

COMPARISON OF END-POINT DETERMINATION BY WET-MASS TIME, PRODUCT TEMPERATURE CHANGE, AND POWER CONSUMPTION FOR SCALE-UP OF HIGH SHEAR GRANULATION OF IMMEDIATE AND CONTROLLED RELEASE FORMULATIONS

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PURPOSE

To determine the most effective end-point method for scale-up of wet granulations using the following methods:

- 1) Wet-mass time (WMT)
- 2) Product temperature change (ΔT)
- 3) Peak power consumption (KW_p)

METHODS

One immediate release (IR) and one controlled release (CR) formulation were used in this study. Formulations and process parameters are shown in Tables 1 and 2. The processes were first optimized in a 75-liter high-shear granulator (Vector GMX-75) to collect end-point parameters (ΔT , KW_p , and wet-mass time). These parameters were then used as methods of determining the end-point for granulations made in a 600-liter high shear unit (Vector GMX-600). Mixer blade tip speed for all processing steps was the same for both the 75 and 600-Liter machines. After granulation, a portion of each batch was dried with 65°C air using a fluid-bed dryer until the product was less than 2.5% moisture content. Product was milled using a Quadro Comil® at 2500 rpm with a 0.050 hole size screen. Sieve analyses were performed to determine the arithmetic mean diameters (D_{50}) for fluid bed dried (FB) and milled granules.

Table 1 – Formulations

Dry Ingredients	Immediate Release	Controlled Release
HPMC, K 4 M	--	30%
Starch 1500	15%	--
MCC, 50M	30%	--
Lactose	55%	70%
Batch Volume (L) - 75L/600L	37.5 / 300	37.5 / 300
Batch Weight (Kg) - 75L/600L	18.3 / 146.7	16.6 / 134.1
Bulk Density (g/cc)	0.489	0.447

