Poster:
T1130-04-20

An Improvement Grade of Hypromellose for Industrial Scale CR Tablet Manufacturing

Quyen Schwing, Shao-Yu Chang, Kapish Karan, and Thomas Dürig

Ashland Specialty Ingredients, Wilmington, DE 19808

CONTACT INFORMATION: qvschwing@ashland.com

aaps PharmSci 360

PURPOSE

Hypromellose is the most commonly-used polymer in extended-release tablets, benefiting patients with reduced dosing frequency, improved therapeutic efficacy, and reduced adverse effects. However, a key limitation of commercially-available Hypromellose is its high strain rate sensitivity and variability in high-speed compaction, which results in tablet defects, weak tablets, or slower production rates than commercially desirable. Herein, we describe a novel grade of Hypromellose, Benecel™ HPMC XRF, that mitigates these shortcomings.

METHOD(S)

Standard extended-release tablets:

Benecel™ K100M XRF was used as drug carrier for standard extended-release tablets. The impact of tableting speed on a directly-compression metformin formulation was evaluated at pilot scale. Metformin HCl was wet granulated with sodium CMC. Metformin granules were blended with other ingredients (Table 1) and compressed into 600 mg tablets at 25kN using 11mm round tooling on an Elizabeth-Hata tablet press (38 stations) in production runs at 20 and 40 rpm for 15 minutes on each tablet blend.

Table 1: Metformin tablet formulation composition Standard extended-release tablets

Material	Tablet w/w (%)	Tablet weight (mg)
Intragranular		
Metformin HCl	49.0	294
NaCMC 7HF	3.9	23.4
Extra granular		
HPMC K100M	35.0	210.0
Avicel PH 102	12.0	72.0
Magnesium Stearate	0.1	0.6
Total	100.0	600.0

The breaking force and strain rate sensitivity at each tableting speed were determined from X value at two different speeds using the equation below:

Strain rate sensitivity index (SRS) [1] =

$$100^{*}\frac{Xrpm\ (\text{low speed}) - Xrpm(\text{high speed})}{Xrpm\ (high\ speed)}$$

Where "X" is tablet strength

Bilayer tablets:

For this formulation of dual-release bilayer tablets, sitagliptin and metformin were used as model drugs in immediate and controlled-release layers, respectively. Controlled-release layers were formulated with Benecel™ K100M XRF and competitor K100M CR. The formulations in Table 2 were compressed into oval-shaped bilayer tablets, with a tapped first layer, the second layer compressed at 15, 20, and 25 kN, using a Styl'One Evolution Compaction Simulator.

Table 2: Composition of bilayer tablets

Immediate release layer	W/W (%)	Tablet Wt (mg)
Sitagliptin 50 mg	25	50
Avicel PH 102	70.5	141.0
Polyplasdone™ XL crospovidone	3	6.0
fumed silicas	1	2.0
Mg Stearate	0.5	1.0
Total	100	200.0
Extended-release layer	**W/W (%)**	**Tablet Wt (mg)**
Metformin HCL 500 mg	58.5	500
Benecel™ K100M XRF or Competitor K100M CR	30	256.4
Avicel PH 102	10	85.5
fumed silicas	1	8.5
Mg Stearate	0.5	4.3
Total	100	854.7

Multilayer tablets:

To evaluate the impact of Benecel™ HPMC particle size on interfacial bonding and mechanical strength of the multilayer tablets, tri-layer tablets consisting of a rapidly-disintegrating layer and two sustained-release hydrophilic matrix layers were prepared using 19.0 x 7.6 mm oval tooling on a Styl'One Evolution Compaction Simulator (Table 3).

Table 3: Composition of tri-layer tablets

Layer	Ingredients	Formulation (% w/w)	Tablet Wt (mg)
1 (CR)	Ibuprofen DC	62.5	250
	Benecel™ K4M XRF or XR	30	120
	Microcrystalline cellulose	7.4	29.6
	Mg Stearate	0.1	0.4
	Layer weight	**100.0**	**400**
2 (IR)	Gabapentin	50	50
	Polyplasdone XL-10	10	10
	Microcrystalline cellulose	39.9	39.9
	Mg Stearate	0.1	0.1
	Layer weight	**100**	**100**
3 (CR)	Gabapentin	62.5	250
	Benecel™ K15M XRF or XR	30	120
	Microcrystalline cellulose	7.4	29.6
	Mg Stearate	0.1	0.4
	Layer weight	**100**	**400**

The interfacial bonding strength and interfacial surface of the bilayer and multilayer tablets were measured using an MTS (Modular Tensile System) Universal testing machine and a Nanovea Laser profilometer.

