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Are Cellulosic Controlled Release Technologies Vulnerable to Dose Dumping in Ethanolic Dissolution Media?

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Introduction

Alcohol dose dumping can pose a significant safety and efficacy issue for certain modified release products. In 2005, the FDA issued a public health advisory on Palladone* (hydromorphone hydrochloride, extended release capsules), a potent narcotic painkiller, due to a 6-fold increase in the peak plasma hydromorphone concentration in healthy subjects co-ingesting Palladone* with 240 mL (8 ounces) of 40% (80 proof) alcohol (1). Alcohol dose dumping can occur due to the solubility of the pharmaceutical excipients, the solubility of the drug, and the formulation's drug release mechanism (2). Cellulosics are the most commonly used polymers in pharmaceutical controlled release technologies. The ethanol vulnerability of tablets made with Klucel™ hydroxypropylcellulose (HPC), Natrosol™ hydroxyethylcellulose (HEC), and Benecel™ hypromellose (HPMC) were investigated with the highly soluble drug Metformin Hydrochloride (METF) and low soluble drug Glipizide (GLIP). Additionally, Aquarius™ SRX coating systems were also evaluated.

Experimental Methods

Wet granulation. 1 kg batches comprising of 25% Metformin Hydrochloride (METF), 30% polymer (Natrosol HEC, Benecel HPMC, or Klucel HPC), and 44.5% MCC were wet granulated in a high shear mixer. After drying, milling, and lubrication, 400 mg tablets were compressed on an instrumented Manesty* Beta Press at 15kN with the flat face, beveled edge (FFBE) tooling. Glipizide (GLIP) tablets were made using the same procedure and conditions.

Direct Compression. 1 kg batches comprising of 25% METF, 30% polymer, and 44.5% MCC were lubricated and pressed into 400 mg tablets at 15kN with the flat face, beveled edge (FFBE) tooling.

Hot Melt Extrusion. 1 kg batch comprising of 60% METF, 30% Klucel HPC HF, and 10% Stearic acid were hot melt extruded at a processing temperature of 145°C and screw speed of 150 rpm using the Leistritz* ZSE 18HP counter-rotating twin screw extruder. The extruded strands were milled, lubricated, and pressed into 1000 mg tablets at 15kN with the 0.750 x 0.343" caplet tooling.

EC Coated Tablets. The METF matrix tablets were coated with a Vector HI Coater at pan speed of 18 rpm, atomizing air pressure of 1 bar, and with a 10.5% of Aquarius SRX (an EC based coating) solution (345 cps) pumped at a feed rate of 11 ml/min. The inlet air temperature was between 75 and 80°C and bed temperature ~ 40°C. The tablets were coated to a 4% weight gain.

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Dissolution testing. The tests were done in a USP apparatus I at 100 rpm. For the aqueous, the METF tablets were put in an 0.1N HCl media (0.1N HCl + 2% SLS for GLIP) for 2 hrs and then transferred to a 6.8 pH phosphate buffer (7.5 pH phosphate buffer + 0.1% Tween 80 for GLIP) for 22 hrs. Similarly for the alcohol media, the METF tablets were put in 60% 0.1N HCl and 40% ethanol media (40% ethanol and 60% of 0.1N HCl + 2% SLS for GLIP) for 2 hrs and then transferred to a 6.8 pH phosphate buffer (7.5 pH phosphate buffer + 0.1% Tween 80 for GLIP) for 22 hrs.

