PTR-111

Evaluation of Directly Compressible Hypromellose in Matrix Mini-tablets

Q. Schwing, J. Greenamoyer, M. Davis, T. Dürig
Ashland Specialty Ingredients, Wilmington, DE 19808, USA

Introduction

Mini-tablets are gaining more attention in oral drug delivery due to their flexibility in dosing and uniform size and shape. They are important for pediatric and geriatric populations not only for ease of use, but also for patient compliance. The potential challenges of content uniformity and powder flow that typically limit the use of direct-compression tableting processes are expected to be significantly greater when manufacturing mini-tablets. This study compares a directly compressible (DC) grade of Benecel™ hypromellose (HPMC) with a standard grade of Benecel HPMC in mini-tablet formulations containing active pharmaceutical ingredients (APIs) that have varying flow, compactibility, and solubility properties.

Methods

Formulations containing a high or low drug loading of API (metformin, cetirizine, or theophylline), Benecel HPMC (DC or standard), microcrystalline cellulose (MCC), and magnesium stearate were evaluated for this study (see Table 1). These formulations were weighed and blended in 500 gram batches for tableting. Prior to tableting, the blends were analyzed for flow using a Brookfield powder rheometer. A total of 24 formulations were prepared.

Table 1. Quantitative Formulations

Ingredient	Low Drug Load (wt %)	High Drug Load (wt %)	Low Drug Load (wt %)	High Drug Load (wt %)	Low Drug Load (wt %)	High Drug Load (wt %)	Low Drug Load (wt %)	High Drug Load (wt %)
API	10	30	10	30	10	30	10	30
Benecel™ K4M Pharm HPMC	30	30	—	—	—	—	—	—
Benecel K4M PH DC HPMC	—	—	—	—	30	30	—	—
Benecel K100M Pharm HPMC	—	—	30	30	—	—	—	—
Benecel K100M PH DC HPMC	—	—	—	—	—	—	30	30
Microcrystalline cellulose	59	39	59	39	59	39	59	39
Magnesium stearate	1	1	1	1	1	1	1	1
Total	100	100	100	100	100	100	100	100

Note: This work was presented at AAPS, November 14, 2017 in San Diego, CA.

After the powder flow tests, the dry-blended materials were compressed using multi-tip tooling (consisting of 10, 2 mm tips per tablet punch) on a 16 station Manesty Betapress at a speed of 54 rpm. A total of four tooling sets were used for each tableting run. The target weight for each mini-tablet was 7 mg. A compression force of 10 kN was consistent throughout each run. The total tableting time for each formulation was 15 minutes and mini-tablets were collected throughout the entire run.

From each sample set, n = 10 mini-tablets were characterized for weight, thickness, hardness, and tensile strength. Additionally, 6.5 g of mini-tablets were tested for friability after 100 drops in 4 minutes. Finally, n = 6 capsules were tested for dissolution as described in Table 2.

Table 2: Dosage Details for Dissolution

API	Capsule Weight (mg)	Dosage (mg)	Media
10% Metformin	1080	108	6.8 pH buffer
30% Metformin	1080	324	6.8 pH buffer
10% Cetirizine	100	10	Deionized water
30% Cetirizine	33.33	10	Deionized water
10% Theophylline	1000	100	6.8 pH buffer
30% Theophylline	333.33	100	6.8 pH buffer

Results and Discussion

Powder flow results are shown in Figures 1 to 3. Flow function is the measure of the amount of strength the powder retains at a stress free surface followed by consolidation to a given stress level. The greater the flow function (ff) value, the more free flowing the powder.

