Demonstrating the Utility of a New High Molecular Weight HPC to Make Smaller Modified Release Tablets

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PURPOSE

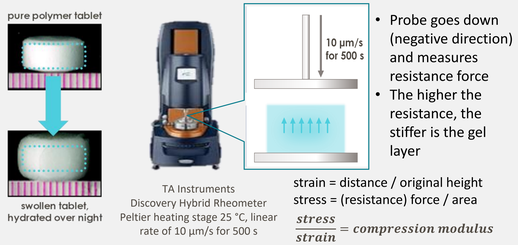
Achieving both immediate and extended release of highly water-soluble drugs like Guaifenesin in a single dosage form may provide many benefits such as reduced dosing frequency, improved efficacy, reduced adverse effects, and improved patient compliance. Broader flexibility to make either a mono- or bi-layer dosage configuration would also reduce production costs. Common hydrophilic matrix forming polymers such as Hydroxypropyl Methylcellulose (HPMC) usually comprise 20- 30% of the weight of a tablet to achieve an acceptable release profile and are subject to the "burst effect" due to poor gel strength of the polymer when used alone. This can make these tablets large, difficult to swallow, and make the drug release less predictable.

OBJECTIVES

In this study the new high molecular weight, controlled release Hydroxypropyl Cellulose (HPC) was used to match the release profile of the bi-layer Mucinex® Maximum Strength and compare to a competitor generic monolayer tablet made by Perrigo® while simultaneously reducing the dimensions of the tablets.

METHODS

The polymer gel strength of the new hydroxypropyl cellulose (HPC), Klucel™ Xtend and hydroxypropyl methylcellulose (HPMC) K100M was determined using a Discovery Hybrid Rheometer (DHR-3) with a Peltier heating stage. Dynamic mechanical analysis was used to test the thermoplasticity of both polymers.



- Probe goes down (negative direction) and measures resistance force
- The higher the resistance, the stiffer is the gel layer

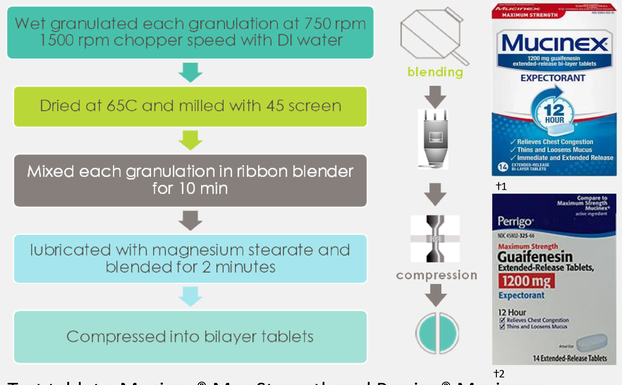
strain = distance / original height

stress = (resistance) force / area

$$\frac{stress}{strain} = compression\ modulus$$

Guaifenesin was wet granulated with Klucel Xtend™ at w/w ratios of 10:90; 15:85; and 20:80 for the controlled release layer, and a ratio of 95:2:5% w/w/w; guaifenesin: Klucel™ ELF: Avicel® PH101 for the immediate release layer respectively. Granules were then dried in an oven at 45°C overnight, then milled with a 45-mesh screen using a Quadro® Comil®. Granules were then mixed with the extra granular materials and compressed into either mono- or bi-layer tablets.

Ingredients	Bilayer tablet formulation			Monolayer tablet formulation	
	Immediate release layer (w/w%)	Controlled release–Blue layer (w/w%)	Wt (mg)	W/W (%)	Wt (mg)
Guaifenesin	95.0		159.1	11.96	159.1
Klucel™ EF hpc	2.0		3.3	0.25	3.3
Microcrystalline cellulose	3.0		5.0	0.38	5.0
				77.77	1034.3
Guaifenesin		90.0	1034.3		
Klucel xtend™ hpc		10.0	114.9	8.64	114.9
Magnesium Stearate			13.3	1.00	13.3
Total	100.0	100.0	**1330.0**	**100.0.0**	**1330.0**