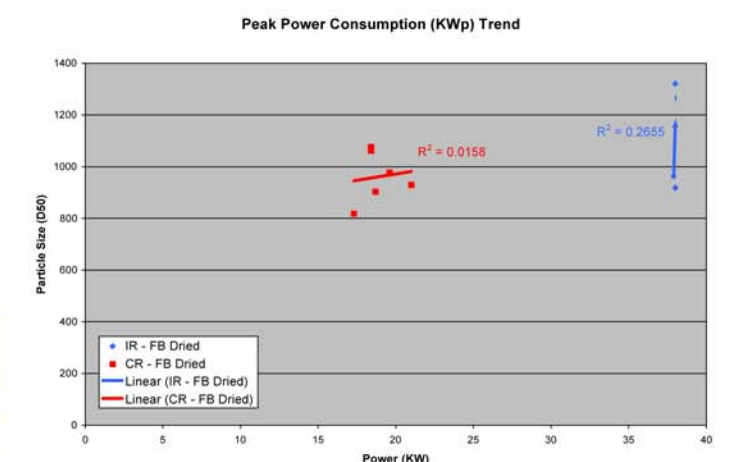
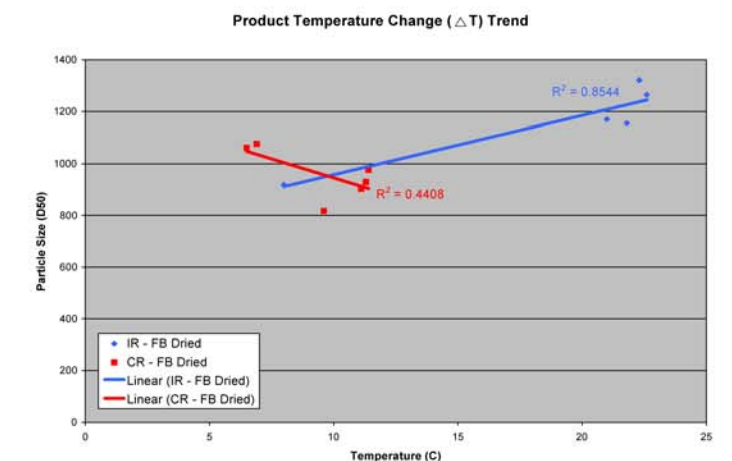
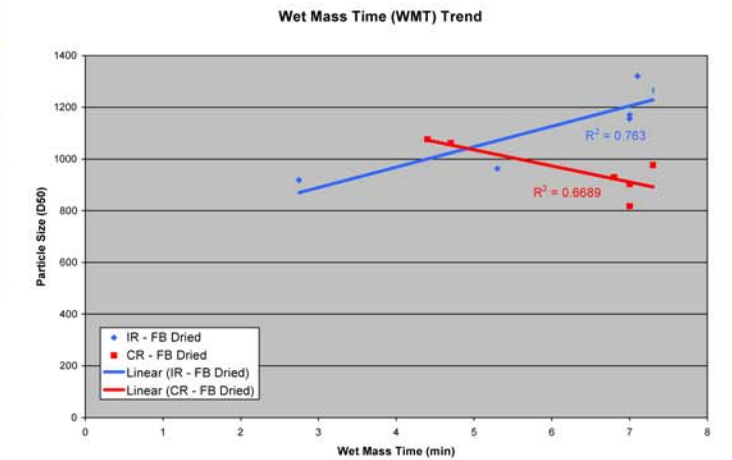
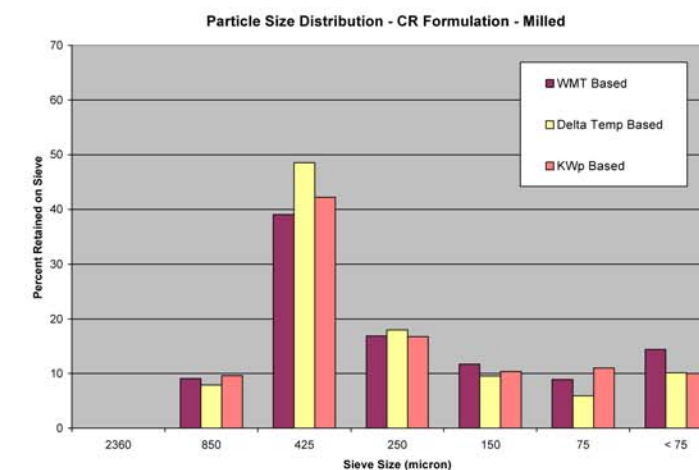
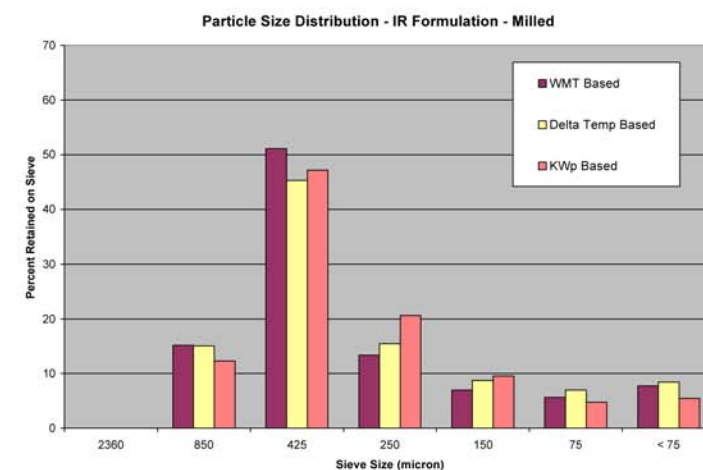
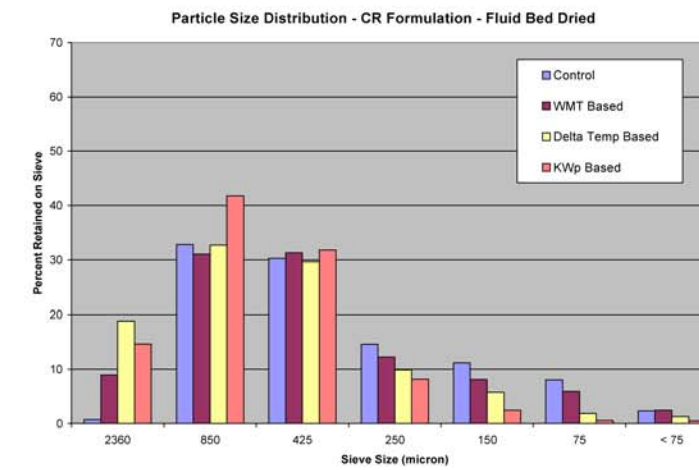
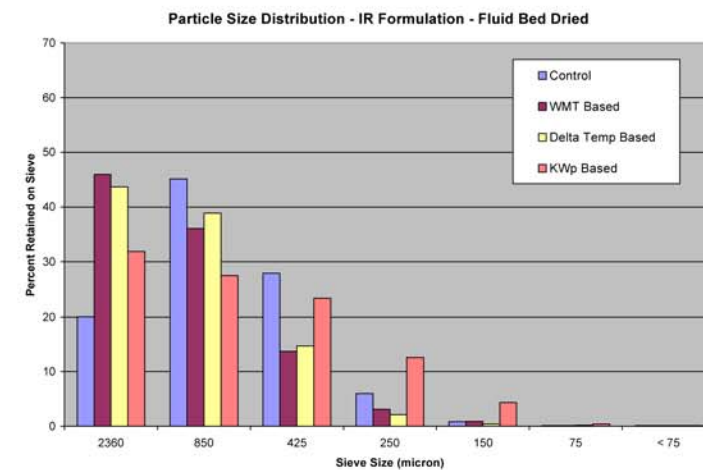
Table 2 – Processing Parameters

Process Parameters	Immediate Release	Controlled Release
Pre-Mix Time	3 minutes	3 minutes
Water Infusion Time	8 minutes, 75L 11.5 minutes, 600L	8 minutes, 75L 10 minutes, 600L
Water Added	24.7 %	28.1%
Wet Mass Time	Varies, see results	Varies, see results

RESULTS

IR Formulation Summary						
Batch Size (Kg)	Method	WMT (min)	ΔT (°C)	KW_p	FB D_{50} , μm	Milled D_{50} , μm
18.3	Control	7.0	22.5	4.6	1157	N/A
146.7	WMT	7.0	21.4	38.0	1163	674
	ΔT	7.2	22.5	38.0	1293	664
	KW_p	4.1	8.0	38.0	941	627

CR Formulation Summary						
Batch Size (Kg)	Method	WMT (min)	ΔT (°C)	KW_p	FB D_{50} , μm	Milled D_{50} , μm
16.6	Control	7.0	12.6	2.7	826	N/A
134.1	WMT	7.0	10.4	18.0	860	567
	ΔT	7.1	11.4	20.3	953	581
	KW_p	4.6	6.7	18.4	1069	566



CONCLUSIONS

All three end-point determination methods (WMT, ΔT , and KW_p) yielded similar granulations for both IR and CR formulations. WMT and ΔT methods appeared to provide better correlation to particle size for unmilled granules than does the parameter KW_p . From this study, KW_p per unit weight for a given formulation was also similar for 75 L and 600 L high shear mixers (0.251 vs. 0.259 KW_p/Kg for the IR formulation and 0.148 vs. 0.141 KW_p/Kg for the CR formulation). Milling equalized the particle size (D_{50} and distribution) no matter which end-point determination method was used. Therefore, the method of end-point determination may not be as critical as the milling process.