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Invulnerability of Cellulosic Controlled Release Technologies to Alcohol Induced Dose Dumping

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Introduction

Alcohol dose dumping can pose a significant safety and efficacy issue for certain modified release products. In 2005, 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* hydromorphone hydrochloride with 240 mL (8 ounces) or 40% (80 proof) alcohol (1). Alcohol dose dumping could be 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 matrix tablets made with Klucel™ hydroxypropylcellulose (HPC), Natrosol™ hydroxyethylcellulose (HEC), and Benecel™ hypromellose (HPMC) was investigated with the highly soluble drug Metformin Hydrochloride (METF).

Experimental Methods

Wet granulation. 1 kg batches comprising of 25% METF, 30% polymer (Natrosol HEC 250 HX Pharm, Benecel HPMC K100M Pharm, or Klucel HPC HXF Pharm), and 44.5% microcrystalline cellulose were wet granulated in a high shear mixer. After drying, milling, and lubrication with 0.5% magnesium stearate, 400 mg tablets were compressed on an instrumented Manesty Beta Press at 15kN with the flat face, beveled edge (FFBE) tooling.

Dissolution testing. The 24-hour dissolution testing of METF tablets was carried out in aqueous as well as hydroalcoholic media using apparatus I. The tablets were exposed to 0.1N HCl or a mixture of 60% 0.1N HCl and 40% ethanol for a period of 2 hours followed by 6.8 pH phosphate buffer up to 24 hours.

Gel Matrix Morphology.

Scanning Electron Microscopy (SEM). Tablets were harvested at 0, 2, 5, and 8 hours during dissolution testing. 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 1000X magnification.

Tablet Swelling Dynamics (Hirox microscope). Tablets were placed in aqueous acidic or hydroalcoholic dissolution medium for 2 hours and titrated with 0.2M tribasic sodium phosphate to 6.8 pH at 2 hours. The Hirox KH-7700 digital microscope was used to continuously image the behavior of the tablets in the dissolution media over time. 1600 x 1200 pixel resolution images were collected every 8 seconds for the first 2 hours and every 40 seconds thereafter.

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Rheology (Gel Strength). The METF tablets were placed in the aqueous and alcoholic dissolution media for 2 hours at 37°C. The deformation of the gel layer formed on the tablet was analyzed using a TA instruments rheometer (Model# AR-G2) in compression mode and an aluminum probe with a diameter of 6.4 mm. The compression stress (resistance of the gel layer) applied to the tablet was plotted against the true compression strain (the degree of gel layer deformation).

Materials

1. Metformin HCl, marketed by Ria International, NJ
2. Klucel™ HPC, marketed by Ashland, Wilmington, DE
3. Natrosol™ HEC, marketed by Ashland, Wilmington, DE
4. Benecel™ HPMC, marketed by Ashland, Wilmington, DE
5. Avicel® MCC microcrystalline cellulose PH 102, marketed by FMC BioPolymer
6. HyQual® magnesium stearate, marketed by Mallinckrodt Inc., a division of Tyco International, St. Louis, MO

Results and Discussion

Matrix tablets comprising Benecel HPMC K100M and Klucel HPC HXF were invulnerable to dose dumping in hydroalcoholic dissolution media. In fact, the dissolution rate in hydroalcoholic media was slightly slower than in aqueous dissolution media (Figure 1). This can be attributed to the fact that Klucel HPC and Benecel HPMC viscosity is highest in alcohol and water co-solvent systems (Figure 2). This results in slower erosion rates. However for Natrosol HEC 250 HX, rapid release was observed in the first 2 hours. This can be attributed to the negligible solubility of HEC in hydroalcoholic solutions.

