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Water-Soluble Cellulose Ethers as Release Modulators for Ethylcellulose Coatings on Multiparticulates

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Introduction

Ethylcellulose (EC) coated multiparticulates function as "mini osmotic pumps." Soluble drug and other core components contribute to the osmotic pressure gradient across the rate controlling membrane, causing diffusion of water into the core. This results in build up of hydrostatic pressure and tensile stress on the EC membrane, causing increased membrane permeability and drug release[1]. Studying multiparticulates coated only with EC, we previously showed that for soluble drugs, release kinetics can be modulated by tailoring EC film mechanical properties, through variation of EC molecular weight (MW), ethoxyl content and solvent choice[2]. A fundamental shortcoming of such systems is that generally there is a loss in osmotic pressure as the drug reservoir is gradually depleted, resulting in declining and often incomplete release patterns in the late time phase. Moreover, for low soluble drugs, osmotic pressure gradients never attain sufficient magnitude to cause substantial film deformation and permeability, thus only small fractions of the total dose are delivered.

To compensate for these inherent shortcomings, water-soluble pore formers are usually incorporated into the rate-controlling EC membrane. Numerous authors have described the use of ethylcellulose- hypromellose (HPMC) combinations[1,3]. However few studies have considered the effects of other film-forming cellulose ethers such as hydroxypropylcellulose (HPC) or the effect of various MW grades of water-soluble cellulose ethers. While HPC and HPMC have similar solubility parameters and should thus have similar compatibility with EC, these polymers differ in their film mechanical properties (Table 1).

Table 1.
Select polymer grades, their physical and film mechanical properties.

Polymer Type	Solubility Parameter ($MPa^{0.5}$)	Molecular Weight (kDA)	Tensile Strength (MPa)	Strain (%)	Modulus (MPa)
EC, N Type, 22 cps[a]	20.2	130	47.6	9.0	2085
EC, N Type, 10 cps[a]	20.2	80	38.6	5.4	1852
HPC JF, xx cps[b]	23.1	140	17.7	22.0	772
HPC EF, 8 cps[b]	23.1	80	10.0	11.96	661
HPMC 2910, 5 cps[b]	23.2	32	40.2	3.3	2516
HPMC 2910, 3 cps[b]	23.2	18	36.4	1.9	2528

[a]5% solids
[b]2% solids

Note: This work was presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, October 29-November 2, 2006, San Antonio, Texas.

The aim of this study was to evaluate the impact of low MW HPC and HPMC grades as release modulators in EC films. Two substrates were studied: drug-layered sugar spheres and spheronized drug-micro-crystalline (MCC) beads. Four model drugs ranking from highly soluble to insoluble were used. These were Venlafaxine HCl (VENLA, 1780 mg/ml at 37°C), propranolol (PROP, 204 mg/ml), acetaminophen (APAP, 20 mg/ml) and carbamazepine (CBZ, 2.5 mg/ml in 0.5% SLS). Two MW grades of EC (N22 EC and N10 EC, 130 and 80 kDa respectively), three MW grades of HPC (HPC EF, HPC LF and HPC JF , 80-140 KDa) and three grades of HPMC Type 2910 (HPMC 3 cps, HPMC 5 cps and HPMC 15 cps) were examined. The percentage of pore forming polymer was increased from 0 to 27.5%, depending on drug sol- ubility. coating weight gains were 5, 7.5 and 10%.

Methods

Drug Layering on Sugar Spheres was done in a Glatt GPCG-5 system equipped with a 7 inch Wurster insert. 2.4 kg batches of sugar spheres, 18-20 mesh, were coated with drug suspension or solution at 28% solids to achieve a target drug load of 30% of total batch weight. The drug dispersions comprised drug, a blend of low viscosity HPC and HPMC binder, talc as anti-adherent and PEG 400 as plasticizer. All drugs were pre-milled to 20 µm particle size. Lastly a seal coat comprising HPC, HPMC, talc and PEG 400 was applied for a total weight gain of 4.5%. Final target drug load was 29-30%. Typical process conditions: 58-60°C inlet temperature, 50-52°C bed temperature, 4.5-5.5 m/s air velocity, spray rate of 30g/min and 2.5 bar atomization pressure.

