

## Formulation and Processing Options for an Amlodipine Besylate Tablet

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### OBJECTIVE

To evaluate the effects of formulation and manufacturing process on an amlodipine besylate tablet.

### MATERIALS & METHOD

Amlodipine besylate was used in this study as model drug with low solubility for a low dose drug product. A direct compression formulation utilizing microcrystalline cellulose (MCC) and dicalcium phosphate, anhydrous (DCP) was prepared as a baseline product. This baseline was created to evaluate the ingredients contained in the innovator product. As an alternative, a direct compression (DC) formulation containing Starch 1500® as the secondary filler was prepared, see tables below. In order to evaluate the effects of processing on this formulation, the Starch 1500 formulation was processed by fluid bed (FB) granulation and by high shear (HS) granulation. In both granulations, half of the microcrystalline cellulose was added dry after granulation. For the FB process, 10% of the Starch 1500 in the formula was slurried in room temperature water at high solids concentration of 14% solids and used as the granulation binder. In the HS process, all of the Starch 1500 was added dry to the granulator bowl and only water was used to granulate.

The blend properties were evaluated. Tablets were compressed on a Piccola instrumented, rotary tablet press. Compaction scans and strain rate scans were performed. Short production runs were monitored for tablet consistency. Dissolution and content uniformity were evaluated for each batch. Products were placed on open dish stability for two months in accelerated conditions.

### DCP Formulation

Ingredient	Percent
Amlodipine Besylate USP [Cadila]	3.47
Microcrystalline Cellulose NF [Microcel® 102, Blanver]	45.78
Dicalcium Phosphate NF, Anhydrous [Emcompress®, JRS]	45.75
Sodium Starch Glycolate NF [Explosol® P, Blanver]	4.00
Magnesium Stearate NF [HyQual®, Mallinckrodt]	1.00
<b>Total</b>	<b>100.00</b>

### Starch 1500® Formulation

Ingredient	Percent
Amlodipine Besylate USP [Cadila]	3.47
Microcrystalline Cellulose NF [Microcel® 102, Blanver]	48.03
Pregelatinized Starch NF [Starch 1500®, Colorcon]	48.00
Colloidal Silicon Dioxide NF Cab-o-Sil® M5P, Cabot]	0.25
Magnesium Stearate NF [HyQual®, Mallinckrodt]	0.25
<b>Total</b>	<b>100.00</b>

