Poster:
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Hydrodynamic robustness of New Hydroxypropyl Cellulose grade for modified release matrix systems

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PURPOSE

Extended-release formulations may provide several benefits, including reduced dosing frequency, improved efficacy, reduced adverse effects, and improved patient compliance. Among the various types of extended-release dosage forms, the hydrophilic matrix is the most widely used platform for drug delivery. Hydroxypropyl methylcellulose (HPMC) is the most commonly-used polymer for controlled release oral dosage forms. To overcome limitations of commercially available HPMC grades, a new high molecular weight hydroxypropyl cellulose (HPC) grade, Klucel™ Xtend HPC, has been evaluated its hydrodynamic robustness in modified release matrix systems

METHOD(S)

Polymer gel strengths of the new high molecular weight hydroxypropyl cellulose (HPC) – Klucel™ Xtend HPC and hydroxypropyl methylcellulose (HPMC) K100M were determined using a TA Instruments Discovery Hybrid Rheometer (DHR-3) with Peltier heating stage. Next, the effect of polymer levels in the tablet formulation on drug release were investigated using Ibuprofen and Metformin as model drugs. Table 1 lists the direct-compression tablet formulation used for each drug, with different polymer levels.

Table 1: Direct compression tablet formulations

Ibuprofen Formulations			Metformin formulations		
Ingredient	**High Polymer formulation**	**Low Polymer formulation**	**Ingredient**	**High Polymer formulation**	**Low Polymer formulation**
Ibuprofen	70.0	70.0	**Metformin HCl**	50	65
CR polymer*	20.0	10.0	**CR polymer**	35	20
DC Lactose	8.5	18.5	**Microcrystalline cellulose**	13.5	13.5
fumed silicas	1.0	1.0	**fumed silicas**	1.0	1.0
Magnesium stearate	0.5	0.5	**Magnesium stearate**	0.5	0.5
Total	100.0	100.0	**Total**	100.0	100.0

Table 2: Melt granulation tablet formulations

Formulation ID	Ibuprofen formulation				Metformin Formulation		
Ingredient	**Granulation F1 (%w/w)**	**Tablet F1 (%w/w)**	**Granulation F2 (%w/w)**	**Tablet F2 (%w/w)**	**Ingredient**	**Granultion (%w/w)**	**Tablet formulation (%w/w)**
Ibuprofen	77.78	70.0	87.5	70.0	**Metformin HCl**	80	65
CR Polymer*	22.22	20.0	12.5	10.0	**CR Polymer**	20	20
DC Lactose		8.5		18.5	**Avicel PH 102**		13.5
fumed silicas		1.0		1.0	**fumed silicas**		1.0
Magnesium Stearate		0.5		0.5	**Magnesium Stearate**		0.5
Total	100.0	100.0	100.0	100.0	**Total**		100.0

*CR polymers: Klucel™Xtend HPC and HPMC K100M

For melt granulation, each drug-polymer was extruded using a Leistritz 18 mm twin-screw extruder. The extrudate of each drug was milled and blended with the other ingredients listed in Table 2. Due to the high melting point of metformin HCl and non-extrudable nature of HPMC, only one level of polymer was evaluated for the metformin tablet formulation.

Table 3: Melt granulation process parameters:

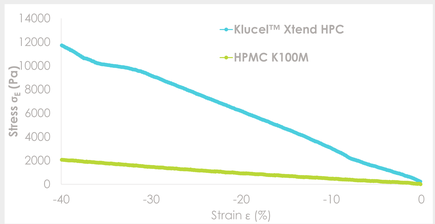
Drug ID	Polymer ID	Extruder Process Temperature (Zone -°C)								Extruder Process Condition	
		1	2	3	4	5	6	7	8	Feeder Speed (rpm)	Extruder Speed (rpm)
Ibuprofen	Klucel™Xtend	30	40	60	80	80	80	80	80	200	200
	HPMC K100M	40	50	100	120	140	140	140	140	100	100
Metformin	Klucel™Xtend	40	80	100	100	120	120	110	110	100	100

Ibuprofen has low melting point (75°C) which can be plasticizer for HME process
The formulation with HPMC can be extruded at high temperature and low feeder speed

Tablets made by direct compression and melt granulation were characterized. Dissolution (n=3) of each formulation was conducted in 900 mL of pH 7.2 phosphate buffer 0.050M (for ibuprofen tablets) and pH 6.8 phosphate buffer 0.05M (for metformin tablets) maintained at 37°C with USP Apparatus 1 (baskets) at 100 RPM. Samples were taken at 0.25 h intervals up to 1 h, then at 1 h intervals to 24 hours; quantitation was by online UV detection.