Drug-MCC Beads by Extrusion Spheronization were made by extruding the wet mass in a LCI MG-55 Multigranulator equipped with a 1.2 mm hole diameter dome die. The extrusion gap and screw speed were 0.2 mm and 50 rpm. Spheronization was performed in a LCI QJ-2307 Marumizer equipped with 2 mm pitch friction plate. Prior to extrusion the dry powder blend comprising 70% MCC and 30% drug was mixed with water in double planetary mixer.

Controlled Release Coating was performed in a Mini Glatt system equipped with Wurster column. The system was fully inerted by using nitrogen as fluidizing and atomizing gas. The base plate and filters were modeled on those available for larger scale equipment. The organic solvent based film coatings comprised various grades of EC, HPC or HPMC, diethyl phthalate as plasticizer and talc and magnesium stearate as anti-adherents. Target viscosity for all systems was 50-100 mPa·s, with a typical solids range of 9-14%. Batches of 280 g of beads were fluidized at gas flow rates of 27 m^3/h. Inlet temperatures were maintained between 30-34°C (25°C bed temperature). A spray rate of 3g/min and atomization pressure of 1.5 bar were typically used. Beads were cured at 60°C for two hours after coating was complete.

Dissolution Testing was performed in a USP apparatus I (basket) at 100 rpm and 37°C. pH 6.8 phosphate buffer was used for VENLA and PROP. For APAP pH 5.8 phosphate buffer was used. For CBZ a 0.5% SLS solution augmented with 0.01% methylcellulose as described else where was used[4].

Free Film Tensile Strength was measured on an Instron 4201 mechanical testing machine in accordance with ASTM D-882.

Scanning Electron Microscopy was performed with a Hitachi S-4000 field emission microscope equipped with Princeton gamma Tech EDX and Oxford CT -1500 cryo unit with samples mounted on a stub, coated with a thin layer of Au/Pt and then examined with secondary electron imaging.

Results

Pore Former Level and Drug Solubility: For soluble and sparingly soluble drugs (PROP and APAP), release is predominantly linear and durations of less than 24 hours can be selected by increasing the fraction of HPC EF over the range of 20 to 30% of total polymer content (Figure 1). Examination of films soaked for 1 hour in water show that the EC and HPC are phase-separated with HPC existing in discrete domains that increase in size as the HPC fraction increases. After soaking in water, the 100% EC film shows no visible pores or cracks. At 80% EC: 20% HPC EF, numerous pores averaging 1 mm or less are found. For 25% HPC EF, pore size increases up to 5 mm and at 27.5% HPC EF, pores ranging up to 10 mm in diameter are seen (Figure 2).

For highly soluble VENLA, release retardation is inadequate at HPC EF levels above 20%. Other release modulating strategies such as increasing coat thickness (Figure 3) are required in addition to including low levels of pore former. For insoluble CBZ it is clear that in addition to augmenting diffusion through inclusion of high levels of pore former (50% HPC EF), formulation of the pellet core is key to enhance solubility, thus allowing dose delivery over a 24 hour period or less.

Pore Former Level and Substrate Type: Release profiles for MCC – APAP beads and APAP-layered sugar spheres were generally similar when coated with EC solutions containing various levels of HPC EF (Figure 4). However, the sugar in the APAP layered spheres was able to dissolve and diffuse through the pores, acting as a channeling agent and causing more linear and faster APAP release in the late time phase.

Effect of Water Soluble Cellulose Ether Type: Both low MW HPC and HPMC are effective pore formers therefore allowing drug release modulation. However at similar levels, HPC causes greater release acceleration (Figure 5). This is somewhat surprising as both polymers are predicted to have similar compatibility with EC based on solubility parameters. Moreover film strengths were not significantly different (Table 3). A possible explanation is the higher MW of HPC EF, which may cause greater swelling and EC membrane disruption. Molecular weight effects are discussed in more detail below.