### RESULTS

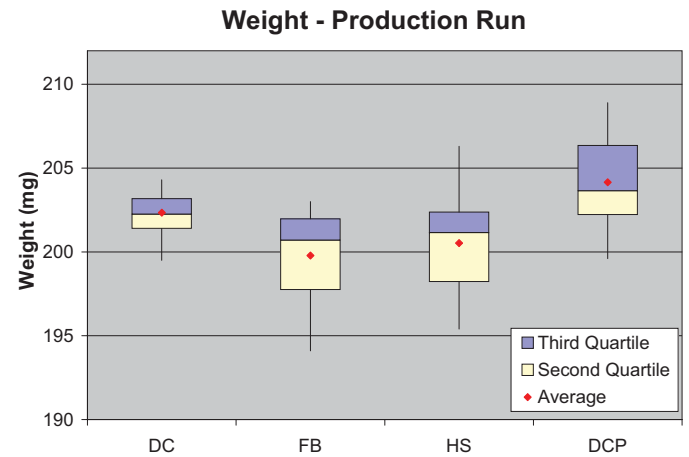
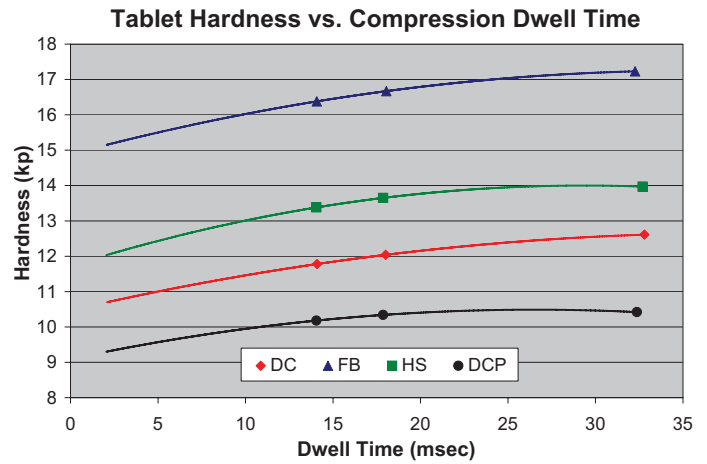
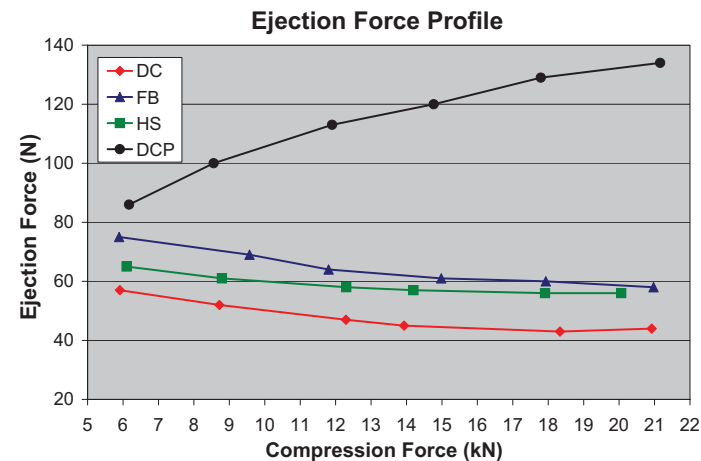
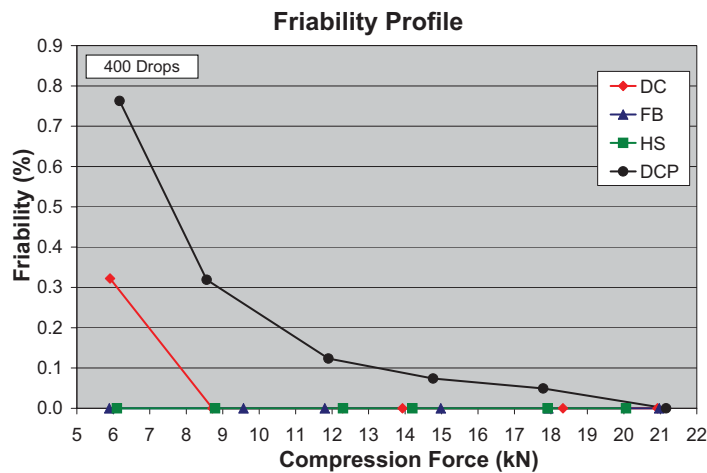
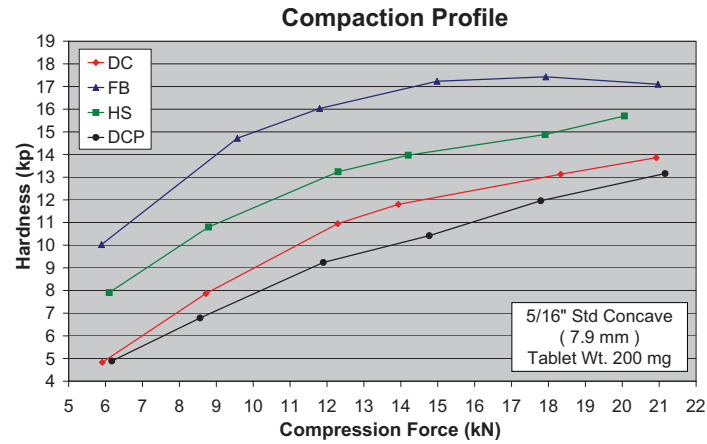
HS granulation produced the largest geometric mean particle size, the largest geometric standard deviation, and the fastest flow rate. The FB process produced the lowest bulk density and the smallest geometric standard deviation.