Figure 1. Effect of polymer type on drug release in aqueous and alcoholic media

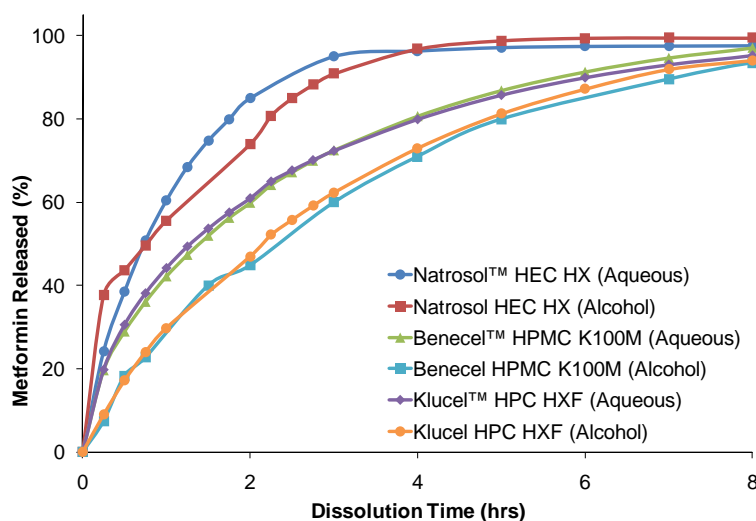
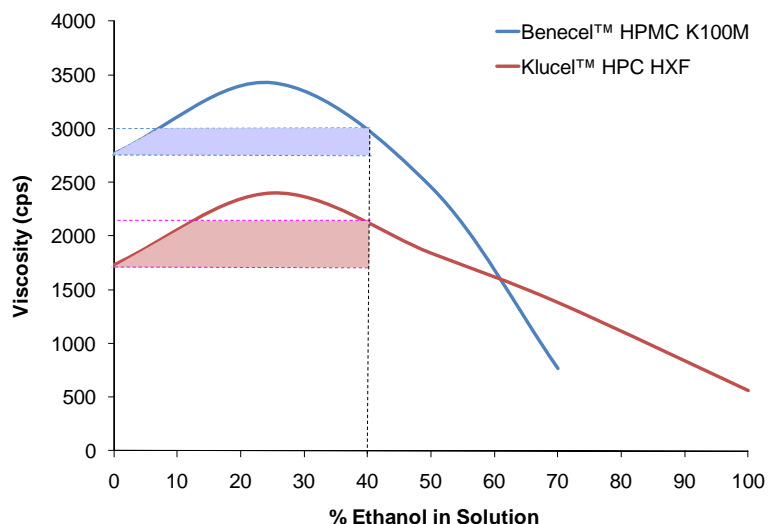
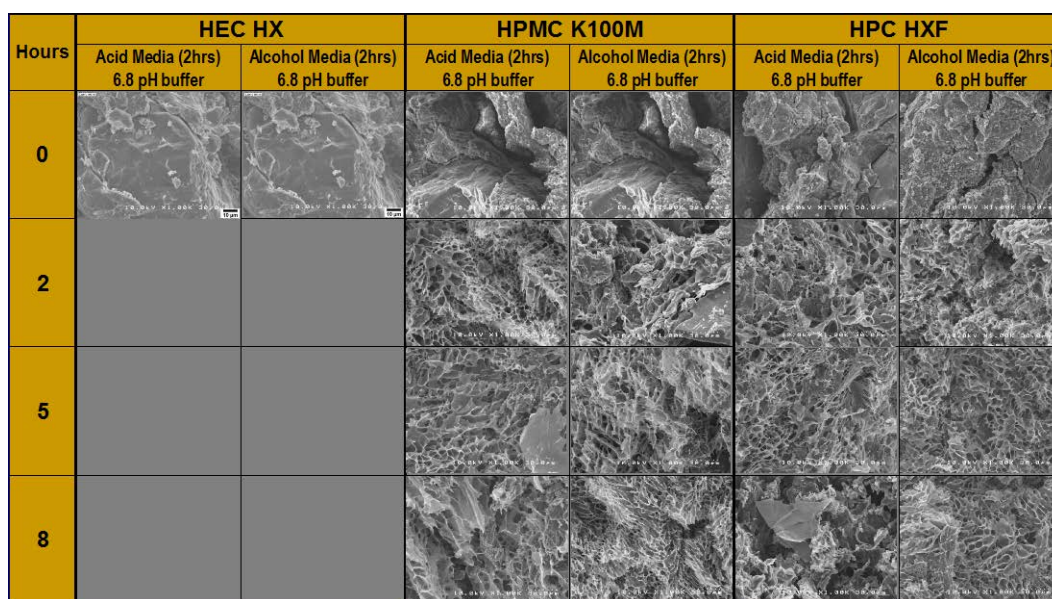


Figure 2. Hydroethanolic viscosity of polymer solutions



The Klucel HPC and Benecel HPMC dissolution results are further supported by the SEM and digital microscope data. As seen in Figure 3, Klucel HPC and Benecel HPMC tablets exposed to hydroalcoholic media maintained a tighter gel network and pore structure for 8 hours whilst the tablets exposed to aqueous media showed significantly larger voids in the gel structure after 8 hours. The higher porosity in the gel networks are indicative of larger amounts of water diffusing into the matrix tablets resulting in greater tablet swelling. This translates into faster drug release.