Effect of Molecular Weight: Release modulation was achieved by varying the MW of water-insoluble EC as well as varying the MW of the water-soluble HPC or HPMC. Consistent with earlier reports (2,3), higher MW N22 EC results in slower release as compared to the lower MW N10 EC (Figure 6). Table 3 shows that the higher MW EC provides greater tensile strength. These strength differences are further magnified for wet film, allowing greater resistance to cracks forming due to accumulated hydrostatic pressure in the bead, thus slowing diffusion of dissolved drug. Increasing the MW grade of pore forming HPC EF (80kDa) to HPC LF (100kDa) or HPC JF (140kDa) has negligible effect on film strength, but release is markedly accelerated at higher MW (Figure 6 & 7). Increased swelling of high MW polymer, allowing faster diffusion through hydrophilic domains of the film may explain this observation.

Conclusion

Composite films comprising water-insoluble EC and HPC or HPMC as water soluble pore formers were shown to be highly effective as release modulators over a wide range of drug solubility (2000 to 2g/ml). Control can be exercised through variation of pore former level, variation of polymer MW and coating thickness. A general observation is that low MW HPC grades are more effective than HPMC as release modulators. Moreover for drugs at the extremes of the solubility range, modification of the drug core solubility should be considered. Future studies will address plasticizer and core formulation effects.

References

[1]Hjärtstam, J. et al, Int. J. Pharm, 61 (1990) 101-107
[2]Ashland Pharmaceutical Technology Report, PTR 33, 2005
[3]Rowe, R. C., Int. J. Pharm, 29 (1986) 37-41
[4]El-Massik, M. A. et al. Drug Dev. Ind. Pharm, 32 (2006) 893-905

Materials

1. Aqualon™ Pharm Ethylcellulose grades N10 and N22 marketed by Ashland Specialty Ingredients, Ashland Inc., Wilmington, DE.
2. Klucel™ Pharm Hydroxypropylcellulose grades EF, LF and JF marketed by Ashland Specialty Ingredients, Ashland Inc., Wilmington, DE.
3. Pharmacoat* Hypromellose NF grades 603, 606 and 615, marketed by Shin-Etsu Chemical Company, Tokyo, Japan.
4. Venlafaxine HCl, USP, marketed by RIA International, Whippany, NJ.
5. Rhodapap* Dense Powder, RWP, Acetaminophen, USP, marketed by Rhodia Incorporated, Cranbury, NJ.
6. Propranolol HCL, USP, marketed by RIA International, Whippany, NJ.

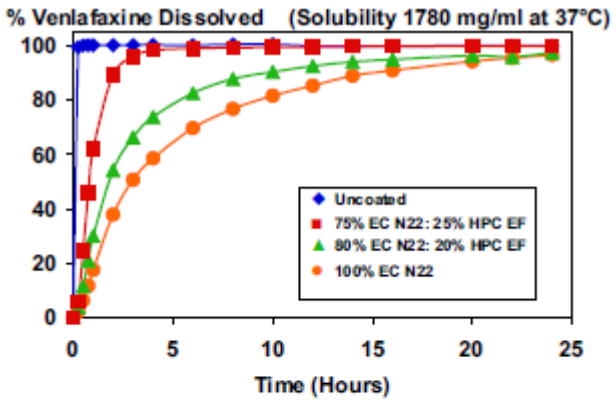
7. Carbamazepine, USP, marketed by RIA International, Whippany, NJ.
8. Avicel* PH101 Microcrystalline cellulose, NF, marketed by FMC Corporation, Philadelphia, PA.
9. Talc, NF, marketed by J.T Baker, a Division of Tyco International, Phillipsburg, NJ.
10. HyQual* Magnesium Stearate, NF, marketed by Mallinckrodt Corporation, a Division of Tyco International, St. Louis, MO.
11. Diethyl Phthalate, NF, marketed by J.T Baker, a Division of Tyco International, Phillipsburg, NJ.
12. Polyethylene glycol 400, NF, marketed by Dow Chemical Corporation, Midland, MI.
13. Sugar Spheres, NF, 18-20 Mesh, marketed by Paulaur Corporation, Cranbury, NJ.