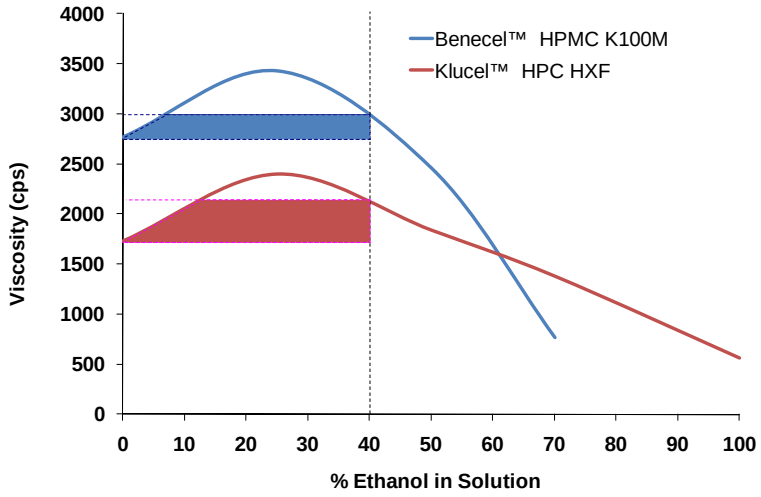
Materials

1. Metformin HCl, marketed by Ria International, NJ.
2. Glipizide, by Ria International, NJ.
3. Klucel™ hydroxypropylcellulose (HPC), marketed by Ashland Incorporated, Wilmington, DE
4. Benecel™ hypromellose (HPMC), marketed by Ashland Incorporated, Wilmington, DE
5. Natrosol™ hydroxyethylcellulose (HEC), marketed by Ashland Incorporated, Wilmington, DE
6. Aquarius™ SRX coating system, marketed by Ashland Incorporated, Wilmington, DE
7. Avicel® PH101 or PH102 Microcrystalline cellulose (MCC), marketed by FMC
8. HyQual® magnesium stearate, NF, marketed by Mallinckrodt Inc., a Division of Tyco International, St. Louis, MO.

Results and Discussion

Matrix tablets comprising of Klucel HPC and Benecel HPMC of various MW showed no evidence of dose dumping. The dissolution rate in hydroalcoholic media was slightly slower than in aqueous dissolution media. The slower dissolution rate can be attributed to the fact that the viscosity of Klucel HPC and Benecel HPMC can be higher in an ethanol/water cosolvent system as compared to a purely aqueous medium (Figure 1).

Figure 1. Hydroalchololic viscosity of polymer solution. The viscosity of 1% polymer (Benecel HPMC K100M and Klucel HPC HXF) in a water/ethanol solution was measured using the Brookfield DV viscometer with spindle 4 at 60 rpm for Benecel HPMC and 20 rpm for Klucel HPC at 22°C.



Higher gel strength and slower erosion rates (Figure 2 and 3) can be expected.

Figure 2. Effect of polymer type. Metformin HCl tablets containing the three types of polymers Natrosol™ HEC, Benecel™ HPMC, or Klucel™ HPC did not show dose dumping in ethanolic media. In fact, the drug release was slightly slower in ethanolic media.

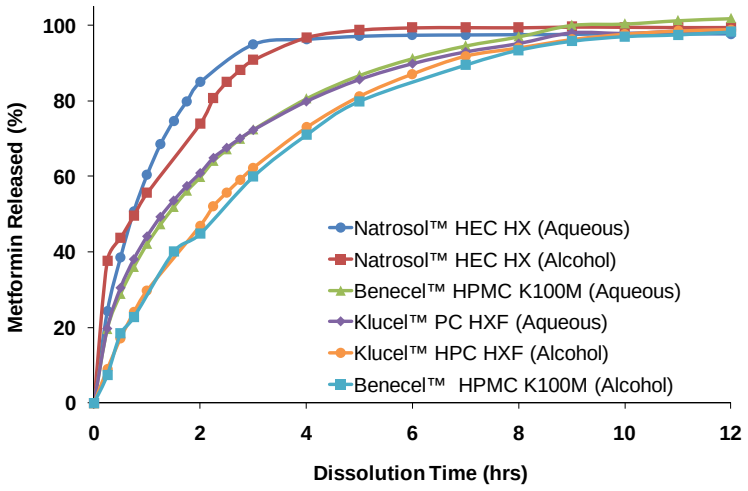
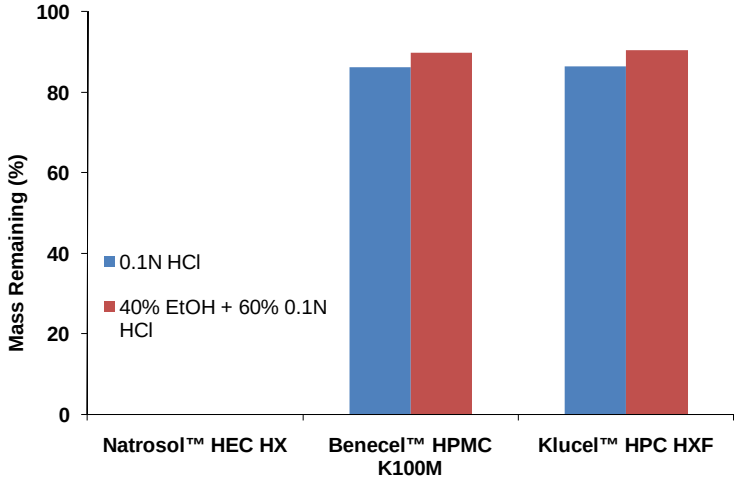


Figure 3. Effect of polymer type: tablet erosion. Metformin HCl tablets containing Natrosol HEC disintegrated after 2 hours in both simulated stomach fluid and ethanolic media. However the tablets made with Benecel HPMC and Klucel HPC had slight erosion and showed no difference in both media.