RESULT(S)

Figure 1: Pure polymer tablet gel strength



Pure polymer characterization showed that the new high molecular weight hydroxypropyl cellulose (HPC) has much higher gel strength (53.3%) than hydroxypropyl methylcellulose (HPMC) K100M, indicating that the , Klucel™Xtend HPC can maintain better hydrated tablet integrity than hydroxypropyl methylcellulose (HPMC).

Figure 2 & 3: Tablet Strength and Dissolution of Direct Compression Ibuprofen tablets in Phosphate buffer pH 7.2

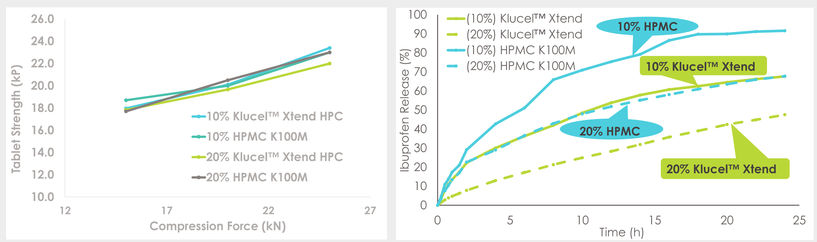
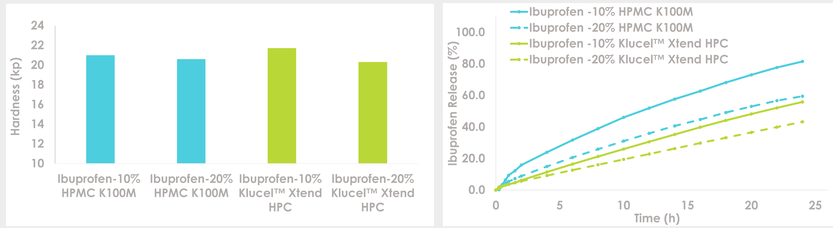
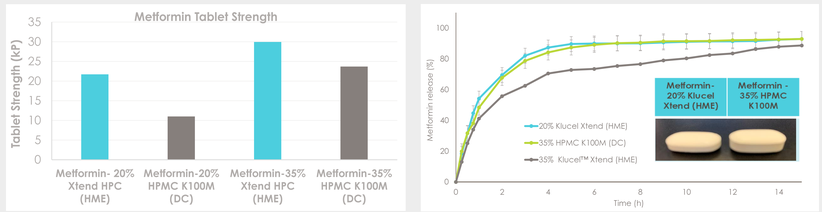


Figure 4 & 5: Tablet Strength and Dissolution of HME Ibuprofen tablets in Phos. buffer pH 7.5



For Ibuprofen tablet formulations made by both direct compression and melt granulation, the tablet formulation with the Klucel™ Xtend HPC grade has similar tablet strength to the formulation with HPMC. However, the tablet formulations with the Klucel™ Xtend HPC have slower drug release than the tablets with HPMC K100M. Due to the greater gel strength, ibuprofen tablets with 10% of Klucel™ Xtend HPC grade show similar drug release profiles to the 20% HPMC formulation.

Figure 6 & 7: Tablet Strength and Dissolution of Metformin tablets in Phosphate buffer pH 6.8



For metformin tablet formulations, direct compression formulations with both polymers also had similar tablet hardness. However, the Klucel™ Xtend HPC tablets have better controlled-release profiles than the HPMC tablets. Due to non-extrudable nature and high melting point of metformin, only 20% polymer can be used for this comparison between two polymers. As a results, the melt granulation tablet formulation with 20% Klucel™ Xtend HPC yielded much harder tablets and slower drug release than the formulation with HPMC.

CONCLUSION(S)

Although HPMC is the most commonly-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) grade, Klucel™ Xtend HPC, has high gel strength, which can limit possible burst effect for delivery of highly-soluble drugs. In addition, the , Klucel™ Xtend HPC not only can enable smaller tablet sizes by usage of lower polymer level in the formulation, but also is excellent for hot melt extrusion or continuous processing technologies.

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