My talk will cover the use of the FBRM in the formulation development laboratory. At Amgen we are studying particle behavior during granulation and dissolution. I want to take a quick survey. Is there anyone here in formulation development? How many people run into formulation people during project team meetings? How many people have faith in their formulation group? (laughs)

Also, I want to make something clear: Our group at Amgen is not studying the behavior of Chinese hamster ovary (CHO) cells or proteins, we’re actually monitoring granulation of a solid dosage form. Amgen is expanding their small molecule efforts, so this is a new and exciting area for the company.
Objective

To study the feasibility of using the Lasentec FBRM D600L to monitor solid dosage formulation development processes in which the in-process particle dynamics are not well characterized or understood.

Our objective is to study the feasibility of using FBRM to monitor particle dynamics that are not well characterized or understood. Traditionally, formulation development is pretty much thought of as an art form. The crystallization group works diligently to produce a beautiful drug substance only to have the formulation group trash it.

Seriously, when you sit in on the project team meetings, how do the formulation folks describe how they determine endpoint? They may have told you that they open up the granulator and feel it with their hands. “It just feels and looks right.” I think it’s apparent that there is a lot of room for improvement in order to effectively understand these particulate processes.
Formulation Development

- Goal: To obtain an in-process method to characterize particle behavior in order to demonstrate control or establish specifications in particulate processes involving high-shear granulation and tablet dissolution.

Variables
- Material Properties
- Impeller Speed
- Fill Volume
- Liquid Addition Rate
- Liquid Addition Method
- Wet Massing
- Granulator Manuf.
- Batch Size / Scale…

Finished Product Attributes
- Mesh Analysis
- Porosity
- Tablet Compactability
- Flow Properties
- Drug Content Uniformity
- Dissolution Profile

Particle processing and granulation truly is a black box operation. Or is this the box the formulation development scientists don’t think outside of? You can see there are many different processing variables that can affect granule growth – impeller speed, liquid addition rate, even a granulator manufacturer’s design can affect the final granulation properties. The process is not easy to control because there really has been no direct method to monitor particle size during processing. The final particle size is typically characterized by mesh analysis. The mesh analysis is performed on the dry product that’s been milled, so it tells you nothing about what happened inside the granulator.
High-shear Granulation

• Why granulate?
  – Increase particle size
  – Improve flow properties
  – Drug uniformity
  – Prevent segregation
  – Enhance tableting characteristics
  – Densify bulky powders

So why do we granulate? The active drug substances are notoriously cohesive and poorly flowing. Often the poor flow is attributed to the fine particle size of the drug substance. This can also lead to segregation and processing issues during scale up. In some instances, it is desirable to lock the drug substance into a granular matrix, which will help with drug uniformity and prevent product segregation. Granulation will increase the particle size of the drug blend, which will facilitate a better flowing powder. We may even want to densify our bulky powders to aid in powder handling.
When we granulate, we have our drug substance and usually filler (bulking) excipients. The filler is generally lactose or microcrystalline cellulose. For high-shear granulation, a binding polymer is typically added in solution.

The bottom figure on this slide shows the relationship between granule porosity and liquid saturation. As more binding liquid is added, the degree of liquid saturation increases and porosity decreases. As shear is applied to the granule, the liquid saturation also increases and the porosity decreases. These are important granule growth regimes to keep in mind when granulating.
This slide shows the FBRM probe location in the granulator. The granulator shown here is a Diosna design. It is a bottom-driven impeller design with angled walls to aid in mixing. Here we have a chopper that’s used to delump large powder masses and help distribute the granulating liquid. The FBRM is located downstream from the liquid addition to avoid coating the probe window.

One of the primary issues with using the FBRM in a granulator is coating of the probe with wet powder. I’ve found that coating the probe tip with polysiloxane is effective at reducing powder caking on the probe tip. I was able to add up to about 26% water, which you’ll see later on in the granulation slides.