Figure 3. Tablet erosion



The greater extent of swelling of Klucel HPC and Benecel HPMC tablets, when exposed to aqueous as opposed to hydroalcoholic media for the first 2 hours, was confirmed by digital microscopy (Figure 4). This is also consistent with the significantly higher gel strengths of the Klucel HPC and Benecel HPMC tablets exposed to hydroalcoholic media for 2 hours (Figure 5).

Figure 4. Tablet Swelling

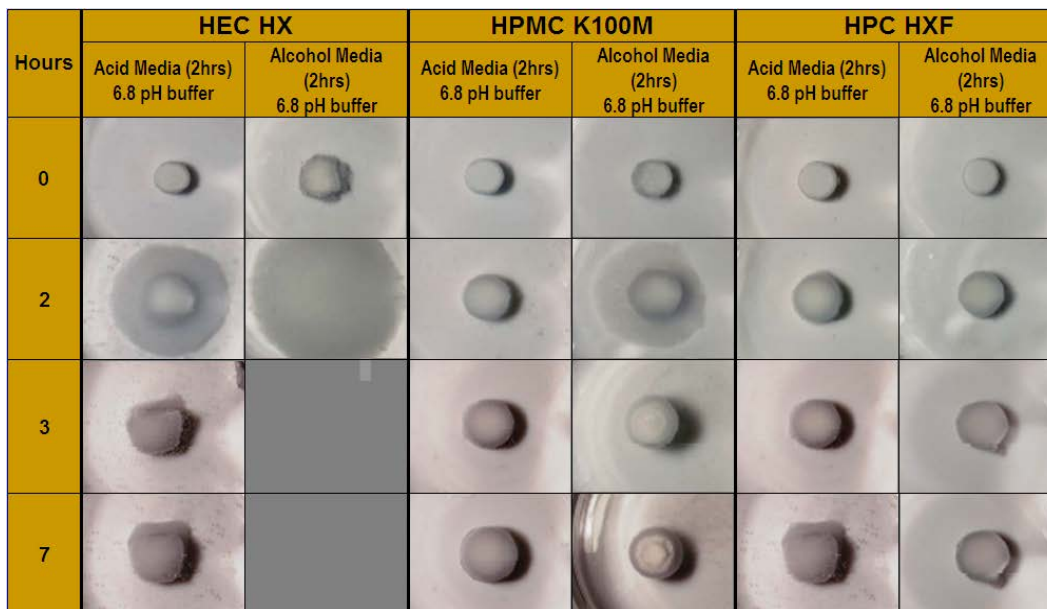
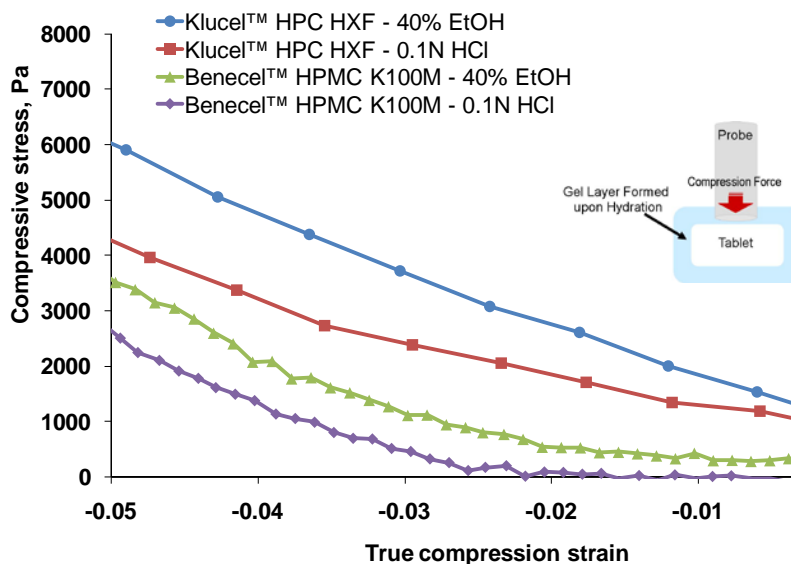


Figure 5. Gel strength of METF tablets exposed to 2 hours of acidic and hydroethanolic media



Conclusions

The Klucel HPC and Beneceal HPMC based matrix formulations used in this study showed no tendency to dose dump, thus indicating the relative safety and robustness of these types of controlled release systems. It appears that for Klucel HPC and Beneceal HPMC, polymer solubility and gel formation is enhanced in ethanol/water co-solvent system which results in stronger gels with slower erosion rates thus guarding against any potential dose dumping.

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>
2. Owens C. Caution Urged on Dose-Dumping Drugs *Manufacturers should consider ethanol vulnerability at design stage*. *Pharmaceutical Formulation & Quality*. 2009 Oct/Nov; 10-11