Evaluating the Versatility of a New High Molecular Weight HPC in Dual Active Diabetic Controlled Release Dosages

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PURPOSE

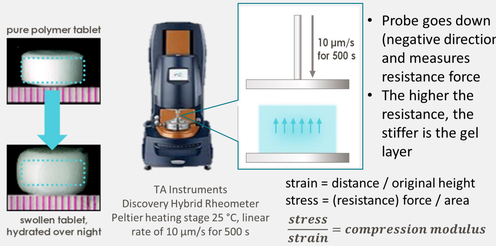
Dual-active controlled-release formulations for Type II diabetes provide several benefits, including reduced dosing frequency, improved glycemic control, and improved patient compliance. Common hydrophilic matrix-forming polymers such as Hydroxypropyl Methylcellulose (HPMC) usually comprise 20- 30% of the weight of a tablet to achieve an acceptable release profile and require intra-granulating binders to prevent the burst effect when dealing with highly water-soluble drugs such as Metformin. This can result in large, hard-to-swallow tablets with complex processing.

OBJECTIVES

This study evaluates the process versatility and the tablet size reduction capabilities of the new high molecular weight hydroxypropyl cellulose, klucel xtend™ to match the release profiles of both, a bi-layer dosage and a metformin HCl core tablet coated with an immediate-release drug substance for dual diabetic drug delivery.

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

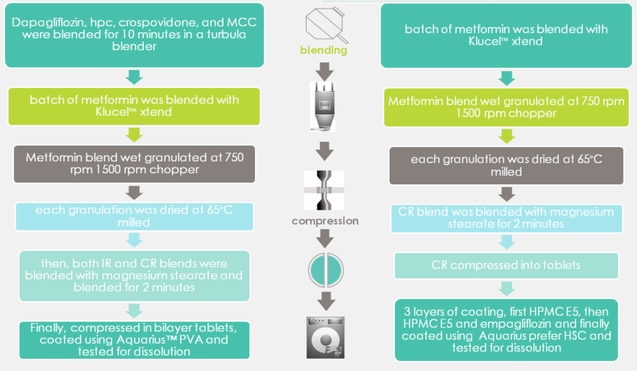
stress = (resistance) force / area

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

Metformin HCl was wet granulated with HPC at a w/w ratio of 85:15. dried in an oven at 65°C overnight, then milled with a 45-mesh Quadro® Comil® screen. Granules were then mixed with extra-granular materials and compressed as either a monolayer core or a bi-layer tablet with the drug dapagliflozin in the IR layer. The monolayer cores were later coated with a barrier layer, followed by a drug layer of empagliflozin using a Freund Vector LDCS® Tablet Coater. Both tablets were then cosmetically film-coated.

Ingredient	Tablet Formulation	
	W/W (%)	Wt (mg)
Immediate release layer		
Dapagliflozin	10	10
Klucel EXF hpc	3	3
Polyplasdone XL-10 crospovidone	10	10
MCC PH 102	76	76
Magnesium stearate	1	1
Total	100	100
Controlled release layer		
Metformin	84	1029
Klucel xtend hpc	15	184
Magnesium stearate	1	12
Total	100	1226
Aquarius™ PVA Film Coating (mg)	***3***	*40*
Total tablet Weight (mg)	**1365**	

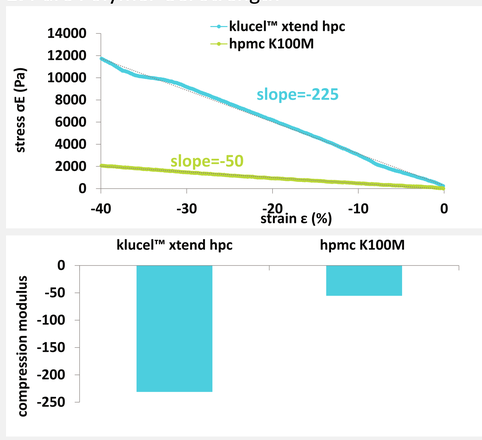
Ingredient	Tablet Formulation	
	W/W (%)	Wt (mg)
Controlled release layer		
Metformin	84	1040
Klucel xtend hpc	15	186
Magnesium stearate	1.0	12
Total	100	1238
Separating layer		
HPMC E5	2	25
Immediate release drug coating		
HPMC E5	1.14	14
empagliflozin	0.86	1
Cosmetic Coating		
Aquarius™ Preferred HSC Film Coating (mg)	*3*	*37*
Total tablet Weight (mg)	**1325**	