*After 2 hours in Dissolution Media (USP Apparatus II, 100rpm)

Figures 4, 5, and 6 show that for Klucel™ HPC and Benecel™ HPMC, factors such as processing (direct compression, wet granulation, or hot melt extrusion), molecular weight of polymer, and drug solubility (highly soluble Metformin Hydrochloride versus low soluble Glipizide) did not precipitate dose dumping. In all cases, a moderate decrease in release was observed.

Figure 4. Effect of process type. Metformin HCl tablets containing Klucel HPC HXF were made by wet granulation, direct compression, and hot melt extrusion. The tablets showed slightly slower drug release in ethanolic media in comparison to aqueous dissolution media. There was no evidence of dose dumping. (Note that the hot melt extruded formula had a higher (60% Metformin HCl) dose of active as opposed to the wet granulated and direct compression formula (25% Metformin HCl)).

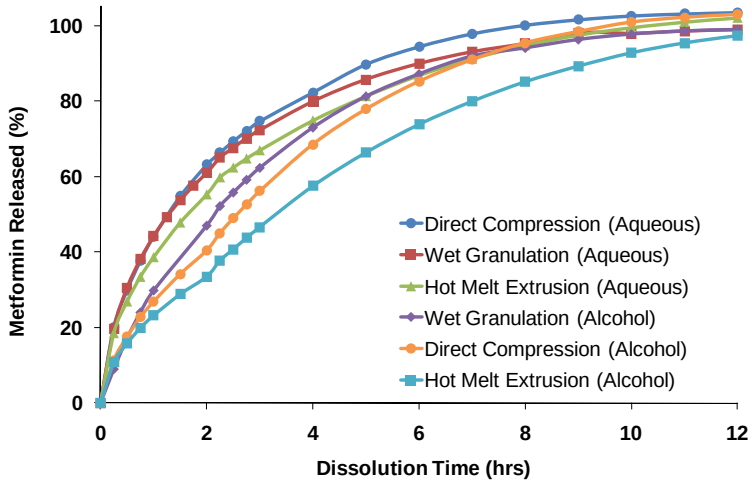


Figure 5. Effect of polymer molecular weight. Metformin HCl tablets containing Klucel HPC having a molecular weight of 1150 kDa (HXF), 850 kDa (MXF), and 370 kDa (GXF) showed the same trend. The drug release was slightly slower in ethanolic media with no evidence of dose dumping.

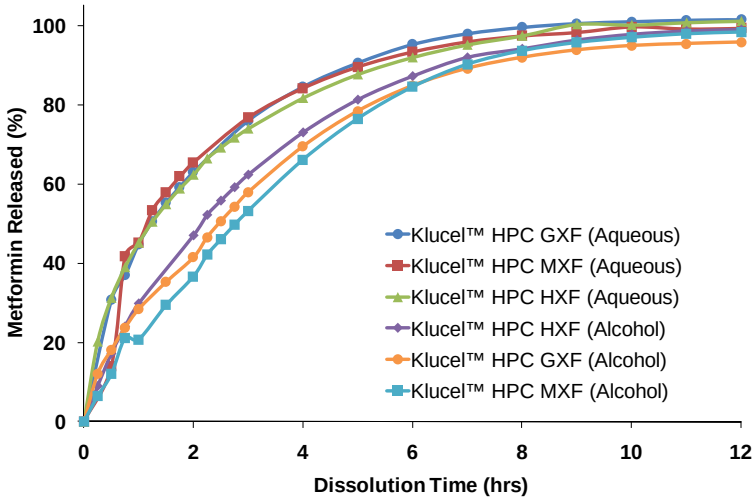
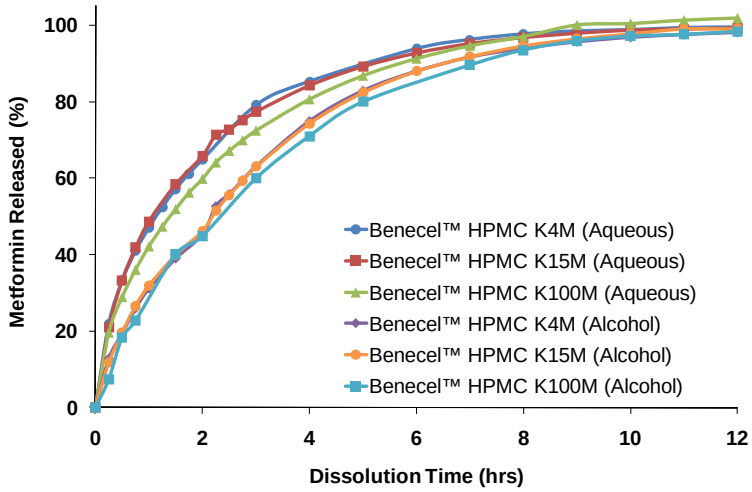
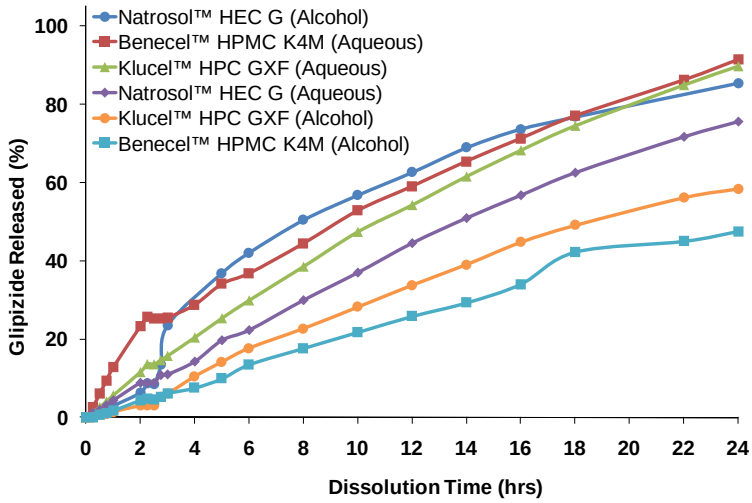