### Blend Properties

Property	Starch 1500			DCP
	DC	FB	HS	
LOD (%)	6.58	6.48	6.54	2.77
Bulk Density (g/cc)	0.51	0.36	0.46	0.55
Compressibility Index (%)	23.3	19.7	17.3	24.2
Flow Rate (g/sec)	4.57	6.68	9.18	6.66
Geometric Mean (micron)	70	132	181	90
Standard Deviation	1.95	1.85	2.15	1.87

All formulations and processes produced excellent tablet hardness, friability, disintegration times, ejection forces, and weight variation as seen in the following graphs.

The FB process produced the highest tablet hardness. The Starch 1500 formulations produced lower ejection forces with less lubricant. Neither formulation nor process showed a major dependence on press speed. Speed data was extrapolated to show expected results for large scale presses. Tablet weight and hardness were more consistent with the direct compression Starch 1500 formula during the production run even though this batch showed the slowest mass flow rate.

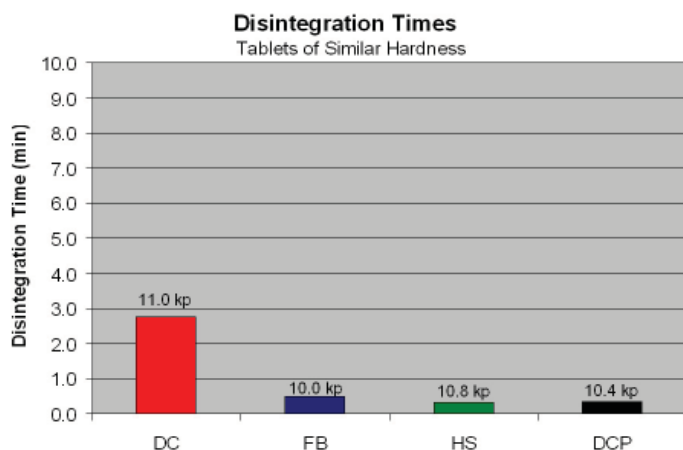


The batches produced were run from a single hopper of granulation on the Piccola so the effects of tote bins, "Y" chutes, and double rotary high speed tableting was not evaluated. Interestingly, the content uniformity (CU) was best with the DC Starch 1500 batch. Processing options such as spraying the drug in FB or longer pre-blending time in HS may improve CU. For both DC batches the drug was pre-blended with either Starch 1500 or MCC, then screened, in order to prepare a homogeneous mixture. For the FB batch, the drug was added directly to the bowl. Since the FB process does not produce shear, agglomerates may have been present. In the HS process the pre-blending time, the speed of the impeller and chopper, and the shape of the blades impact uniformity. Two to three minutes of mixing at high speed is typically sufficient pre-blending time. In this study a Glatt VG-25M with a 10L bowl was used. The VG chopper blades are flat rather than "U" shaped as in most granulators, and may not produce sufficient shear for uniform mixing in a short period.