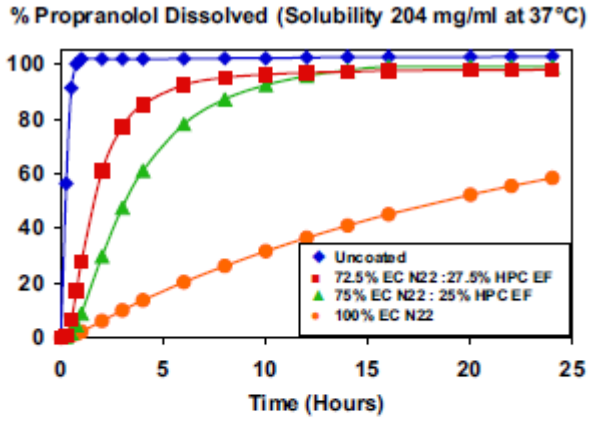
Table 2.
Mechanical Properties of Dry and Wet EC: HPC or HPMC Composite Films. Formulations also contained Diethyl Phthalate, Magnesium Stearate and Talc.

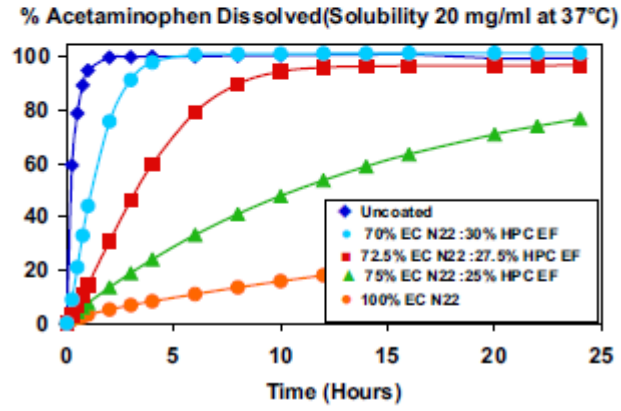
EC Type	Pore Former	Dry Film Properties		Wet Properties (1 hour soak)	
N22 EC (%)	HPC EF (%)	**Peak Stress (MPa)**	**Modulus (MPa)**	**Peak Stress (MPa)**	**Modulus (MPa)**
100	0	11.16 (0.83)[a]	1193 (183)	9.01 (1.02)	694 (88)
90	10	9.24 (1.1)	1126 (84)	5.65 (0.19)	533 (69)
80	20	10.26 (0.61)	999 (51)	4.65 (0.165)	414 (65)
75	25	5.31 (0.56)	911 (161)	3.31 (0.46)	293 (43)
72.5	27.5	7.34 (1.09)	875 (113)	2.84 (0.42)	325 (43)
N22 EC (%)	HPC JF (%)				
100	0	11.16 (0.83)	1193 (183)	9.01 (1.02)	694 (88)
90	10	10.57 (1.86)	957 (177)	6.04 (0.27)	402 (11)
75	25	8.47 (1.41)	788 (45)	3.53 (0.29)	214 (39)
72.5	27.5	7.07 (1.99)	635 (124)	2.61 (0.28)	150 (31)
N22 EC (%)	HPMC 5 cps (%)				
100	0	11.16 (0.83)	1193 (183)	9.01 (1.02)	694 (88)
90	10	7.83 (1.62)	942 (139)	3.83 (1.07)	310 (57))
80	20	10.91 (2.62)	1480 (96)	3.37 (1.06)	436 (39))
75	25	9.1 (1.32)	1244 (63)	1.93 (0.22)	73 (14)
72.5	27.5	4.88 (0.27)	1265 (69)	1.34 (0.247)	280 (85)
N10 EC (%)	HPC EF (%)				
100	0	9.10 (1.88)	1199 (109)	4.77 (2.09)	471 (184)
90	10	7.45 (1.98)	921 (126)	4.13 (1.42)	379 (64)
75	25	7.47 (0.36)	838 (6)	3.24 (0.7)	292 (90)
72.5	27.5	6.92 (2.32)	865 (105)	2.27 (0.78)	192 (36)

[a]Represents Standard Deviations

Figure 1.
Effect of HPC pore former level and drug solubility. 7.5% coating comprising N22 EC, HPC EF, Diethyl phthalate, Magnesium stearate and Talc in Ethanol: Water (90:10).