Figure 1: Powder Flow of Metformin Formulations

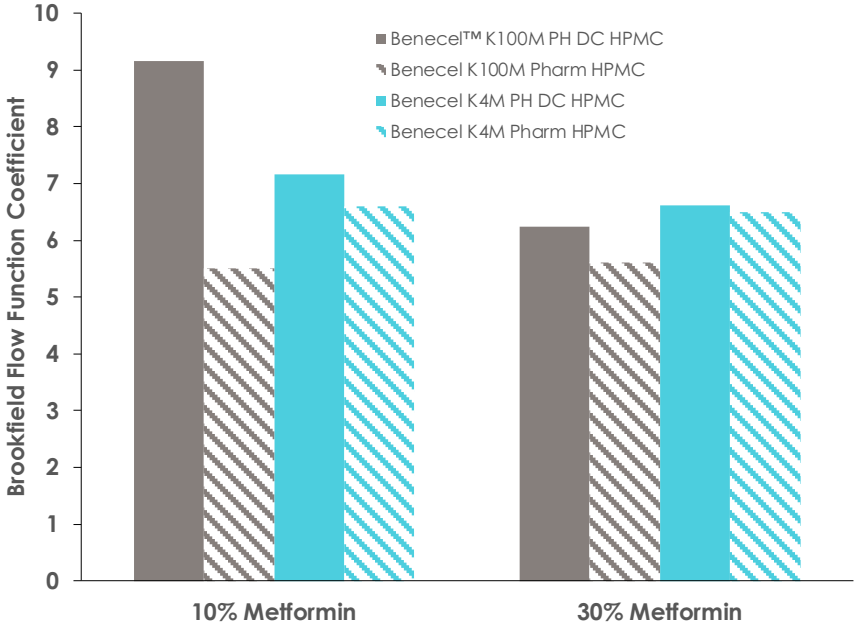


Figure 2: Powder Flow of Cetirizine Formulations

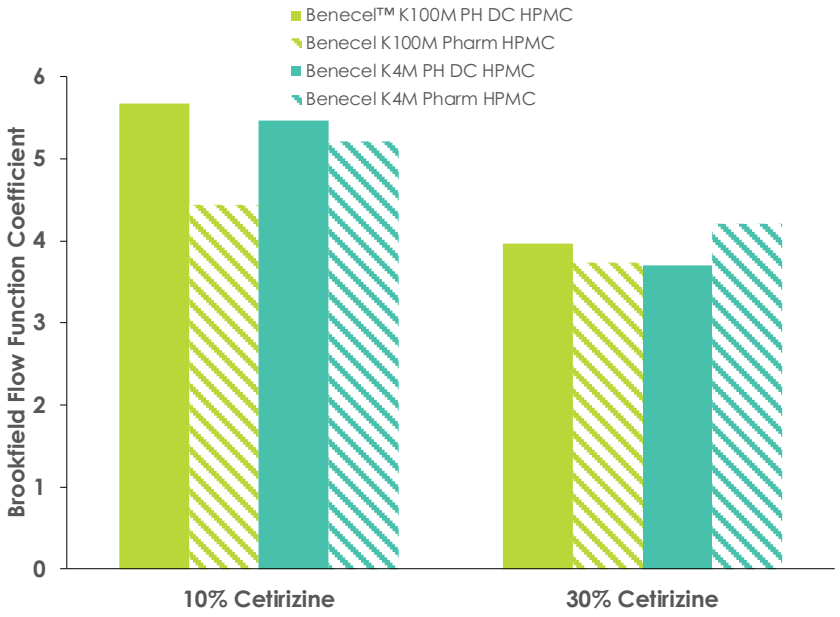
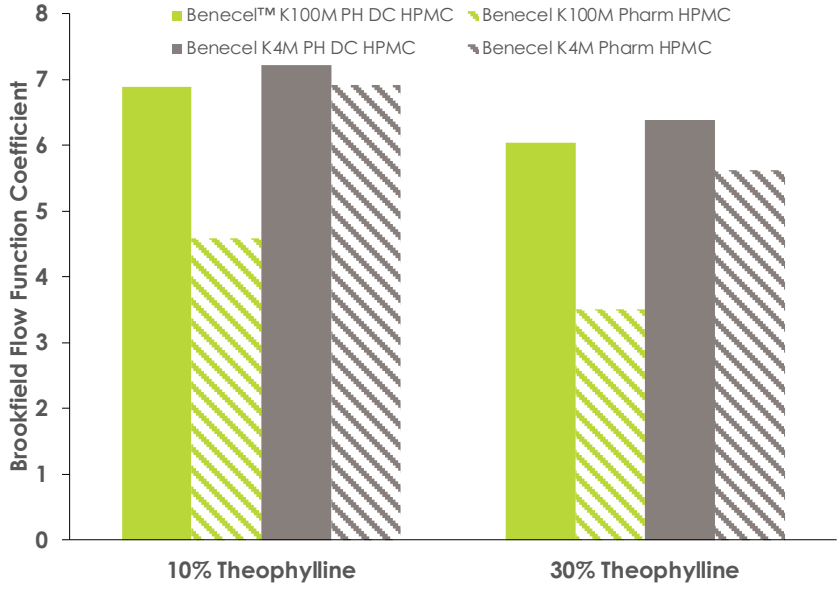


