

High Shear Granulation with Starch 1500[®], Partially Pregelatinized Maize Starch - Evaluation of Process Parameters by Design of Experiments (DOE)

OBJECTIVE

The objective of this study was to evaluate the impact of process variables and formulation on the granulation and tablet properties of formulations, utilizing Starch 1500[®], partially pregelatinized maize starch, as a binder and disintegrant through Design of Experiments (DOE).

MATERIALS AND METHODS

A placebo formulation containing lactose monohydrate, microcrystalline cellulose, and Starch 1500 was used along with a combination of water soluble dye and dextrose in place of a soluble drug. A Niro TK Fielder PMA 10 was used to granulate 2.0 kg batches. All materials were added to the granulator and water was used as the granulating fluid. Water was sprayed into the granulator utilizing a binary spray nozzle and atomizing air pressure of 5 psi. Impeller speed was kept constant through the granulation process for each batch/run. Chopper speeds were run on high (3000 RPM) for pre-blending and for wet massing. For the infusion step, the chopper speed was set to low (1500 RPM). Drying was performed in a Glatt GPCG-3 fluid bed. All granulations were dried to approximately 3%. The granulations were then sieved with a Quadro Comil (2mm grater screen at 3400 RPM). Each granulation was lubricated with 0.75% magnesium stearate in a twin shell V blender for 5 minutes. Blends were compressed on a Piccola, rotary tablet press at 30 RPM. Tablet properties were analyzed on an Erweka Multicheck.

Ingredient	Percent	mg/ tablet
Dextrose Monohydrate USP [Roferose, Roquette]	4.90	19.60
FD&C Yellow No. 5 Dye	0.10	0.40
Lactose Monohydrate NF [Lactochem Powder, Friesland Foods Domo]	80.00 to 65.00	320.00 to 260.00
Pregelatinized Starch NF [Starch 1500, Colorcon]	5.00 to 20.00	20.00 to 80.00
Microcrystalline Cellulose NF [Emcocel 50M, JRS]	10.00	40.00
Total	100.00	400.00

DOE Fusion Pro from S-Matrix Corp. was used to generate and analyze the DOE. A model robust screening design was used and evaluated five levels for each factor in 16 runs.

Factor	Low	High
Water Quantity (%)	5	15
Starch 1500 Quantity (%)	5	20
Impeller Speed (RPM)	150	500
Spray Rate (g/min)	50	200
Wet Massing Time (min)	1	5

Responses are shown in the Results section. The geometric mean particle size was analyzed before and after sieving. The percentage of fines created from sieving was determined as the quantity passing through a 100 mesh screen.

RESULTS

The study produced a wide range of results which are summarized in the table below. Each response is also depicted in the graphs to follow. The study showed that water quantity had the largest impact on the granule and tablet properties overall.

Response	Min	Max
Geometric Mean – Unsieved (μ)	78	845
Geometric Mean – Sieved (μ)	76	254
Geometric Standard Deviation	1.67	2.29
Fines Created from Sieving (%)	0.0	26.5
Bulk Density (g/cc)	0.54	0.68
Tapped Density (g/cc)	0.68	0.81
Hardness @ 15kN (kp)	4.5	8.3
Friability @ 15kN (%)	0.00	0.33
Disintegration @ 15kN (min)	0.5	8.4

The unsieved particle size was impacted by water quantity, wet massing time, and Starch 1500 level, Figure 1. The widest range of particle size was seen with the upper end of the moisture level. The mid and low water levels show only a small effect on the wet massing time and starch level, Figure 2.

Figure 1

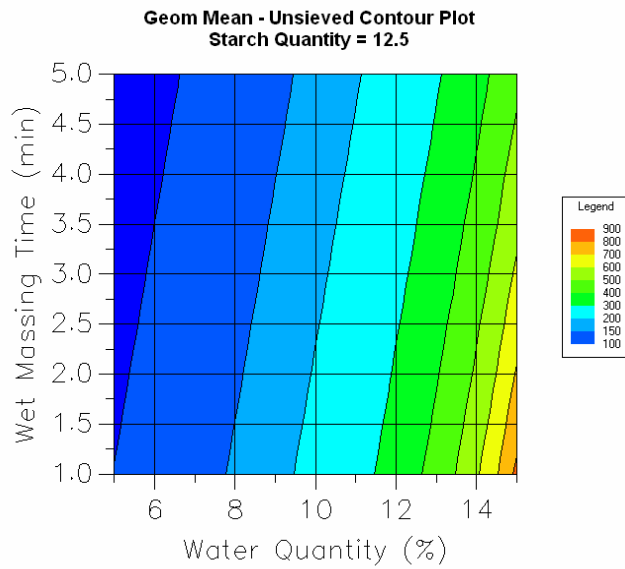


Figure 2: Effect of Water Level on Unsieved Particle Size



The amount of fines created after sieving related to the granule strength, Figure 3. Higher impeller speeds produced stronger granules that survive the sieving process. Sieved particle size was influenced by water quantity, starch quantity, and impeller speed. Increasing these created larger particles, Figure 4.

