

PTR-086

Controlling the Release of a High Dose Highly Soluble Drug by Hot Melt Extrusion with Cellulose Ethers

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Introduction

Delivering high doses of highly soluble actives in matrix tablets is challenging as it necessitates the minimum addition of release controlling excipients to limit tablet size for ease of swallowing. Typically maximum weights for swallowable tablets range from 800 to 1000 mg. However, the density of the granules and final tablet also have to be considered when attempting to minimize unit dose volume. In this study, highly soluble Metformin Hydrochloride (METF) was chosen as a model high dose compound (1500 to 3000 mg daily). Previous work has demonstrated the feasibility of using hot melt extrusion (HME) as an alternative to wet granulation (WG) for developing controlled release formulations of high dose, high soluble drugs. In this study, we investigate using thermoplastic Klucel™ hydroxypropylcellulose (HPC) and Aqualon™ ethylcellulose (EC), as hydrophilic and hydrophobic controlled release polymers for HME.

Experimental Methods

Hot Melt Extrusion. 1.5 kg batches comprising of blends of METF, the polymer (Klucel HPC HF and/or Aqualon EC N10), and the plasticizer stearic acid were hot melt extruded using the Leistritz ZSE 18HP counter-rotating twin screw extruder without a die (Figure 1). A screw and feed speed of 150 rpm was used. The processing temperature for the different barrel zones is shown in Table 1. The extrudates were milled and lubricated with 0.25% magnesium stearate. 1000 mg tablets were precompressed at 3 kN and then compressed at 15 kN on an instrumented Manesty Beta Press equipped with 0.750 x 0.343" caplet tooling. Dissolution was done in an USP apparatus I with 6.8 pH phosphate buffer at 37°C.

Figure 1. Extruder Setup



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Table 1. Extruder settings

	Material			Temperature (°C)							% Load on Motor
	% METF	% Klucel™ HPC HF	% Aqualon™ EC N10	Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7-8	
F1	75	0	20	60	80	95	115	120	120	120	27
F2	75	3	17	60	80	95	115	120	120	120	34
F3	75	25	0	110	140	145	160	160	160	155	40
F4	70	0	29	60	80	95	115	120	120	120	20
F5	70	29	0	60	80	95	115	120	120	120	33

Wet granulation. 1 kg batches comprising of 75% METF, 29% polymer, and 1% stearic acid were wet granulated in a high shear mixer using an 80% ethanol aqueous solution. After drying, milling, and lubrication, 400 mg tablets were precompressed at 3 kN and then compressed at 15 kN on an instrumented Manesty Beta Press with the flat face, beveled edge (FFBE) tooling.

Tablet Erosion with the Scanning Electron Microscope (SEM). Tablets were harvested at the end of the 24-hour dissolution study. The wet tablets were flash-frozen in liquid nitrogen and lyophilized overnight. The dried tablets were then flash-frozen in liquid nitrogen and fractured with a razor. The fractured tablet face was coated in Au/Pd for imaging using the Hitachi S-4000 FE-SEM at 500X magnification.

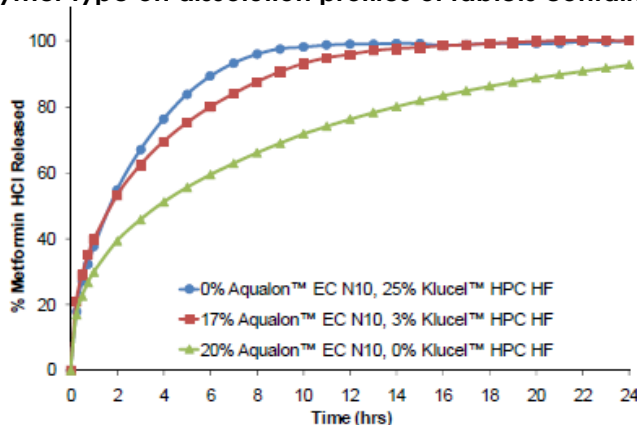
Materials

1. Metformin HCl, marketed by Ria International, NJ
2. Klucel hydroxypropylcellulose (HPC), marketed by Ashland, Wilmington, DE
3. Aqualon ethylcellulose (EC), marketed by Ashland, Wilmington, DE
4. Avicel* microcrystalline cellulose (MCC) PH 102, marketed by FMC BioPolymer
5. HyQual* magnesium stearate, marketed by Mallinckrodt Inc., a division of Tyco International, St. Louis, MO

