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

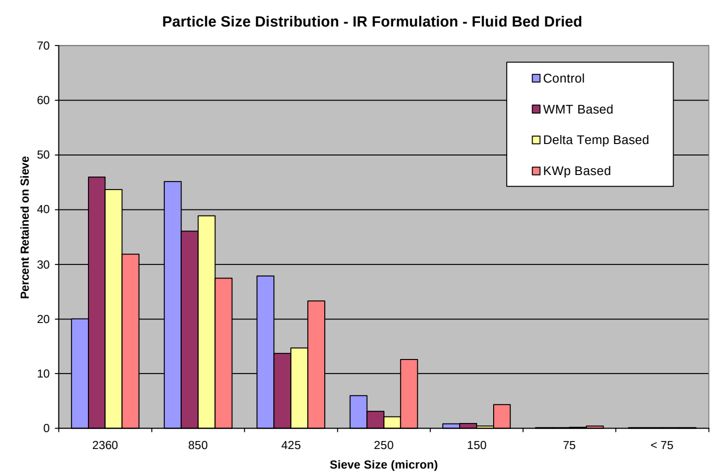
RESULTS

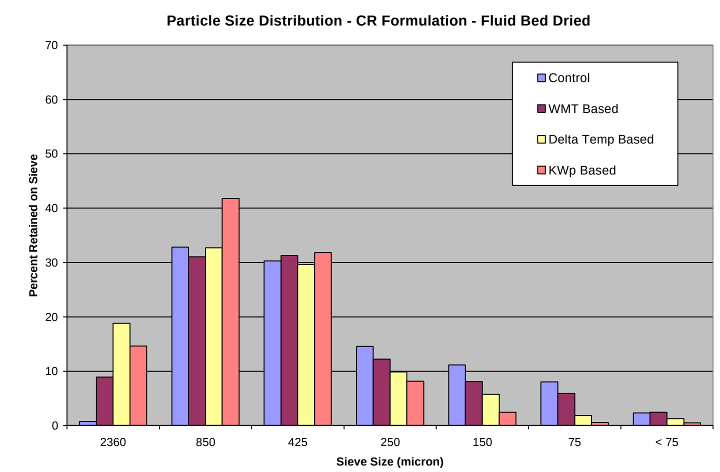
IR Formulation Summary

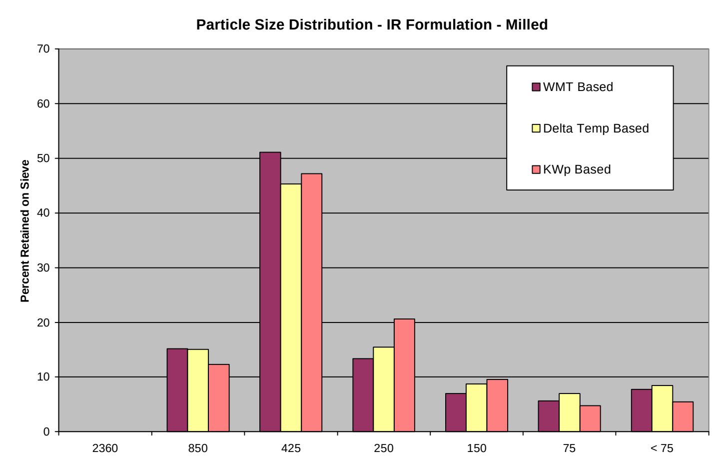
Batch Size (Kg)	Method	WMT (min)	ΔT (°C)	KW_p	FB D50, µm	Milled D50, µm
18.3	Control	7.0	22.5	4.6	1157	N/A
146.7	WMT	7.0	21.4	38.0	1163	674
	ΔT	7.2	22.5	38.0	1293	664
	KW_p	4.1	8.0	38.0	941	627