Figure 3

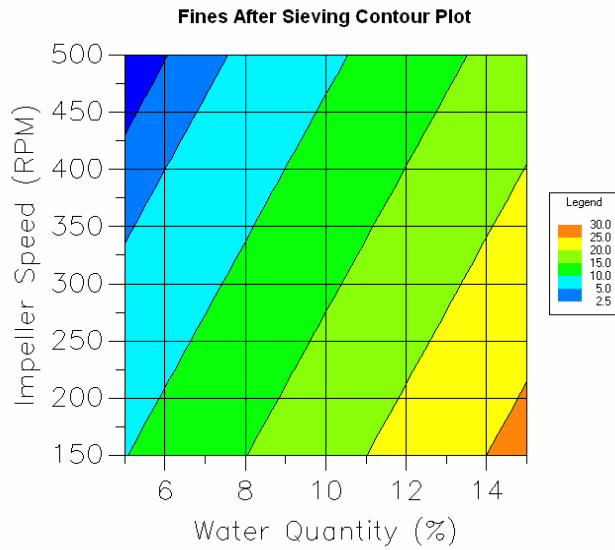
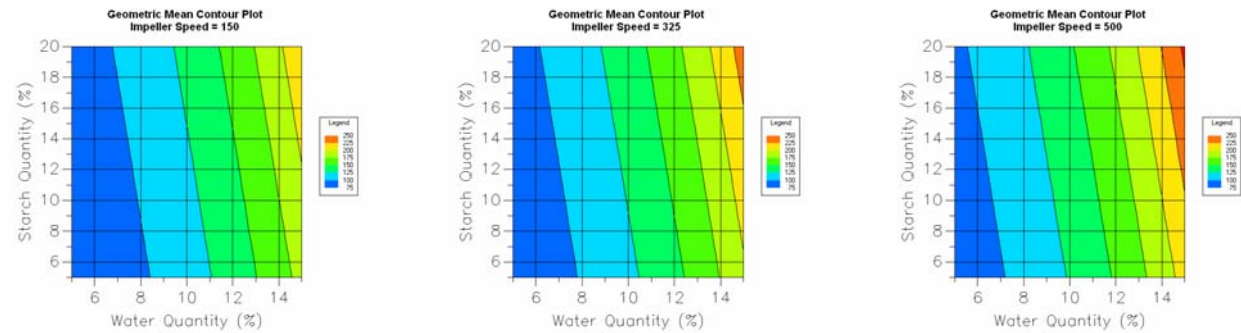
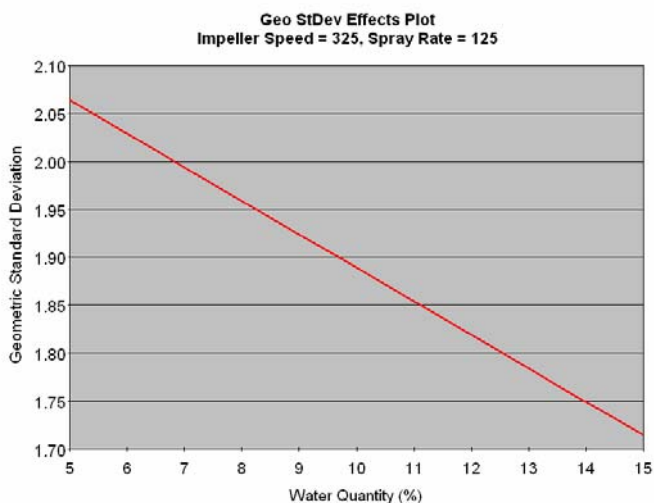