The probe angle was about 15 degrees from vertical. We didn’t want to angle it too much because then it becomes a factor in the particle dynamics (i.e., you create a surface where you are impacting your granules). We wanted to make sure we were measuring flow past the window, not granulating on the window.
Granulation Study 1

- 2-L Diosna High-shear Granulator
- 650 rpm Impeller Speed (5.2 m/s tip speed)
- 300 g Anhydrous Lactose
- 15% Povidone K29/32 Binder Solution
- 15 g/min Solution Addition Rate
- Added 49.8 g Binder Solution (12% water)

For the first granulation study, we used a two-liter Diosna high-shear granulator. Usually when you see scale up a granulator, you’ll scale the impeller speed with the tip speed. When you get into a larger production scale, the manufacturers will give you two settings: high and low. Usually manufacturers set 5.2 m/s as the low tip speed and 6.5 m/s as the high tip speed. We are using a 300-gram anhydrous lactose placebo formulation. The binding (granulating) solution is 15% of a polyvinyl pyrrolidone (Povidone, PVP) K29/32 grade. The addition rate was 15 grams per minute to a target of 2% of the binder in the granulation, which is about 12% total water added.
Think back to the first time you used FBRM in your process, you’re reaction was probably, “Wow, I can’t believe we’re actually seeing this. We think we know what happens, there’s some theory, but now we are seeing that what we had believed to be occurring actually is.” That’s what happened to us… we were amazed!

After about two minutes of dry blending, we add our solution and immediately see that our fines are decreasing in population. Where are they going? The pink, red, and yellow distribution lines on this graph we’ll designate the fines range. The light blue and dark green lines are the coarser populations. I’ve normalized the counts on the left-hand side (i.e., the colored lines correspond to the left-hand side). The black curve is the length weighted mean of the chord (the software’s notation), which is actually the granule square-weight distribution.

After one minute of solution addition, we can see that the granule growth is fairly quick. After two minutes, we reach a maximum on our mean distribution. After we stop our solution addition, we have an additional mixing time of about one minute. What we end up doing is further consolidating our primary granules.
Let’s take a look at the chord length distributions. The red curve is the dry powder blend. After one minute of granulation with the solution, we see that our total particle counts are dropping because our fines population is decreasing by creating the coarser particles.
With further addition of solution and additional mixing at the end of solution addition, we are consolidating our coarse particles and narrowing our distribution. We have our original distribution of the dry powder and we are creating a nice, uniform final granulation particle distribution.
Granulation Study 2

- 2-L Diosna High-shear Granulator
- 650 rpm Impeller Speed (5.2 m/s tip speed)
- 75 g Avicel PH 102 (microcrystalline cellulose)
- 200 g Anhydrous Lactose
- 9.8 g Povidone K29/32 Added Dry
- 98.5 g Water (26% total contents)
- 15 g/min Water Addition Rate

The second study was also in the two-liter Diosna, but this time we are using Avicel, which is microcrystalline cellulose, with anhydrous lactose again, and we added the Povidone K29/32 dry. This time our goal was to challenge the FBRM. I think Rich mentioned that somewhere around 15% was the highest water content Lasentec had granulated, so we wanted to challenge that value and see how high we could go without coating the probe window.
Notice where the PVP was added. It was interesting that the PVP further dispersed some of the coarser particles. We probably had electrostatic agglomeration of the Avicel and/or lactose, which was disrupted by the addition of PVP somehow.

After solution addition, we see there is about a three-minute lag time. It takes about three minutes to finally wet the Povidone and Avicel and start granule growth. Avicel will absorb quite a bit of water. You can see once the material is wetted, the particles grow rapidly. After two minutes we are getting maximum particles size – about 23% water. But as we continue to add solution, we may have started dissolving some of the lactose and getting a fines population that is much greater than what we started with. We are either over-granulating or over-wetting. We usually don’t operate in this range.
If we look at our chord length distributions, after about three minutes we see the onset of granule growth and a distribution similar to before.
At about the five-minute time point, we get what we think is an optimum distribution. From about six minutes on, we get poor granule growth. This is a good example of the utility of the FBRM to aid in the selection of appropriate processing variables. We can choose our endpoint during granulation by selecting a distribution. It does not need to be arbitrary.
Summary of Granulation Feasibility

- FBRM successfully monitored the granulation process
- Up to 26% water content without window obstruction
- Polysiloxane coating was effective at reducing window obstruction due to product buildup
- FBRM is useful tool in formulation and process development of high-shear granulations
  - Study granulation kinetics
  - Process endpoint determination
  - Scale-up
  - Troubleshooting formulations

Using the FBRM, we were able to successfully monitor the granulation process and use up to 26% water without window coating. The polysiloxane really helped avoid coating of the probe window. I think this is just the beginning of monitoring granulation monitoring and control. We’ve found we can use the FBRM to study granulation kinetics and for endpoint determination, scale up, and troubleshooting formulation composition.