Figure 3: Powder Flow of Theophylline Formulations



For all three APIs, formulations containing Benecel PH DC HPMC demonstrated better flow properties compared with formulations containing Benecel Pharm HPMC, as indicated by higher flow function values. Mini-tablet characterization results for formulations containing Benecel K100M PH DC HPMC and Benecel K100M Pharm HPMC are shown in Table 3. Formulations containing Benecel K100M PH DC HPMC demonstrated less tablet weight variability and higher tablet tensile strength compared with formulations containing Benecel K100M Pharm HPMC . Additionally, the formulations containing Benecel K100M PH DC HPMC produced mini-tablets with better friability results compared with those containing Benecel K100M Pharm HPMC.

Table 3: Mini-tablet Characterization for Formulations Containing Benecel™ K100M Pharm HPMC and Benecel K100M PH DC HPMC

Formulation	Mini-Tablet Weight Mean (mg); N=10		Tablet Weight Coefficient of Variability (% CV)		Tablet Tensile Strength (kN/cm^3)		Friability (%)	
	Benecel™ K100M Pharm HPMC	Benecel K100M PH DC HPMC	Benecel K100M Pharm HPMC	Benecel K100M PH DC HPMC	Benecel K100M Pharm HPMC	Benecel K100M PH DC HPMC	Benecel K100M Pharm HPMC	Benecel K100M PH DC HPMC
10% Metformin	6.05	7.58	4.76	1.21	0.3238	0.4264	0.38	0
30% Metformin	6.84	7.92	7.27	2.21	0.2345	0.3315	0.79	0
10% Cetirizine	6.5	6.81	6.96	1.62	0.498	0.4793	1.29	0.4
30% Cetirizine*	6.32	7.11	6.14	2.92	0.5406	0.5031	1.5	1.16
10% Theophylline	5.78	6.96	5.98	4.29	0.1903	0.2256	0.92	0.48
30% Theophylline*	6.62	7.46	5.27	3.64	0.2299	0.2318	1.76	1.32

*1% Silica added to formulations containing standard HPMC to improve flowability to produce tablets

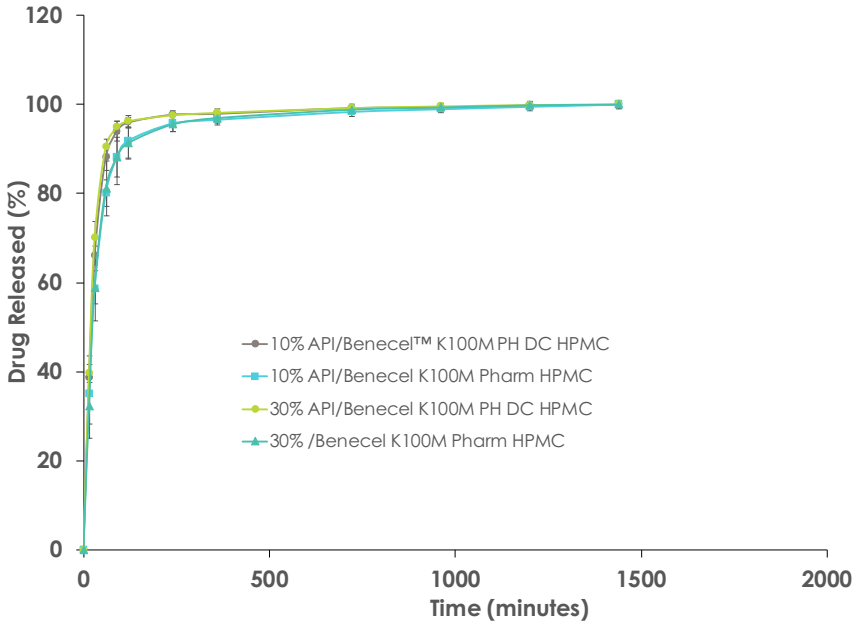
Mini-tablet characterization results for formulations containing Benecel K4M PH DC HPMC and Benecel K4M Pharm HPMC are shown in Table 4. Formulations containing Benecel K4M PH DC HPMC demonstrated less tablet weight variability and higher tablet tensile strength compared with formulations containing Benecel K4M Pharm HPMC. Additionally, the formulations containing Benecel K4M PH DC HPMC produced mini-tablets with better friability results compared with those containing Benecel K4M Pharm.