Figure 4: Sieved Geometric Mean Particle Size



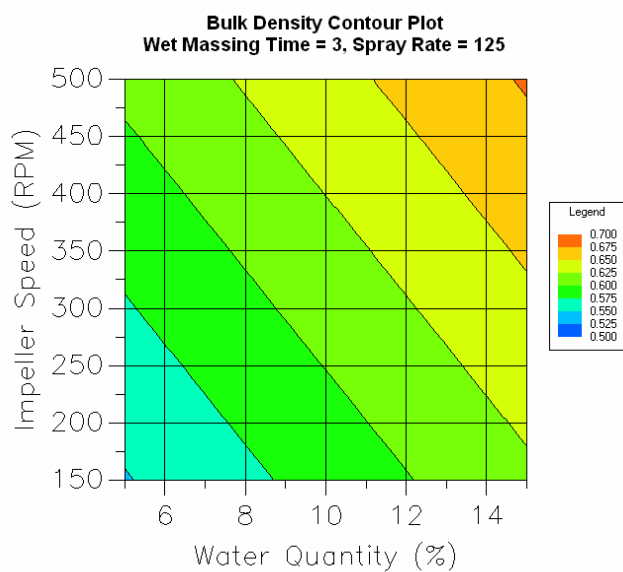
Particle size geometric standard deviation was only affected by water quantity, Figure 5. Higher levels of water decreased the geometric standard deviation.

Figure 5



The bulk density was affected by water quantity, impeller speed (Figure 6), spray rate, and wet massing time. The full range of these effects is also shown in the nine plots in Figure 9 (following page).

Figure 6



Tapped density was similar to bulk density. Tablet hardness was affected by impeller speed and wet massing time, Figure 7. Tablet friability was affected by impeller speed only, but most likely is a secondary effect of tablet hardness, Figure 8. The effects on tablet hardness and friability can be linked to bulk density. As water quantity, impeller speed and the length of time in the granulator increased, the density of the granules increased. This resulted in lower tablet hardness and higher friability.