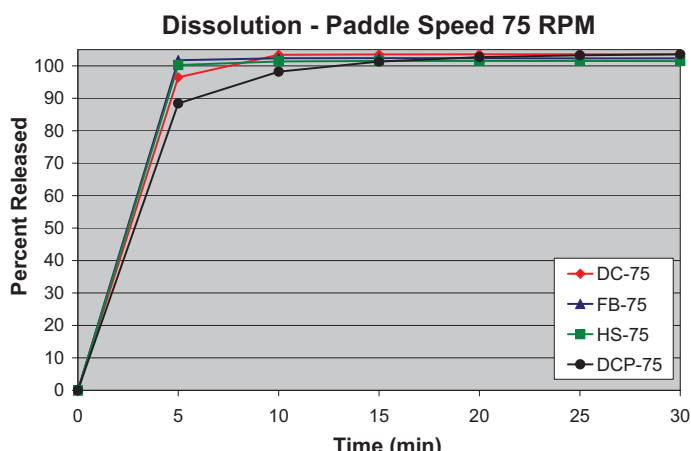
## Content Uniformity

	DC	FB	HS	DCP
Avg %	101.8	99.6	99.9	98.9
RSD %	1.06	3.04	2.66	2.10

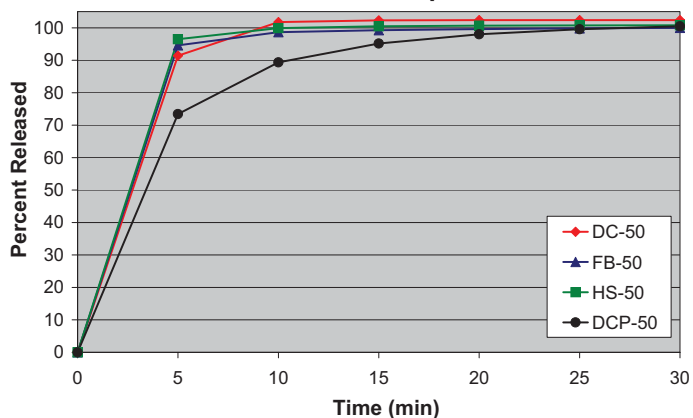
Since Starch 1500 has disintegrant functionality, the super disintegrant was removed for the batches with Starch 1500. Disintegration of the DCP based tablets was faster than the DC Starch 1500 based tablets, but the dissolution of all Starch 1500 batches were faster than the DCP formulation. Interestingly, the Starch 1500 batches showed faster disintegration after granulation. This is typically not the case with polymeric granulation binders.



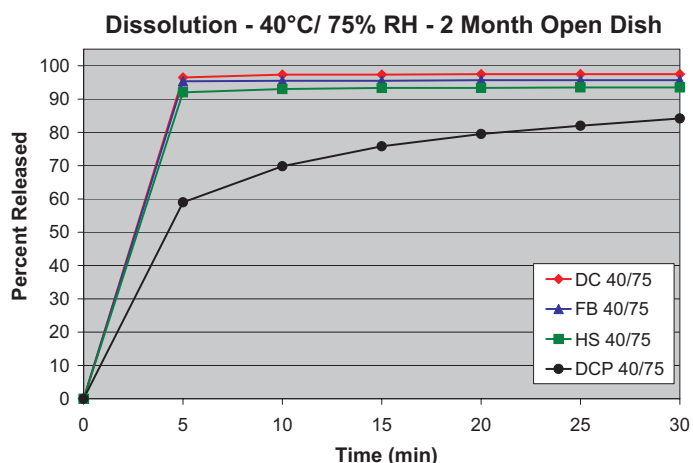
The Starch 1500 batches showed no dependence on paddle speed regardless of the manufacturing process. On the other hand, the DCP formulation showed slower drug release at lower paddle speed. This may be due to the heavy, insoluble DCP trapping drug at the bottom of the dissolution vessel.



## Dissolution - Paddle Speed 50 RPM



In open dish testing, the DCP formulation showed a sharp decrease in the dissolution rate after one month. All Starch 1500 batches remained unchanged. The changes in the DCP dissolution may be driven by changes in the DCP, changes in the disintegrant, or by a lack of moisture control in the overall formulation.



## CONCLUSIONS

A base of microcrystalline cellulose and Starch 1500 produced an excellent product with high mechanical strength, fast dissolution, stable stability, and good process flexibility that was superior to DCP in many aspects. The multifunctional characteristic of Starch 1500 provided more processing flexibility than DCP. The use of Starch 1500 allowed the elimination of super disintegrant and a reduction of lubricant. The versatility of Starch 1500 permitted the use of different processing routes to produce excellent drug products.

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