Figure 6. Effect of polymer molecular weight. Metformin HCl tablets containing Benecel™ HPMC having a molecular weight of 1220 kDa (K100M), 771 kDa (K15M), and 533 kDa (K4M) showed the same trend. The drug release was not faster in ethanolic media.



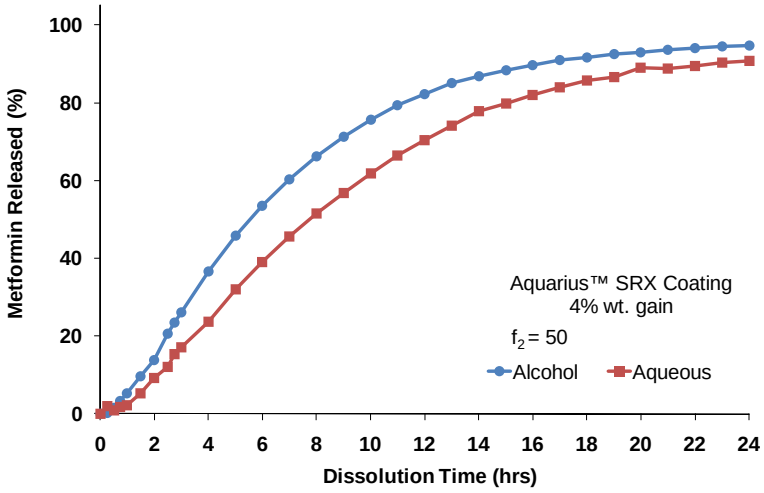
In the case of Natrosol™ HEC, only the highest molecular weight grade, Natrosol HEC 250HX was robust. Lower molecular weight grades resulted in dose dumping (Figure 7). This can be attributed to the negligible solubility of Natrosol HEC in ethanolic solutions.

Figure 7. Effect of polymer molecular weight. Glipizide tablets containing Benecel HPMC or Klucel HPC did not show faster drug release in ethanolic media.



For matrix tablets coated with Aquarius™ SRX coating systems, a small increase in drug release and membrane permeability in hydroalcoholic media was observed. However, there was no significant evidence of dose dumping ($f_2 \geq 50$) (Figure 8).

Figure 8. Effect of Aquarius SRX coating systems. Metformin tablets coated with Aquarius SRX coating systems showed a small increase in drug release with no significant evidence of dose dumping.



Conclusion

The Klucel™ HPC and Benecel™ HPMC based matrix formulations of soluble and insoluble drugs as well as matrix tablets coated with Aquarius SRX coating systems had no tendency to dose dump and showed the robustness of these types of controlled release systems. For Klucel HPC and Benecel HPMC, the higher viscosity in a blend of ethanol and water results in stronger gels with slower erosion rates. The inherent hydroalcohol solubility properties of these polymers guards against any potential dose dumping. In this light, the concern around alcohol dose dumping seems negligible for these polymers.

References

1. FDA Alert for Healthcare Professionals (July 2005): Hydromorphone Hydrochloride Extended-Release Capsules (marketed as Palladone™). http://www.fda.gov/cder/drug/InfoSheets/HCP/hydromorphoneHCP.pdf
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