Results and Discussion

Formulations comprising of Aqualon EC N10 Pharm and Klucel HPC HF Pharm were easily processed by hot melt extrusion. Generally, the formulations containing Aqualon EC required a maximum processing temperature of 120°C. The Klucel HPC formulation needed up to 160°C (Table 1). As shown in Figure 2, hot melt extrusion was highly effective in retarding the drug release of 750 mg Metformin tablet over a period of 12 to 24 hours. By using 25% Klucel HPC HF, a faster dissolution profile was achieved with 100% released in approximately 10 hours. Whilst when 20% Aqualon EC N10 was used, 100% release was achieved in approximately 24 hours.

Figure 2. Effect of polymer type on dissolution profiles of tablets containing 75% Metformin HCl



Intermediate release profiles can be achieved by using blends of Klucel™ HPC and Aqualon™ EC. In such formulations, Klucel HPC acts as a channel former as shown in the SEM images (Figure 3). The addition of Klucel HPC into the Aqualon EC matrix resulted in the formation of larger and more numerous channels in the tablet matrix during dissolution resulting in faster drug release. Additionally, blends of Klucel HPC and Aqualon EC also resulted in stronger tablets (Figure 4).

Figure 3. SEM images of the cross-section of METF tablets at 0 and 24 hours of dissolution testing

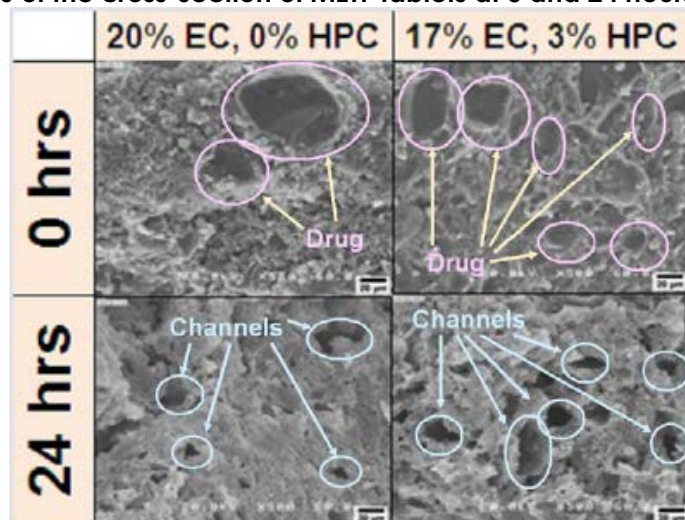
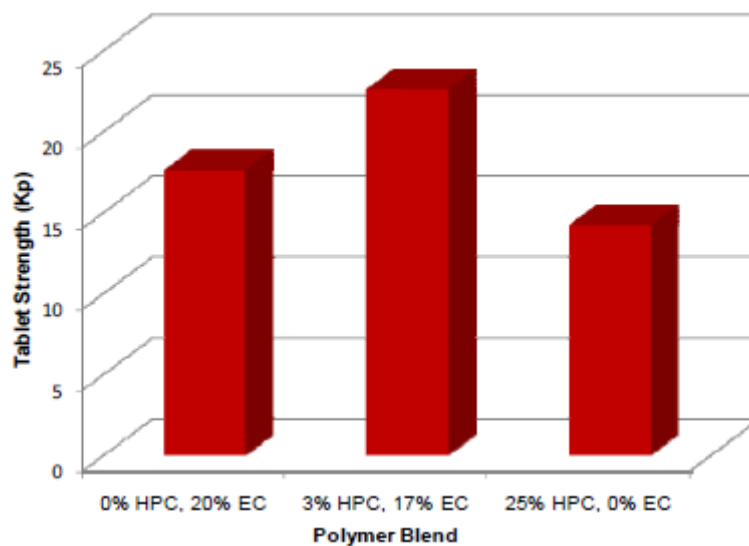


Figure 4. Tablet hardness of 75% METF tablets



Extrusion processing, as compared to wet granulation, had a significant retarding effect on drug release (Figure 5). Using wet granulation, 100% drug release was achieved in 2 hours for Aqualon™ EC and 6 hours for Klucel™ HPC. In contrast, extrusion processing resulted in a 100% drug release at 16 hours for Aqualon EC and 10 hours for Klucel HPC. Tablets prepared from extruded granules were significantly stronger as compared to those prepared with wet granulation (Figure 6).