All tablets, including the bi-layer Xigduo® XR and core/coated dual drug Synjardy® XR were characterized for dimensions, hardness, friability, and dissolution release profiles. Dissolution of each formulation was conducted in 900 mL of pH 6.8 0.05M phosphate buffer maintained at 37°C with USP Apparatus 1 (baskets) at 100 RPM. Samples were taken at intervals of up to 24 hours; quantitation was by HPLC with UV detection for all three drugs.

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: Comparison of tablet physical properties

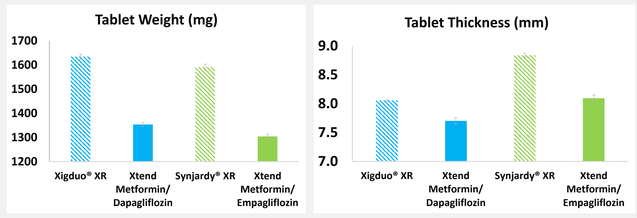


Figure 3: (Top) klucel xtend™ HPC Bi-layer Metformin/ Dapagliflozin; 1000/10 mg CR Tablet vs. Xigduo® XR (bottom) klucel xtend™ HPC Metformin/Empagliflozin; 1000/10 mg CR Tablet vs. Synjardy ®XR Tablet

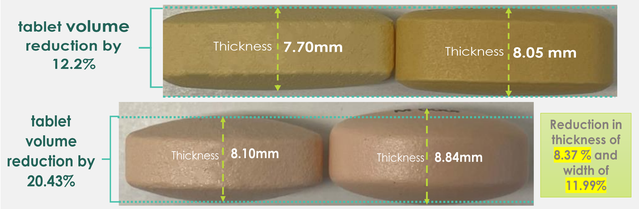
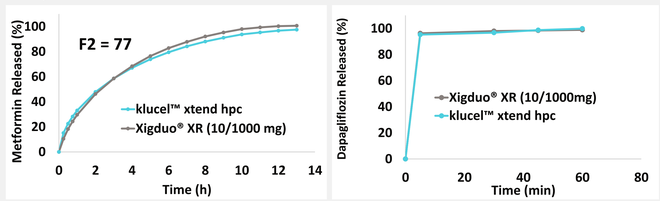
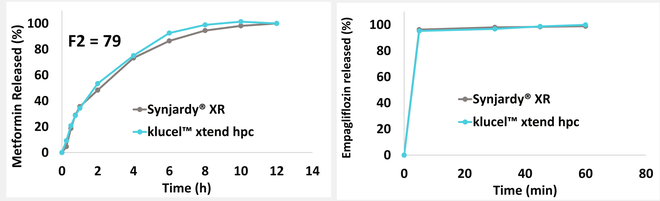


Figure 4: Dissolution profile of dapagliflozin – metformin (10/1000) bilayer tablets



Dapagliflozin-metformin; 10/1000 mg per combination tablets made with klucel xtend™ showed comparable drug release to marketed Xigduo XR at the same dosage with a comparison factor of 77% (fig. 4) with considerably lighter and thinner tablet attributes. Empagliflozin-metformin; 10/1000 mg per combination tablet made with klucel xtend™ showed a comparison factor of 79% (fig. 5) to that of Synjardy XR while also being considerably lighter and thinner.

Figure 5: *D*issolution profile of empagliflozin – metformin (Synjardy® XR 10/1000) tablets



These results were achieved without the need for intergranular polymers such as polyethylene oxide or sodium carboxymethylcellulose in the wet granulation of the Metformin which would have been necessary with the lower gel strength HPMC as the controlled release polymer to prevent the burst effect of such a highly water-soluble drug.

CONCLUSIONS

Although HPMC is the most used polymer for controlled release, it is not suitable by itself for very highly water-soluble drugs like Metformin. New high molecular weight hydroxypropyl cellulose (HPC) has high gel strength, which can limit any burst effect for the delivery of highly soluble drugs. In addition, the new HPC can not only enable smaller tablet sizes by using lower polymer level in the formulation, but also is excellent for bi-layer and coated formulations, where the release profile becomes more complex.

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