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Evaluation of Directly Compressible Hypromellose in Commercial-Scale Manufacturing of a Modified-Release Matrix Tablet

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PURPOSE

The challenges of content uniformity and powder flow have limited the adoption of direct-compression tableting processes, particularly for the manufacture of modified-release formulations. This study compared two recently introduced directly compressible (DC) grades of hypromellose (HPMC) with a conventional controlled-release (CR) grade, with equivalent molecular weights, in commercial-scale tablet production of modified-release formulations of low and high doses (5% and 50%) of poorly flowable and poorly compactible metformin hydrochloride (HCl).

METHOD

Formulations comprised 5% and 50% metformin HCl, either Benecel™ K100M PHARM CR (controlled release), Benecel™ K100M PH DC (direct compression), or Methocel™ K100M Premium DC2 (direct compression) grades of HPMC, microcrystalline cellulose (as filler in low-dose formulations), colloidal silicon dioxide (with Benecel™ K100M HPMC PHARM CR and Methocel™ K100M Premium DC2), and magnesium stearate. Formulation details are listed in **Table 1**.

Table 1: Quantitative Formulae

	Formulation (weight %)					
Ingredients	**1A**	**1B**	**2A**	**2B**	**3A**	**3B**
Metformin HCl	5.0	50.0	5.0	50.0	5.0	50.0
Benecel™ K100M PHARM CR HPMC	49.0	49.0	--	--	--	--
Benecel™ K100M PH DC HPMC	--	--	49.5	49.5	--	--
Methocel™ K100M Premium DC2 HPMC	--	--	--	--	49.0	49.0
Colloidal Silicon Dioxide	0.5	0.5	--	--	0.5	0.5
Microcrystalline Cellulose	45.0	--	45.0	--	45.0	--
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5
TOTAL	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

The dry-blended materials were compressed to a target weight of 500 mg using 7/16” standard concave tooling on a 38 station Elizabeth Hata HT-AP38-MSU rotary press at a turret speed of 30 RPM. Pre-compression and main compression forces were maintained at 2 kN and 15 kN, respectively throughout each run. Tablet samples were taken at 10-minute intervals, and at the end of the run.

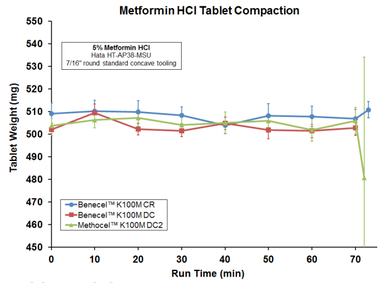
From each sample, 10 tablets were characterized for weight, thickness, crushing strength, and friability after 100 drops in 4 minutes.

Dissolution (n=6) of the 30-minute tablet samples from each batch was conducted in 900 mL of pH 6.8 phosphate buffer 0.050M maintained at 37°C with USP Apparatus I (baskets) at 100 RPM. Samples were taken at 0.25 hr intervals up to 1 hr, then at 1 hr intervals to 24 hours; quantitation was by online UV detection.

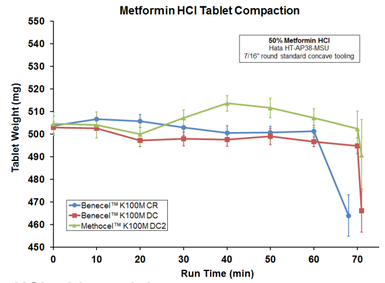
The swelling and erosion behavior of the 30-minute tablet samples was assessed by immersion of pre-weighed tablets in pH 6.8 phosphate buffer, using apparatus and conditions identical to the dissolution test above. Samples were run in triplicate. At 1, 4, 8, 16 and 24 hours, the samples were withdrawn from the medium, excess moisture was removed, and the samples were weighed. The samples were then dried overnight under vacuum at 105°C, and re-weighed.

RESULTS

Plots of tablet weights and crushing strength throughout the compression runs are shown below in **Figures 1–3**.



tablet weight



HCl tablet weight

Weight variation of the tablets made with the Benecel™ DC HPMC was equal to or superior to the CR grade at all sample times. However, under challenging flow (50% poorly flowing metformin) the formulation incorporating Methocel™ DC2 HPMC showed a clear drift in both tablet weight and hardness over the course of the compression run, necessitating constant manual weight adjustment.

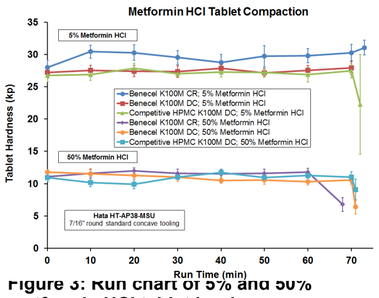


Figure 3: Run chart of 5% and 50% metformin HCl tablet hardness

Also, these batches exhibited greater fluctuations in both tablet weight and hardness as the blend began to run out, compared to either the CR or DC grades of Benecel™ HPMC. This indicates poorer flow of Methocel™ DC2 HPMC when used with a high loading of a poorly flowing and poorly compressible drug.

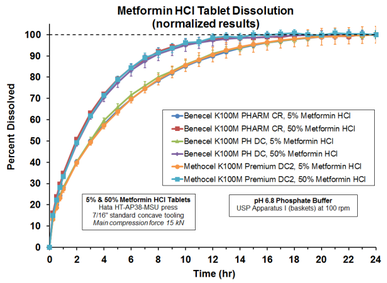
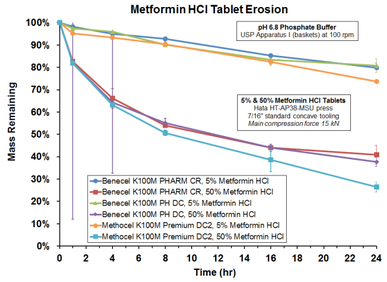
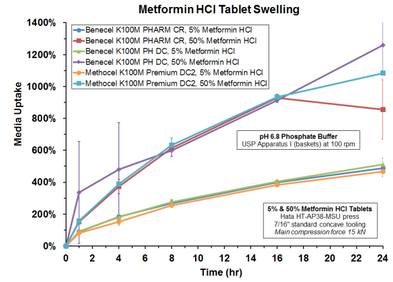


Figure 4: Dissolution results for 5% and 50% metformin HCl tablets

Dissolution profiles of each batch were superimposable within the low and high dose groups, as shown in **Figure 4** (left).

Finally, the results of the *in vitro* erosion and swelling tests, shown in **Figures 5** and **6** (below), confirm the similar behavior of the DC grade polymer to the conventional grade at both low and high drug loadings.





Figures 5 and 6: Erosion and swelling results for 5% and 50% metformin HCl tablets

CONCLUSION

The directly compressible grade of Benecel™ K100M PH DC HPMC was shown to yield tablet crushing strength equivalent to the controlled-release grade, while affording better flow characteristics under difficult flow conditions. The same modified-release profiles were attained when using the Benecel™ DC HPMC at both low and high drug loading as when using the CR grade, indicating no adjustment in formulation would be required when the DC grade is used. This was confirmed by comparable swelling and erosion results at low and high drug loading.

In all, the use of the DC grade of Benecel™ HPMC may allow for a simpler manufacturing process, with associated cost savings.

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