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High Shear Wet Granulation Scale-Up Using Basic Principles

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PURPOSE

To evaluate the scale-up of a high shear wet granulation process by maintaining impeller speed and the same number of impeller revolutions.

METHODS

The formulation utilized is shown in Figure 1. A development scale batch was prepared using a Collette Gral 300. A process was developed using an impeller speed of 185 RPM with a 5-minute spray time for binder solution and a 3-minute wet massing time. In the Gral 300 running at 185 rpm, the impeller will make 925 revolutions in 5 minutes. The batch was scaled up using a Freund GMX-1200 high shear granulator. Batch sizes were 132 kg (granulated in two sublots) and 352 kg (granulated in two sublots). An equivalent tip speed was calculated for the GMX-1200, and the impeller speed was set to 103 rpm. At this impeller speed, to make 925 revolutions takes 9 minutes. The lower RPM (equivalent tip speed) requires a longer time to complete the same number of revolutions in the GMX-1200 granulator. Figure 2 shows the parameters for each batch manufactured.

Figure 1: Formulation

Ingredient	% (w/w)
API USP (BCS Class I)	90.91
Hydroxypropyl Cellulose NF (6.8% solids)	2.50
Sodium Starch Glycolate NF	5.09
Silicon Dioxide NF	0.50
Magnesium Stearate NF	1.00

METHODS CONTINUED

After granulating and fluid bed drying two sublots of granulation, dry additions were blended into the product. Tablets were compressed at target hardness on a rotary press and an aesthetic film coating was applied to the tablets. Dissolution profiles were tested for each batch and an F2 comparison was performed.

Figure 2: Process Parameters

	Gral	GMX
Impeller Speed (RPM)	185	103
Tip Speed (m/ sec)	7.8	7.7
Spray Time (min)	5	9
Number of Revolutions	925	927
Wet Massing Time (min)	3	5
Number of Revolutions	552	515

RESULTS

Bulk and tapped density, particle size and dissolution were evaluated to assess the product at the two scales.

Figure 3 shows the product properties of each batch manufactured. The longer granulation time at the larger scale may have contributed to the slightly increased density of the granulation.

One difference between the two scales was the loading in the granulator due to the desired commercial batch size. In the Gral 300, the loading was 57% but in the GMX-1200, it was reduced to 38%.

Figure 3: Product Properties

	Gral	GMX
Bulk Density (g/ cc)	0.50	0.54
Tapped Density (g/ cc)	0.59	0.66
Particle Size Distribution		
Cumulative on 60 mesh (%)	40.4	39.1
Cumulative on 120 mesh (%)	13.6	13.7
Cumulative in pan (%)	45.6	48.0
Geometric Mean (µm)	124	109
Dissolution @10 min (%)	55	62
Dissolution @15 min (%)	79	78
Dissolution @20 min (%)	90	84
Dissolution @30 min (%)	96	91
Dissolution @45 min (%)	99	95

CONCLUSIONS

The techniques utilized produced a similar granulation after scale-up with similar dissolution (F2 = 65). The larger scale batch did produce a slightly smaller particle size with slightly less coarse particles and slightly more fines. This difference in particle size may also contribute to the higher density values also seen. One other technique utilized for scale up is to utilize similar tip speed while maintaining the granulating times from the smaller scale. Should this method had been chosen, the granulation would likely have produced an even smaller particle size. While minor differences are noted, it is felt that this technique is an effective method to scale-up the high shear wet granulation process.