Table 4: Mini-tablet Characterization for Formulations Containing Benecel K4M Pharm HPMC and Benecel K4M PH DC HPMC

Formulation	Mini-Tablet Weight Mean (mg)		Weight Coefficient of Variability (% CV)		Tensile Strength (kN/cm^3)		Friability (%)	
	Benecel™ K4M Pharm HPMC	Benecel K4M PH DC HPMC	Benecel K4M Pharm HPMC	Benecel K4M PH DC HPMC	Benecel K4M Pharm HPMC	Benecel K4M PH DC HPMC	Benecel K4M Pharm HPMC	Benecel K4M PH DC HPMC
10% Metformin	7.44	7.66	4.75	2.83	0.4159	0.4742	0.08	0
30% Metformin	8	8.15	6.82	2.18	0.2333	0.2813	0.38	0.11
10% Cetirizine	7.18	7.87	3.58	2.61	0.4917	0.6395	0.42	0.09
30% Cetirizine*	8.15	6.9	7.59	4.78	0.4199	0.4968	0.91	0.65
10% Theophylline	6.46	7.28	6.7	3.82	0.24	0.2951	0.43	0.28
30% Theophylline*	5.85	6.9	7.78	3.06	0.1792	0.2639	0.64	0.37

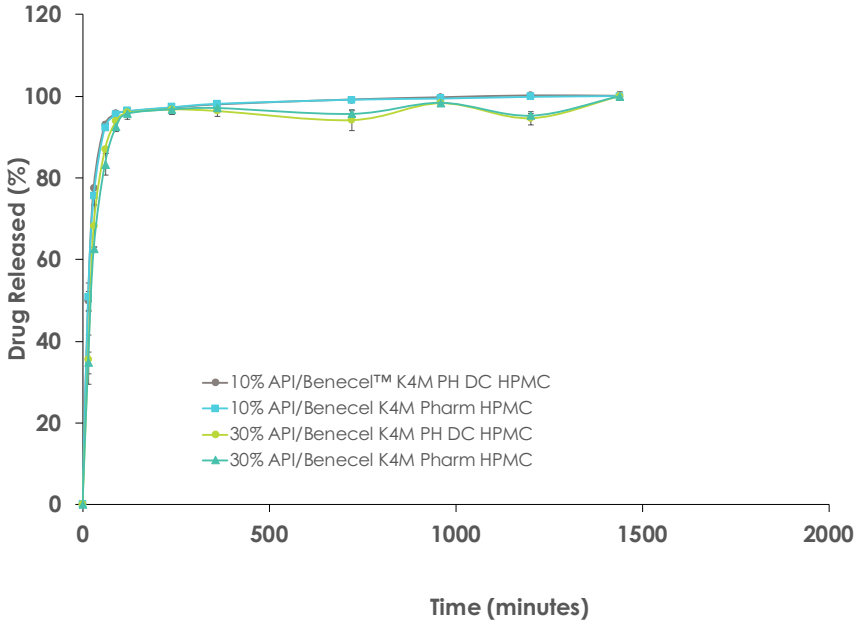
*1% Silica added to formulations containing standard HPMC to improve flowability to produce tablets

Figure 4: Dissolution Results for Capsules Containing Metformin Mini-tablets with Benecel™ K100M Pharm HPMC or Benecel K100M PH DC HPMC



