

# Powder Flowability of a New Direct Compression Grade Hypromellose Using Limiting Flow Rate Analysis

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## **Abstract**

Direct compression is a tableting process in which a dry blend of ingredients is placed into a tablet hopper and compressed into tablets. Direct compression requires that the powder blend have good flowability. A new grade of hypromellose with improved flow has been developed for direct compression, controlled release applications. This improvement is not the result of decreased particle cohesion (as measured by ring shear tests), but rather improved permeability of the material. This work applies the concept of limiting flow rates to the new direct compression grade hypromellose and emphasizes its importance as a key measure of flowability for fine materials.

## **Introduction**

Direct compression (DC) is a tableting process in which a dry blend of ingredients is placed into a tablet hopper and compressed into tablets. Direct compression requires that the powder blend have good flow. Reliable flow of pharmaceutical mixtures out of tablet press hoppers is a key to problem-free tablet press operation and consistent tablet properties. Failure to ensure reliable flow can result in both considerable manual interventions for the table press hopper and poor tablet physical properties, such as high tablet-to-tablet weight variability and tablet hardness.

A new grade of hypromellose with improved flow has been developed for direct compression, controlled release applications. This improvement is not the result of decreased particle cohesion (as measured by ring shear tests), but rather improved permeability of the material. This work applies the concept of limiting flow rates to the new DC grade of hypromellose and emphasizes its importance as a key measure of flow for fine materials. Limiting flow rates are caused by the inability of the flowing solid to dilate in the conical section of the hopper as a result of low gas permeability of the bulk solid.

## **Experimental**

### **Materials**

Limiting flow rates were determined for two grades of hypromellose, METHOCEL™ K4M Premium CR and METHOCEL™ K4M Premium DC, as supplied by The Dow Chemical Company. All evaluations were performed on the material as received.

The materials used for the laboratory-scale tableting trial were the hypromellose materials, as noted above, metoprolol tartrate (Mulji Mehta & Sons, LTD), Supertab 11 SD lactose (Mutchler, Inc.), Starch

1500 (Colorcon, Inc.), and magnesium stearate (Spectrum).

## **Methods**

**Limiting Flow Rate Determination.** The three key measurements used to determine the limiting flow rate are cohesive strength, permeability, and compressibility. Cohesive strength was measured in a Schulze RST01-01 shear tester. Permeability measures the air permeation characteristics under similar loads while compressibility measures the bulk density as a function of load. Both were measured in custom-made equipment. These data were then used in a program that solves a series of differential equations to determine the limiting flow rate (1).

**Laboratory Scale Tableting Trial.** The raw materials to be tableted were prepared in 5-kg batches. The composition of the blends is shown in Table 1. The blends were transferred directly from the V-blender to the hopper of the tablet press.

**Table 1. Formulations for tableting trial.**

<b>Material</b>	<b>CR</b>	<b>DC</b>
Metoprolol tartrate	10%	10%
Hypromellose METHOCEL™ K4M Premium CR METHOCEL™ K4M Premium DC	25% —	— 25%
Lactose	54.5%	54.5%
Starch	10%	10%
Magnesium stearate	0.5%	0.5%

A 16-station Manesty Beta Press was used to produce tablets. The tooling used was 13/32 inch, and it produced round, flat-faced, beveled-edged

tablets. The speed was 18 rpm, target compression force was 5000 lb, and the total run time was approximately 40 min. The flow behavior of the blends was visually monitored throughout the trial. AeroFlow (Amherst Process Instrument, Inc., avalanche method) data were also used to compare the flow properties of the CR and DC formulations. Tablet hardness and weight variability were also determined.

Once the press was properly configured, the formulations were tableted, with each run lasting about 40 min. Sample tablets were collected at 5-min intervals. Each sampling consisted of collecting about 100–150 tablets. Tablet physicals were determined on 20 tablets from each of the thirteen collection times. Each tablet was weighed using a Mettler balance and then each tablet was crushed using the Ht-300 Hardness Tester.