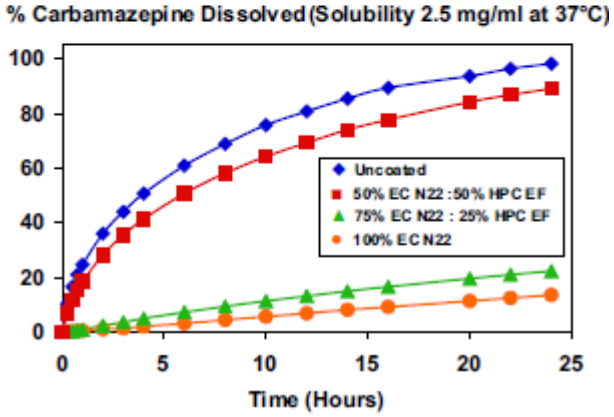


Figure 2.
Scanning electron micrographs showing increasing pore size in 1 hour soaked films as HPC EF fraction increases. a) 100% N22 EC, b) 80% N22 EC: 20% HPC EF, c) 75% N22 EC: 25% HPC EF, d) 72.5% N22 EC: 27.5% HPC EF. Films also comprised Diethyl Phthalate, Magnesium Stearate and Talc in Ethanol: Water (90:10).

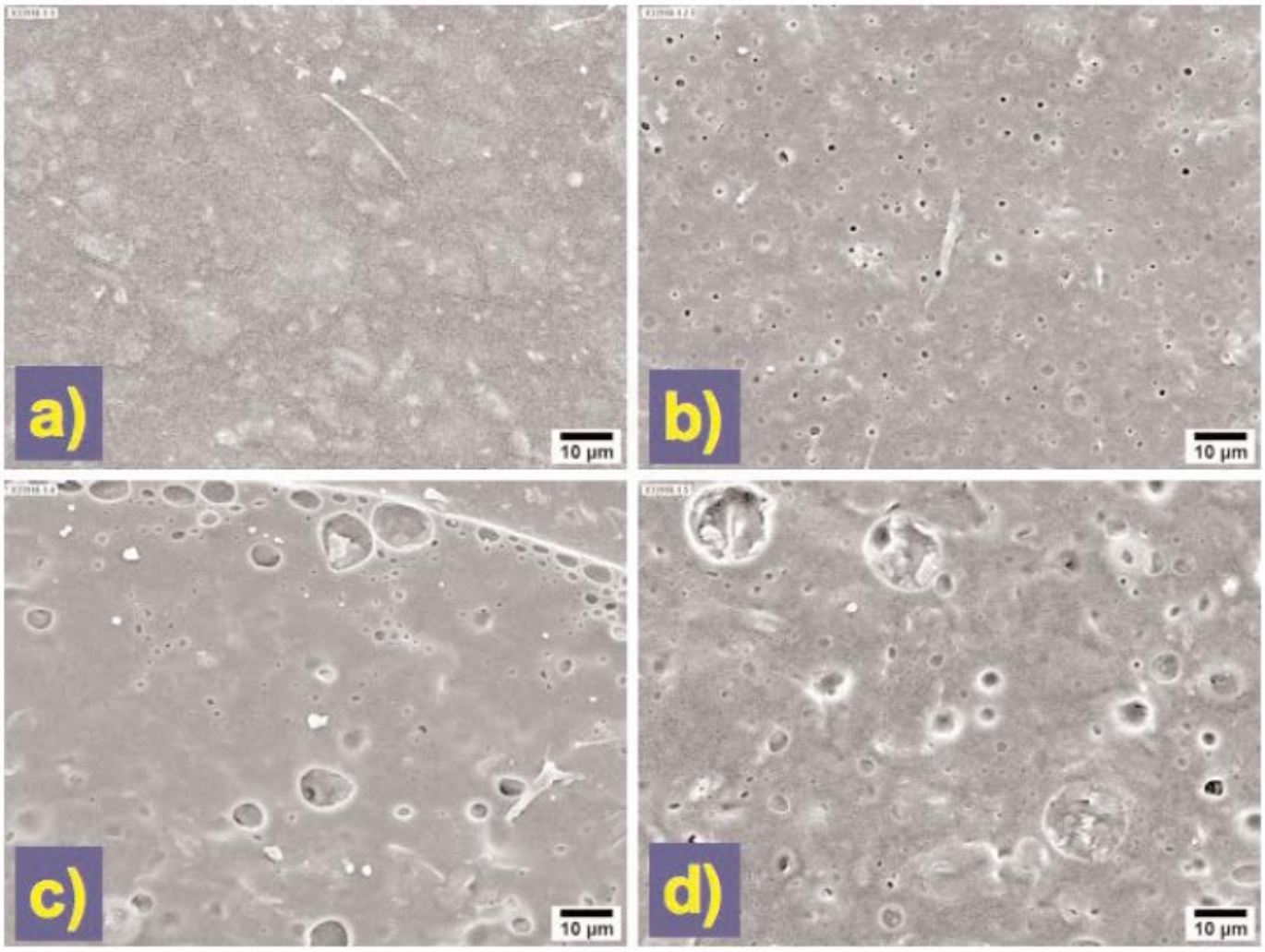


Figure 3.