Figure 7

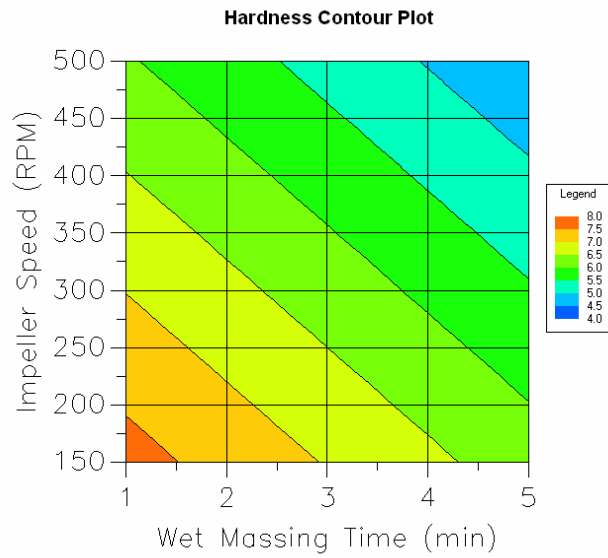


Figure 8

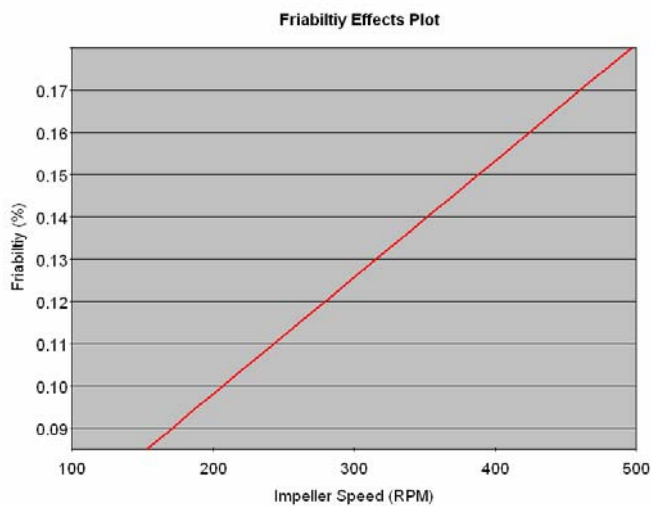
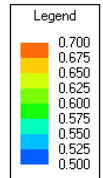
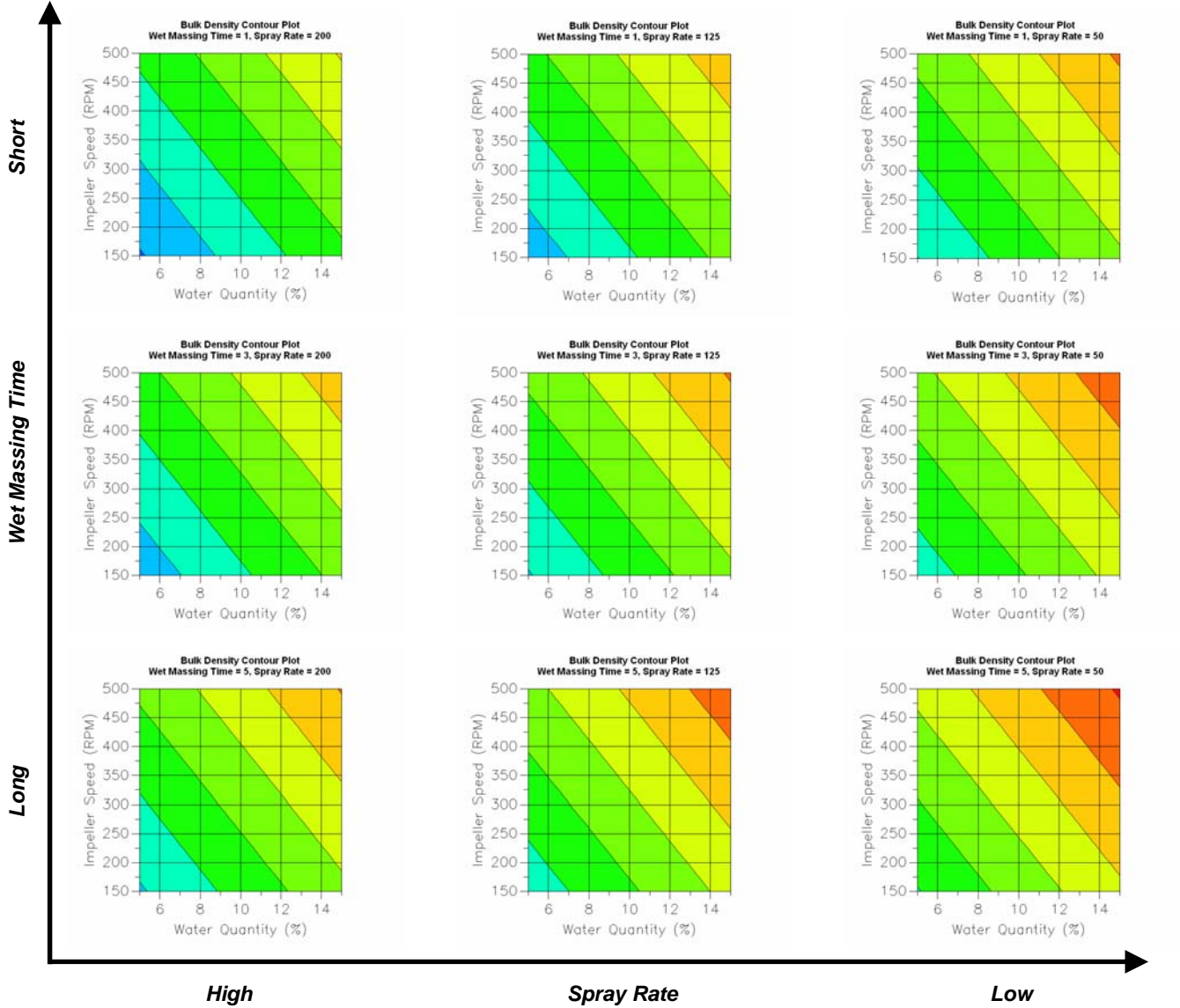


Figure 9: Effect of Four Parameters on Bulk Density



Disintegration time was only affected by water quantity, Figure 10. Higher levels of water created denser granules that took slightly longer to disintegrate. This work can be used to establish a design space that will predict product performance based on granulation parameters, Figure 11. The area in white shows the range where product meeting the optimization targets are met or exceeded.

