so that was encouraging.
We went on to measure the kinetics of our drug substance. This is a very important pharmaceutical product in production, and particle size control is important. Unfortunately, the particle size distribution is variable. Batches fail on particle size alone. They must be reworked, which is expensive.

The electron micrograph of the material is fairly typical. Particles are discrete. There is some agglomeration, but they are reasonably well behaved.
We looked at the MSMPR for measuring the kinetics of drug substance. It is generally accepted that to achieve steady state we need to run the crystallization for ten residence times. That means if we have 0.5 liters in the crystallizer, we need a 5-liter reservoir of solution for addition – and that is quite a lot of drug substance. So we cheated a little by drawing off slurry from the crystallizer, passing it through a heat exchanger to dissolve the solid, and then passing the solution back into the crystallizer. This has exactly the same effect and we don’t have to worry about balancing to the draw-off and addition rates.

However, when we tried this, we found we were getting classification in the draw-off pipe. The finer particles were being removed and the coarser particles were sedimenting down the tube. This was bad news. We weren’t getting a representative draw from the crystallizer and, as a result, the larger particles were growing disproportionately inside the crystallizer.

We decided that if we added a second loop to the draw-off pipe (which is operated at a very fast speed compared to the peristaltic pump that draws off slurry very slowly), instead of drawing from the crystallizer itself, we could draw from the fast flow pipe. This solved the problem completely. We were getting very representative draw off from the crystallizer and found we could successfully achieve steady state using a relatively small amount of drug substance.
Using FBRM, we monitored trends within the crystallizer. We can monitor the crystallization onset and any changes in the particle size distribution as the crystallization proceeds. We monitor fluctuation in the particle counts. Eventually, these stabilized to give us a steady state.
As the crystallization continues, we see that after about five half-lives we have steady state. When we did the kinetics plots, we got a curved line, though we could fit a straight line to a portion of the curve and get growth rate. What causes the curvature? It could be size-dependent growth, where the smaller particles grow at a different rate than the larger particles, it could be growth rate dispersion, or it could be agglomeration. Because the electron micrograph showed a degree of agglomeration, I think the curvature is probably due to agglomeration.

When we compare the results we got with FBRM (the red line), with results obtained from laser light scattering (the blue line), the lines are fairly well correlated. The slopes are not the same, but the intercept is. The laser light scattering results were acquired using traditional techniques. A sample was taken, the solids were isolated and dried, and the particle size distribution was measured.
Growth rates and supersaturation

- Supersaturation adjusted by,
  - residence time
  - steady state temperature

<table>
<thead>
<tr>
<th>Residence time (s)</th>
<th>Growth rate, G ms⁻¹</th>
<th>Growth rate, G ms⁻¹</th>
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<tr>
<td></td>
<td>FBRM</td>
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<td>2400</td>
<td>9.90E-09</td>
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<tr>
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<td>2.59E-08</td>
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Growth rate changes with relative supersaturation, so we must measure the growth rate at different levels of supersaturation. We can adjust the supersaturation within the MSMPR quite easily by either adjusting the residence time or by adjusting the steady state temperature. We chose to adjust the residence time and, by adjusting the temperature in the jacket, we maintained the same temperature for all of the experiments.
When we plot the growth rate versus residence time we got a straight line as expected. The FBRM results gave the blue line and the laser light scattering results gave the red line.
If we plot growth rate versus relative supersaturation, we have two lines, both passing through the origin. The difference between the two lines is due to the different methods of measurement. With the FBRM, we are measuring chord length distribution rather than particle size distribution.
So what do we get from the growth kinetics we measured?
What happens when we seed within the metastable zone and cool the reaction mixture at the natural cooling rate? Growth rate will peak very rapidly and then start coming down. Supersaturation will also peak and then come down. If we cool naturally, supersaturation follows a path – shown here by the green line – where it crosses the crystallization curve into the region where we get spontaneous nucleation.

In an ideal situation, we would seed and keep the relative supersaturation at more or less the same value within the metastable zone. We want the green line to be flat so that the growth rate is constant. That would give us an optimal particle size distribution for our process.

Because we seed within the metastable zone, we should not get primary nucleation. Growth will occur by secondary nucleation on the seed that has been added. If we know the size of the seed crystals we’ve added, we should be able to control the particle size distribution of the final product.
Knowing the growth kinetics, we can use the equation shown to work out the best cooling profile to give us this supersaturation. We have a computer program (DynoChem) that allows us to do this calculation.