## Results and Discussion

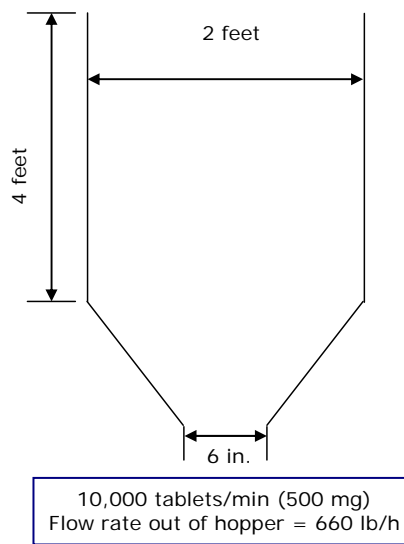
Many pharmaceutical systems with fine powders exhibit significantly reduced flow rates due to the two-phase flow that must occur in the conical section of a tablet press hopper. Solids must dilate or reduce in bulk density as they approach the hopper outlet. If, in the case of fine materials, they are insufficiently permeable to gas flow, a limiting flow rate of solids results. The reduction in flow can be significant, and it is not unusual to observe decreases in flow of several orders of magnitude or complete stoppage of flow. A very important consideration is the permeability of the bulk powder. Permeability is the ability of air to migrate into the base of the hopper as the powder flows out. In general, coarser particles are more permeable.

A tablet hopper that manufactures 500-mg tablets at a rate of 10,000 tablets per minute requires a flow rate of 660 lb/h of material out of that hopper. In this case, for a hopper with a 6-inch diameter outlet, as shown in Figure 1, the limiting flow rate for the DC grade hypromellose was calculated to be 2400 lb/h, while the limiting flow rate for the CR grade hypromellose was calculated to be 100 lb/h (2).

Laboratory-scale experiments were performed to corroborate these results. Metoprolol tartrate was selected as a model drug. It is highly soluble in water, has a particle size of approximately 150  $\mu\text{m}$ , and has the reputation of being difficult to process via DC. Its small particle size contributes to segregation issues, and it has poor flow properties.

The flow properties of the CR and DC blends were monitored throughout the tableting trial. The CR formulation required manual intervention to maintain even flow. Conversely, the DC formulation exhibited much improved, steady, powder flow behavior.

**Figure 1. Hopper dimension for limiting flow rate analysis.**



The powder flow and tablet properties are summarized in Table 2.

**Table 2. Summary of metoprolol tartrate formulation performance.**

Parameter	CR	DC
Powder flow MTA <sup>a</sup> , s	9.1	5.5
Tablet weight, mg	378	401
Std. dev., mg	31.4	4.1
Rel. std. dev., %	8.3	1
Tablet compressive strength, kp	25.5	23.5
Std. dev., kp	8.7	2.4

<sup>a</sup>MTA = mean time to avalanche

The DC formulation exhibited significantly lower MTA values, indicating a better flowing powder. The tablet weight variability was also much lower for the DC formulation, again indicating improved flow.

## Conclusions

Limiting flow rates are caused by the inability of the flowing solid to dilate in the conical section of the hopper as a result of low gas permeability of the bulk solid. The influence of low permeability can be quite dramatic with decreases in flow rates of several orders of magnitude compared to the unimpeded flow rates of coarser materials. For the new DC grade hypromellose, the flow is approximately 25 times better than the conventional CR grade hypromellose based on the limiting flow rate analysis.

These results were corroborated via a laboratory-scale tablet trial using metropolol tartrate as a model drug. Improved flow of the formulation incorporating DC grade hypromellose was noted during the tableting trial and confirmed via AeroFlow testing. A smaller variation in tablet weight was also observed for the DC formulation.

## References

1. D.A. Craig and R.J. Hossfeld, Jenike & Johanson, Inc., "Measuring Powder Flow Properties," Chemical Engineering, September, 2002.
2. "Permeability and Limiting Flow Rate of Hydroxypropyl Methylcellulose", performed under contract by Jenike & Johanson, Inc., October 25, 2007.

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