Figure 10

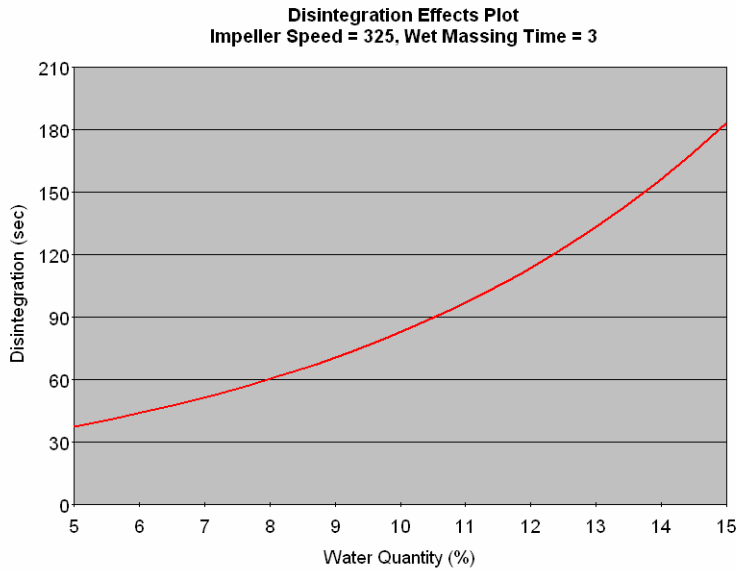
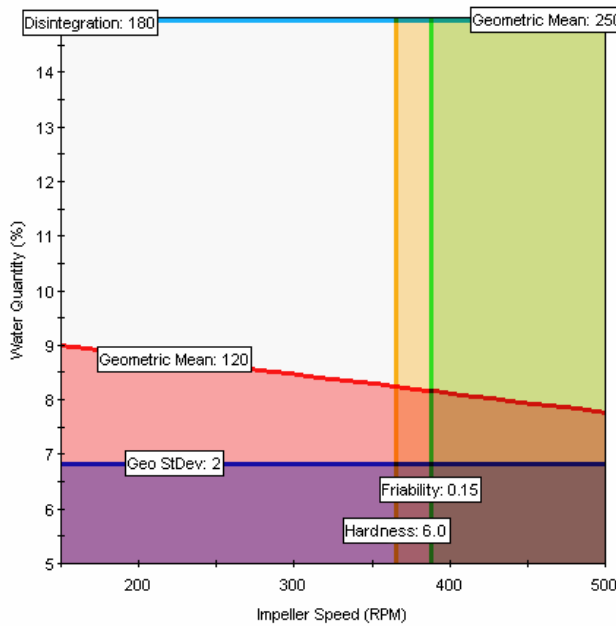


Figure 11 – Design Space



Fixed Factors:

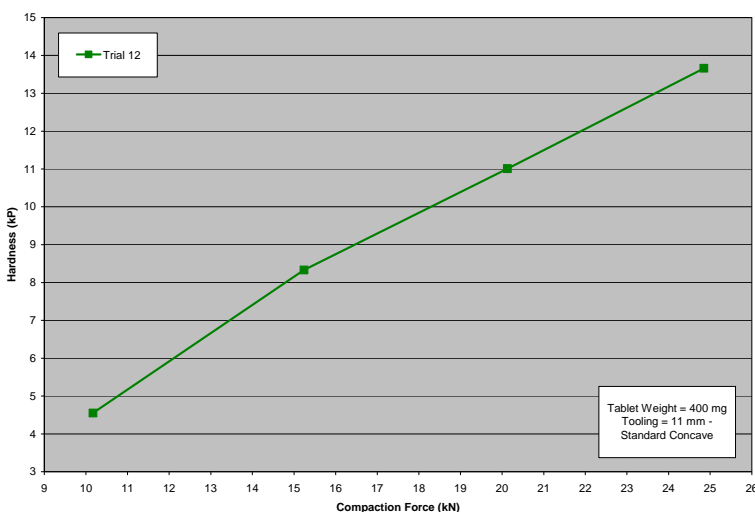
Starch 1500 Level 20%
Wet Massing Time 1.5 min
Spray Rate 170 g/min

Optimization Targets:

Geo Mean 120–250 μ
Geo St Dev < 2
Hardness > 6 kp
Friability < 0.15%
DT < 180 sec

In this study, optimal parameters were water quantity 9 – 11%, Starch 1500 level 10 – 15%, impeller speed less than 200 RPM, spray rate of 200 g/min, and wet massing time less than 1.5 minutes. A compaction profile from an optimal run is provided in Figure 12.

Figure 12: Compaction Profile - Optimal Run



CONCLUSIONS

The formulation and granulation parameters impacted the resultant granule and tablet properties. Optimal granule and tablet properties were obtained when a moderate amount of water was utilized with low impeller speeds, fast spray rates, and short wet massing times. This produced a granulation with low bulk density and resulted in higher tablet hardness. The use of Starch 1500 as both binder and disintegrant produced excellent granulations, that resulted in robust tablets with fast disintegration times. The formulation utilized in the study was a low dose, soluble drug. Results may vary with different drug load and drug solubilities.

This ADS was adapted from the poster presented at AAPS 2007. Author: Gus LaBella

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