Figure 5. Effect of unit process (wet granulation vs. hot melt extrusion) on dissolution profiles of tablets containing 70% Metformin HCl

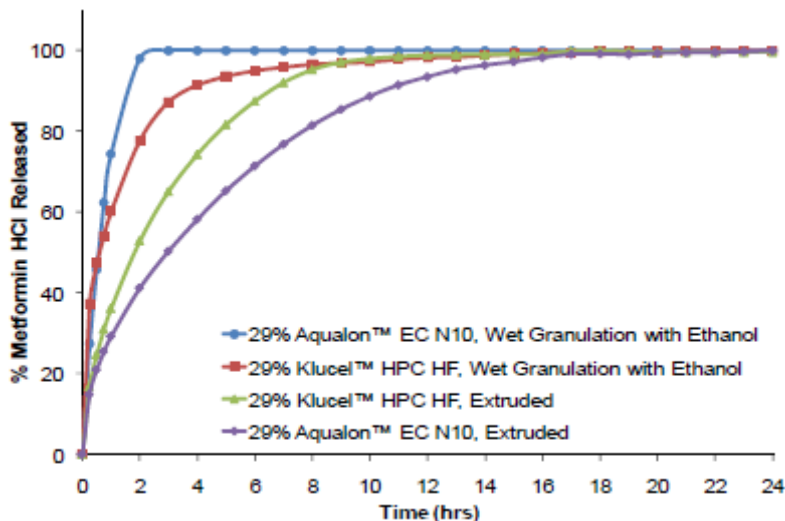
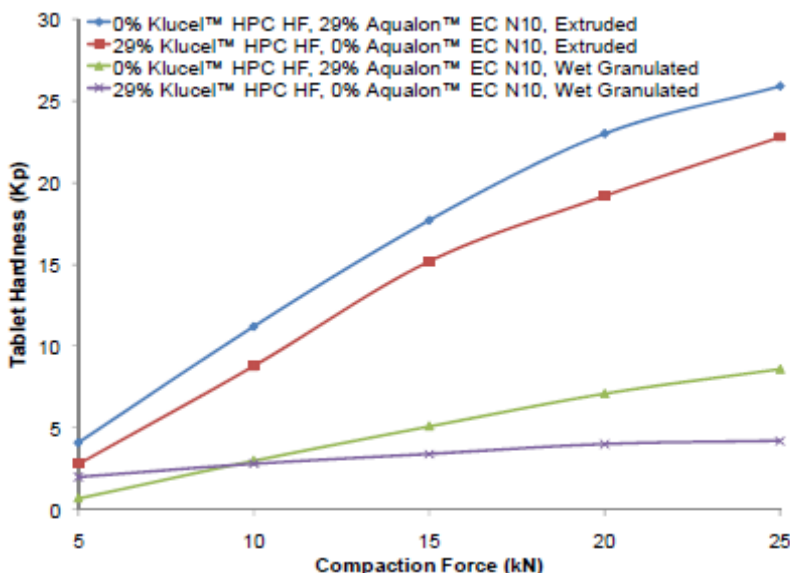


Figure 6. Effect of unit process (wet granulation vs. hot melt extrusion) on tablet strength of 70% METF tablets



Conclusion

Aqualon™ EC and Klucel™ HPC are efficient thermoplastic release retarding agents that enable the delivery of high doses of highly soluble Metformin Hydrochloride (75% drug loading) over a period of 12 to 24 hours. Hot melt extrusion using both polymers was found to result in greater release retardation and improved tableting and mechanical properties as compared to wet granulation. Drug release profiles can be modulated by using Klucel HPC for faster release, Aqualon EC for slower release, or blends of the two for intermediate release.

Reference

1. G. Gusler, J. Gorsline, et. al. Pharmacokinetics of metformin gastric-retentive tablets in healthy volunteers, J Clin, Pharmacol. 2001; 41: 655-661.