You can see from the crystallization profile that the supersaturation is flat, the growth rate is flat, and the calculated cooling rate (which the equation has given us) is an inverse cooling curve. It has gone from about 60°C to 42°C, and the crystallization yield has gone from 0 to 96%, which is more or less what we would expect. We also get an expected particle size mean from the calculation, based on the seed size.

The FBRM result gave us an optimum cooling time of 80 minutes. That cooling rate will give us the particle size we want over a period of 80 minutes.
If we apply that same equation to laser light scattering, we get the same sort of traces, but this time we get an optimum cooling time of 45 minutes. That’s quite a large difference. We don’t really know yet which one is correct. It may be that the correct cooling time lies between these values.
What next?

- Apply calculated cooling curves to actual crystallization and measure PSD
- Compare PSD with calculated mean
- Measure supersaturation using ATR-IR or ATR-UV

In future work we will apply the calculated cooling curves to the actual crystallization and measure the particle size distribution for the crystal size and seed size used. We will compare particle size distribution and calculated mean. We also wish to measure the supersaturation using ATR-IR or maybe ATR-UV.
I’d like to acknowledge the help I got from Zoe, who did the particle size measurement; Terry, my student who worked extremely hard to get the MSMPR to work; Francois and Joerg, who did the modeling; and Paul Barrett.
Q: In that curve you had, couldn’t the crystals be small because they don’t grow very well?

Kaz: Yes, and that is an assumption we have to make for MSMPR. We are going to look at putting in a correction for size-dependent growth. I’m not sure that it is size-dependent growth, though that may have been a contributing factor. I think it is more likely agglomeration.

Q: Do you verify that you have re-dissolved everything before putting it back in the reactor?

Kaz: Yes, we check the solution going into the reactor very carefully.

Q: You had two pumps, one for the slow recirculation and one for the fast recirculation. Is the second pump a centrifugal pump?

Kaz: They are both peristaltic pumps.

Q: You didn’t see any breakage?

Kaz: No, we ran the fast peristaltic pump for a long time and monitored the particle size distribution. There was no change at all, which was very encouraging. We expected we would get some crystal damage, but we didn’t.
RB: How did you identify that you had segregation with recirculation in the first place? I understand that you might have used the FBRM to show that you didn’t see attrition or breakage, but how did you know you got segregation?

Kaz: You can see the coarse particles dropping down the pipe because the flow rate was quite slow. Although we were drawing solution out, we could see the coarse particles dropping back down the tube.

RB: How would you extrapolate that to larger recirculation lines? Say you have a 1000-liter reactor and recirculation lines going to some sort of filtration. Based on this experiment, would you assume that those lines were uniformly drawing off or would there be some segregation as well?

Kaz: That’s a difficult question. I’m not sure whether we could do that or not.

RB: When we’ve monitored both in the tank and in recirculation lines, the recirculation lines have always had fewer coarse particles, unless they come right off the center of the bottom, then they have fewer particles. Depending on how the recirculation line is done, we either measure a lot more fines or a lot more coarse particles, but it is always different than in the reactor.

Kaz: On a large scale we would have to look at the way we do this more carefully. But we are only doing this on a small scale where the mixer is pretty good so we are not too worried about homogeneity of the mixture. We are not getting classification within the vessel. The only classification we saw was in the draw-off line.
RB: How do you keep the temperature constant in the recirculation lines?

Kaz: We don’t need to. We only need to keep the temperature constant within the crystallizer. To keep the solution from crystallizing when it came out of the heat exchanger, we put a heater on that pipe. But once everything was running at a steady state, the only thing we needed to do was adjust the jacket temperature of the crystallizer to bring it back to the original temperature where we did the residence time experiments.

Q: How well do the nucleation and growth rates you measured in the steady state translate to batch crystallizations?

Kaz: The idea was that we would measure the kinetics of a typical solid primarily so we could then apply cooling curves that we had calculated from laboratory experiments. This is a difficult question because CFD and hydrodynamics within a large vessel are going to influence the crystallization and certainly the nucleation. You have to start somewhere. If you have an optimum cooling rate, then you can start applying the CFD calculations and the scale-up rules. But you have to start based on kinetic measurements so you know what the baseline is.
PB: In the graph comparing growth rate to supersaturation for the two instruments (slide 17), if instead of using a linear line you used a parallel line and modeled the fit to the data, you would probably have more success extrapolating it over a wider supersaturation range.