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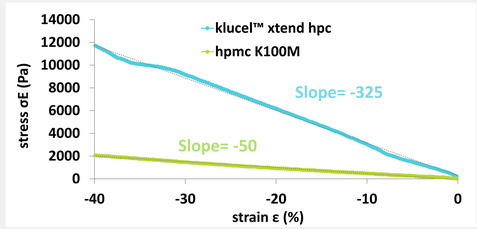
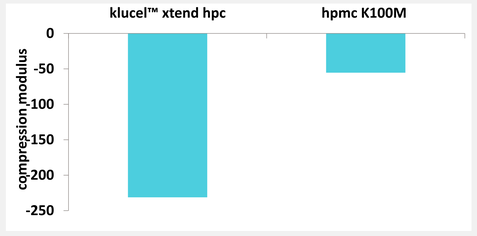
Test tablets, Mucinex® Max Strength and Perrigo® Maximum Strength Guaifenesin Extended Release were characterized for dimensions, hardness, friability and drug release profiles. Dissolution (n=3) of each formulation was conducted in 900 mL of pH 6.8 phosphate buffer 0.050M and maintained at 37°C with USP Apparatus 1 (baskets) at 100 RPM. Samples were taken at 0.25-hr intervals up to 1 hr, then at 1-hr intervals up to 24 hours; quantitation was by online UV detection.

†1- Mucinex® is a registered trademark of Reckitt Benckiser LLC. †2 Perrigo® is a registered trademark of L. Perrigo Company.

RESULTS

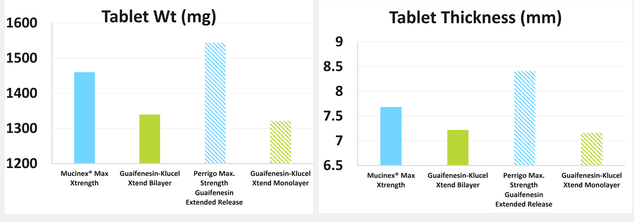
Figure 1: Pure polymer Gel Strength





Pure polymer gel strength characterization showed that the new hydroxypropyl cellulose (HPC) had six times higher gel strength than (HPMC), indicating better-hydrated tablet integrity.

Figure 2: Guaifenesin Tablet characterization



The tablet formulations with Klucel® Xtend yielded significantly lower tablet weight, smaller tablet, and slightly stronger tablets than Mucinex for Bilayer and Perrigo for Monolayer tablets.

Figure 3: (Top) klucel xtend™ Bi-layer Guaifenesin Tablet vs. Mucinex® Max Strength (bottom) klucel xtend™ Monolayer Guaifenesin Tablet vs. Perrigo® Guaifenesin Max Strength *Tablets.*

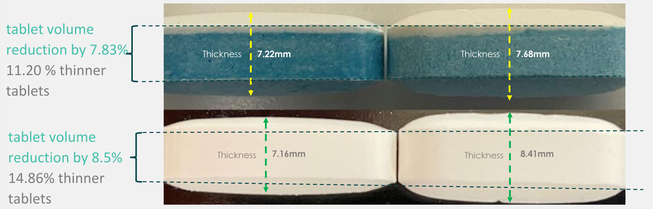
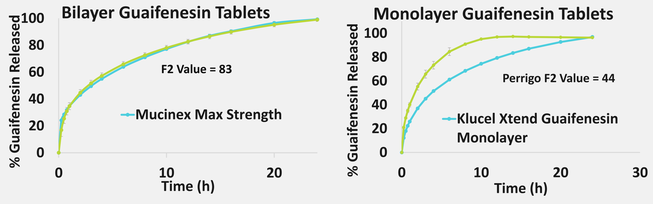


Figure 4: (left) Dissolution of Mucinex® Max Strength vs. klucel xtend™ Bi-Layer Guaifenesin tablet, (right) Dissolution of Perrigo® Max Strength vs. klucel xtend™ Mono-layer Guaifenesin tablet



Guaifenesin tablets with klucel xtend™ hpc showed comparable drug release to marketed Mucinex® Max Strength at similar tablet hardness and better controlled release than Perrigo Guaifenesin tablets.

CONCLUSIONS

Although HPMC is the most widely used polymer for controlled release, one limitation is that HPMC is not suitable for very highly water-soluble drugs. New high molecular weight hydroxypropyl cellulose (HPC) has a higher gel strength, which can limit possible burst effect for delivery of highly-soluble drugs. In addition, the new polymer not only can enable smaller tablet sizes by lower polymer usage level, but also is versatile enough for bi-layer and monolayer formulations, where the release profile becomes more complex and greater control is required.