RESULT(S)

Mono-layer Standard extended-release tablets:

Figure 1: consistently higher tablet strength with less variation

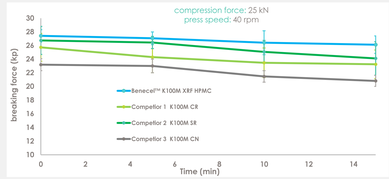
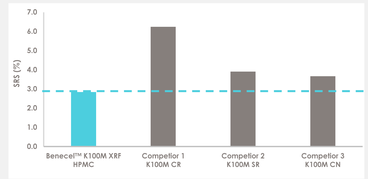


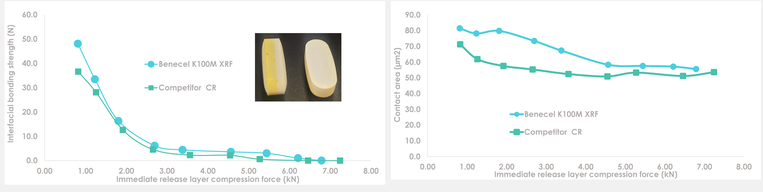
Figure 2: Strain rate sensitivity index (SRS) compared to competitors



For metformin tablets prepared on a compaction simulator, Benecel™ K100M XRF yields stronger tablets than the competitor's Premium CR. The tabletability and compressibility of several metformin tablet formulation blends were observed to be speed dependent. Even at very high tablet press speeds, Benecel™ K100M XRF yielded strong tablets with the lowest strain rate sensitivity, indicating plastic deformation becomes the less dominant mechanism during the compaction process.

Bi-layer tablets:

Figure 3: Interfacial bonding strength (IBS) and surface waviness of bilayer tablets as a function of first layer compression force (CF)



For sitagliptin and metformin bi-layer tablets, tablets incorporating Benecel™ K100M XRF HPMC were less porous than those made with competitor CR grade, indicating Benecel™ K100M XRF HPMC promoted greater particle-particle bonding area. Benecel™ K100M XRF HPMC with smaller particle size enables stronger bilayer tablets than CR. The tablets made with Benecel™ K100M XRF HPMC possessed higher IBS than CR, which is attributed to larger bonding area of Benecel™ K100M XRF HPMC at the interface.

Tri-layer tablets:

Figure 4: Hardness and friability of tri-layer tablets

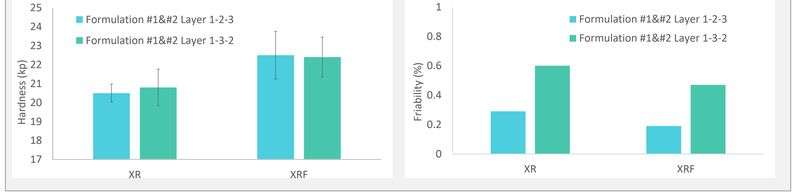
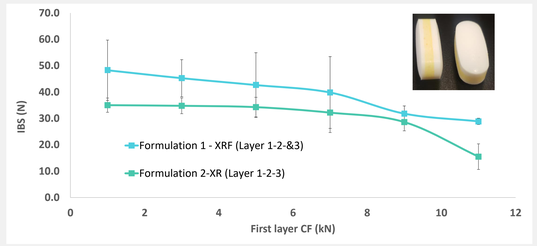


Figure 5: Interfacial bonding strength (IBS) of tri-layer tablets as a function of first layer compression force (CF)



For ibuprofen and gabapentin multilayer tablets, tablets made with Benecel™ K4M and K15M XRF HPMC were harder, less friable, better bonding between layers, indicating Benecel™ K4M and K15M XRF HPMC promoted greater particle-particle bonding area due to smaller particle size. Also, the drug release of gabapentin and ibuprofen with Benecel™ XRF HPMC is slower than the formulation with XR HPMC.

CONCLUSION(S)

Benecel™ K100M XRF demonstrated superior strain rate sensitivity and is therefore recommended as a preferred HPMC for large-scale production. Benecel™ K100M XRF yielded stronger tablets than competitor Hypromellose; smaller particle size of Benecel™ XRF HPMC could create greater interfacial bonding strength and greater tablet strength, compared to competitor CR. Because of its superior strain rate sensitivity and tablet strength, Benecel™ XRF can simplify process development, support tablet production at higher tableting speeds, and ultimately improve process economics.

REFERENCE

1. Jeffrey M. Katz, Ira S. Buckner. Characterization of strain rate sensitivity in pharmaceutical materials using indentation creep analysis. International Journal of pharmaceutics 442 (2013) 13-19.

VISIT ASHLAND'S BOOTH # 719 FOR MORE INFORMATION

Ashland always solving

efficacy usability allure integrity profitability