Kaz: Yes, we are getting to a high level of supersaturation, so to have good linearity it probably would have been better to have more points. To give low levels of supersaturation, the residence times would have been so long that we would have had to stay overnight to do it.

PB: The FBRM kinetics are lower than the kinetics from laser diffraction and it looks like laser diffraction may be overestimating the size. If you overestimate the size, you overestimate the kinetics. Looking at slide 19, if you use overestimated kinetics to design your optimum cooling curve, you will do what that green line is doing and cut across your metastable zone and get secondary nucleation. The FBRM data, while not absolute, might have underestimated the kinetics, giving you a more conservative cooling curve and helping you avoid something like this.

Kaz: Also, to get the laser light scattering data, we had to remove material, filter it, and wash it, which could have removed quite a lot of fines. Then in the drying, we could get agglomeration, solids losses, breakage, etc. All sorts of things can happen. It would be great if FBRM could give us the value we want, but according to the calculation, we are getting a large difference between the two and this is something we have to verify experimentally.
Q: Couldn’t the growth rate also be temperature-dependent? Is that taken into account in your cooling curve?

Kaz: Yes, temperature will affect supersaturation and that could be another way to adjust supersaturation. However, we chose to adjust supersaturation by residence time.

Q: You had problems with segregation, so you added a high-speed pump. How are you sure you are now getting representative samples with the high-speed pump if you had segregation before?

Kaz: We don’t. But the only other way we could have done it is to take it straight out the side of the vessel and we weren’t going to do that because it would have been quite difficult. By looking at the particle size we were getting, it was laminar flow. I don’t think there was any chance of coarse material dropping out. If we continue this, we will have to be absolutely sure there is no classification.

Q: If you think about particle growths as a rebirth of dissolution, dissolution is dependent on particle size. How do you find that growth rate is independent of particle size?

Kaz: With citric acid, we get a straight-line portion of a curve and a curvature. That curvature, the small particles, will indicate what you are saying. That portion is quite small, so we are assuming that we are getting size-independent growth on the larger particles. As we are only using the straight-line portion of the curve, we can effectively ignore the effect from the smaller particles.
Q: Could you design a process similar to this that is foolproof in production? Is the technology there?

Kaz: We are a long way from being able to dial out the particle size we want. But what we can do is reduce the number of batches that are failing by having a rational approach during the early stages. This type of kinetics will indicate where we should be going and the rate of cooling. If we can get that right, then that’s just another parameter out of the equation. However, there are other things like hydrodynamics, vessel geometry, impurity profiles, etc., that also play a part. Even if we reduce the number of failed batches by 10%, that’s going to save the company a huge amount of money.

RB: On slide 11, we can see that these particles are more of a rhomboid than a cube. Laser diffraction will typically size the longest length of a particle. In this case, the spherical equivalent diameter of the longest length of a rhomboid has a significantly greater volume and will show a much greater growth rate, which will be significantly overestimated. If you use that growth rate, you will be in trouble.

Kaz: We did use a shape factor measured by microscopy.

RB: You took the laser diffraction data and reconverted it?

Kaz: We used the shape factor to calculate little n. We took the FBRM chord length, assumed that was a sphere, and applied the shape factor to bring it down.
RB: So you took the chord length data and made the volume smaller when you should have made it bigger. With laser diffraction, if you used the same shape factor, then you were taking this great big volume and exaggerating it again. You increased your laser diffraction data when you should have decreased it and decreased your FBRM data when you should have increased it, so you separated your growth curves.

Kaz: I see what you mean. It could be an interesting calculation to do.

RB: Based on particle fundamentals, it looks like you went in the opposite direction by using a shape factor. That’s why I always worry about shape factor. By taking FBRM data and then using a shape factor back to a rhomboid, the net result reduced the size of the chords that were measured and therefore reduced the growth rate. With the laser diffraction data, it was just the opposite. It increased the size of the assumed particles and therefore increased the growth rate, when in fact the laser diffraction was already oversized.

Kaz: Rather than worrying about individual particles, I think what we need to be doing is applying corrections for the agglomeration. This is another issue, but I think it is where the length problems lie.

Q: Can you use other methods besides MSMPR to calculate kinetics?

Kaz: There are a lot of methods out there, but MSMPR is the workhorse of kinetics measurement and is generally regarded as the most accurate.