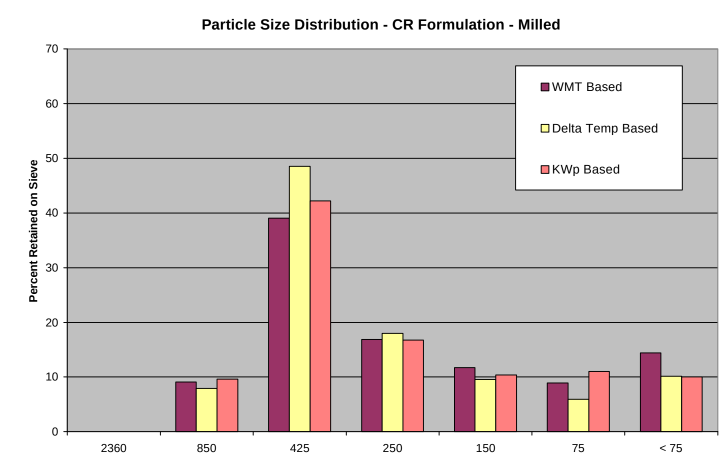
CR Formulation Summary

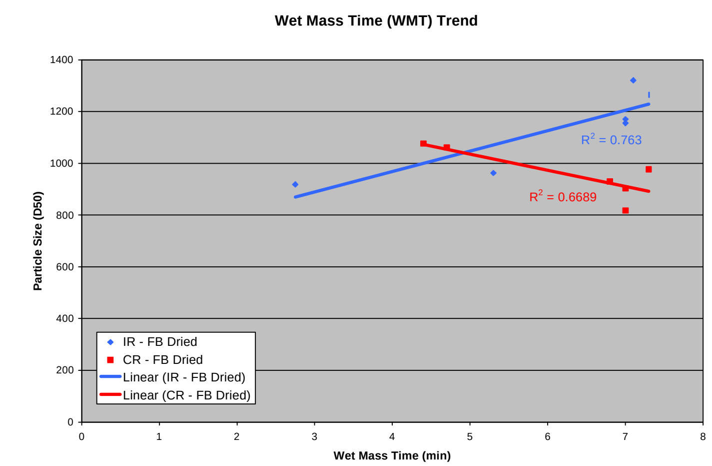
Batch Size (Kg)	Method	WMT (min)	ΔT (°C)	KW_p	FB D50, µm	Milled D50, µm
16.6	Control	7.0	12.6	2.7	826	N/A
134.1	WMT	7.0	10.4	18.0	860	567
	ΔT	7.1	11.4	20.3	953	581
	KW_p	4.6	6.7	18.4	1069	566

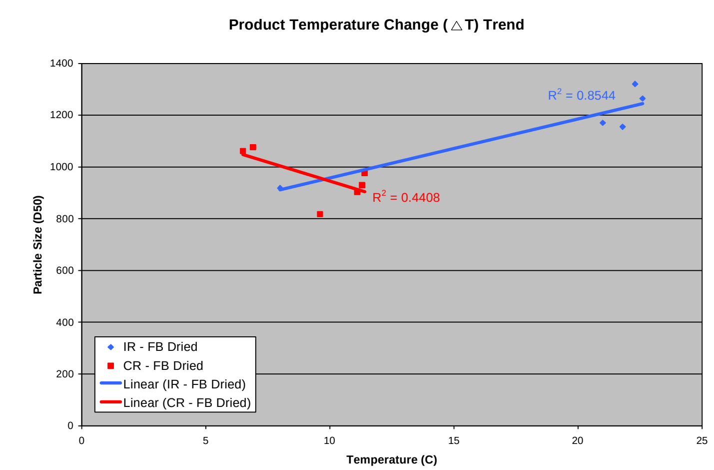


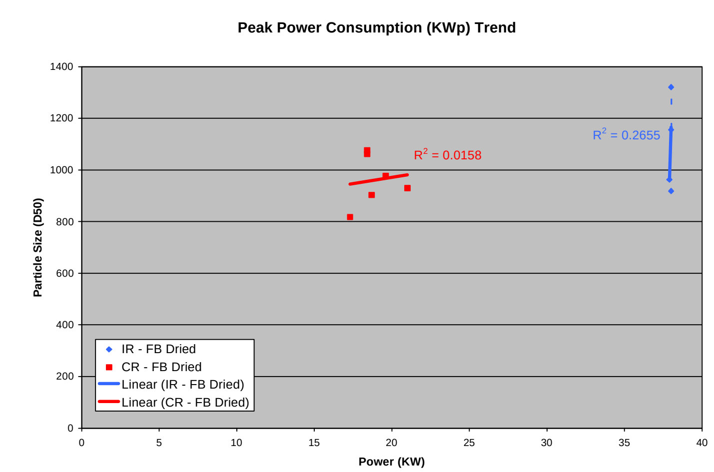












CONCLUSIONS

All three end-point determination methods (WMT, ΔT, and KWp) 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 KWp. From this study, KWp per unit weight for a given formulation was also similar for 75 L and 600 L high shear mixers (0.251 vs. 0.259 KWp/Kg for the IR formulation and 0.148 vs. 0.141 KWp/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.

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