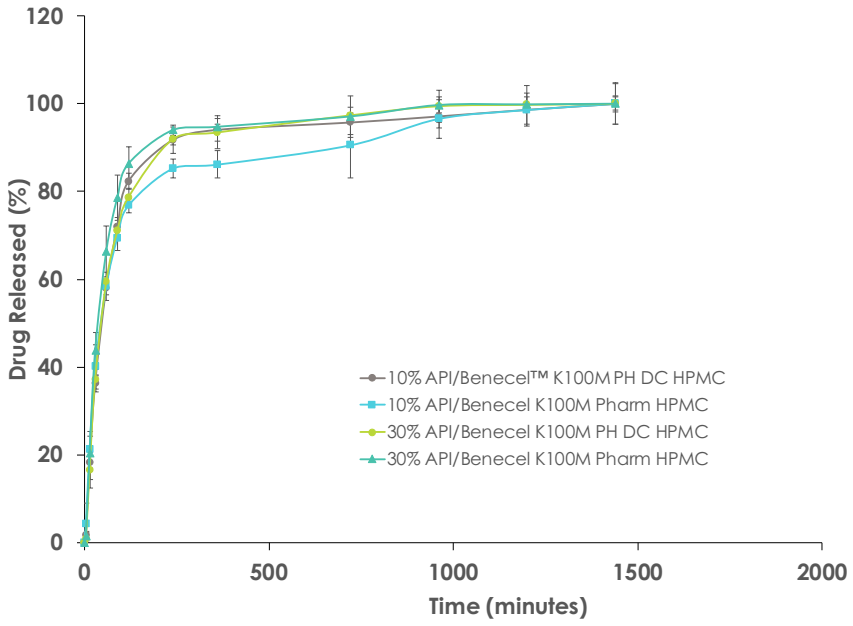
These dissolution results demonstrate similar release profiles when using Benecel K100M PH DC HPMC versus Benecel K100M Pharm HPMC at high and low drug loads of a highly soluble API.

Figure 5: Dissolution Results for Capsules Containing Metformin Mini-tablets with Benecel K4M Pharm or Benecel K4M PH DC



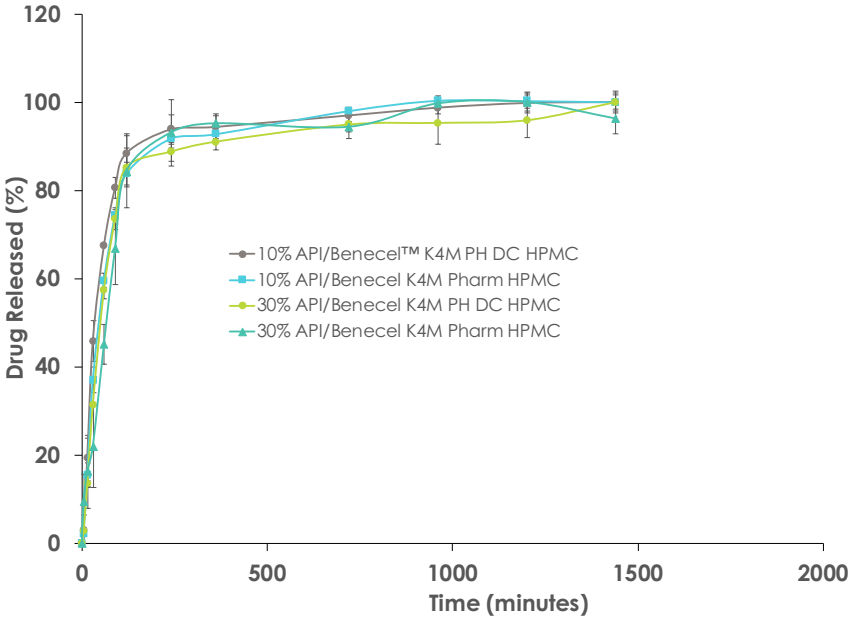
These dissolution results demonstrate similar release profiles when using Benecel K4M PH DC HPMC versus Benecel K4M Pharm HPMC at high and low drug loads of a highly soluble API.

Figure 6: Dissolution Results for Capsules Containing Cetirizine Mini-tablets with Benecel™ K100M Pharm HPMC or Benecel K100M PH DC HPMC



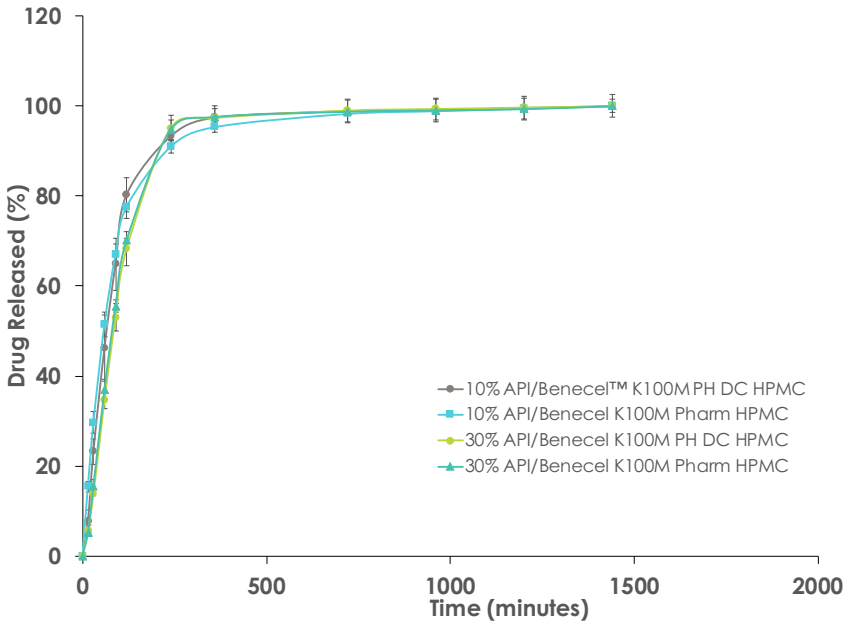
These dissolution results demonstrate similar release profiles when using Benecel K100M PH DC HPMC versus Benecel K100M Pharm HPMC at high and low drug loads of a moderately soluble API.

Figure 7: Dissolution Results for Capsules Containing Cetirizine Mini-tablets with Benecel K4M Pharm HPMC or Benecel K4M PH DC HPMC



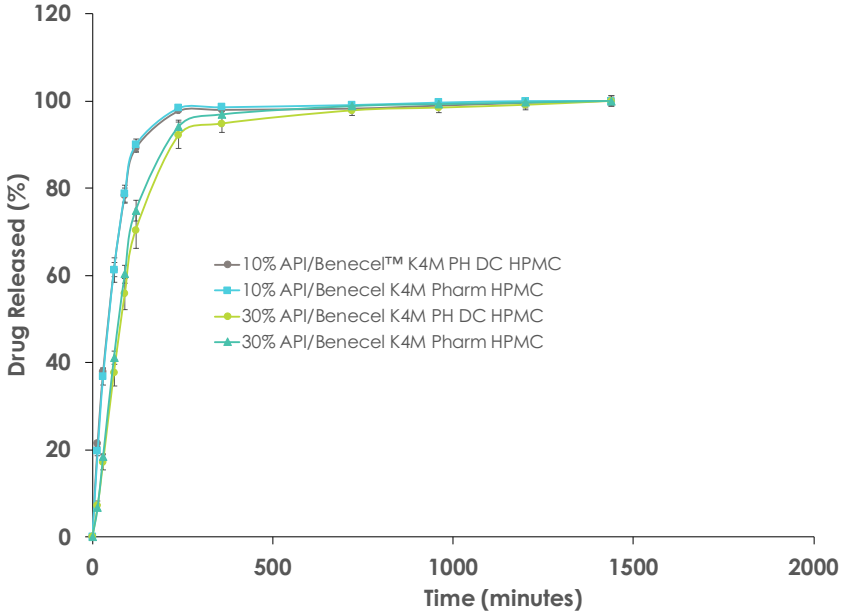
These dissolution results demonstrate similar release profiles when using Benecel K4M PH DC HPMC versus Benecel K4M Pharm HPMC at high and low drug loads of a moderately soluble API.

Figure 8: Dissolution Results for Capsules Containing Theophylline Mini-tablets with Benecel™ K100M Pharm HPMC or Benecel K100M PH DC HPMC



These dissolution results demonstrate similar release profiles when using Benecel K100M PH DC HPMC versus Benecel K100M Pharm HPMC at high and low drug loads of a moderately soluble API.

Figure 9: Dissolution Results for Capsules Containing Theophylline Mini-tablets with Benecel K4M Pharm HPMC or Benecel K4M PH DC HPMC



These dissolution results demonstrate similar release profiles when using Benecel K4M PH DC HPMC versus Benecel K4M Pharm HPMC at high and low drug loads of a moderately soluble API.

Conclusion

Model mini-tablet formulations containing Benecel™ PH DC HPMC exhibited better flowability, less tablet weight variability, comparable or higher tensile strength, and comparable dissolution profiles compared with formulations containing Benecel Pharm HPMC. These results demonstrate the main benefit of using Benecel PH DC HPMC, which is improved flow. Benecel PH DC HPMC offers the additional benefits of improved tablet hardness and decreased tablet weight variability.