Effect of Coating Weight Gain and HPC pore former level on APAP release from spheronized MCC beads. Coating comprises N22 EC, HPC EF, Diethyl Phthalate, Magnesium Stearate and Talc in Ethanol: Water (90:10).

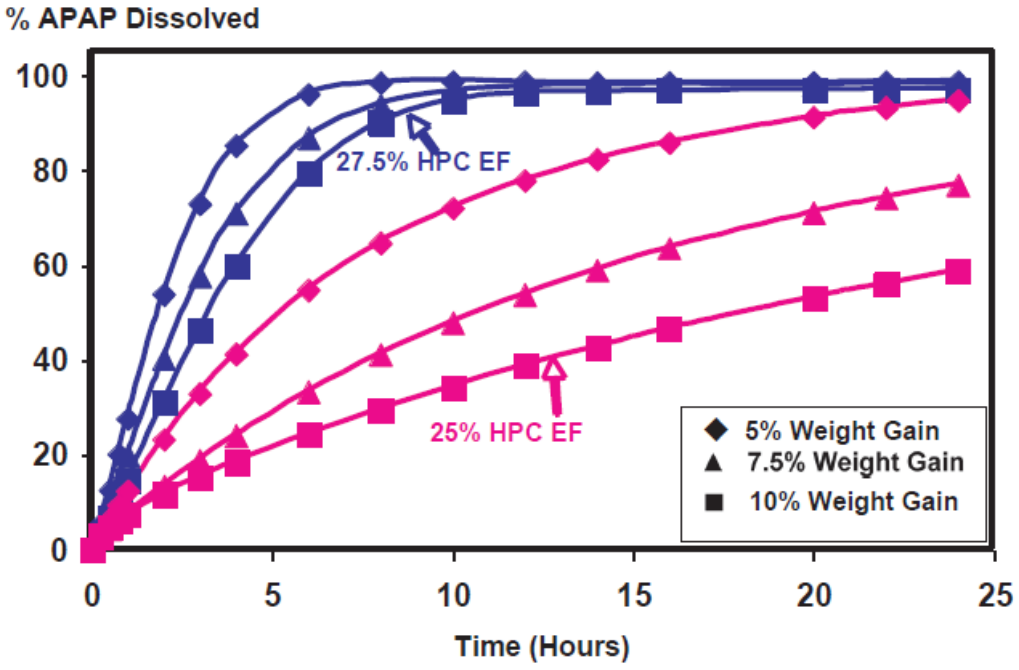


Figure 4.
Effect of HPC pore former level on APAP release from spheronized MCC based beads and drug- layered sugar spheres. 7.5% coating comprises N22 EC, HPC EF, Diethyl Phthalate, Magnesium Stearate and Talc in Ethanol: Water (90:10).

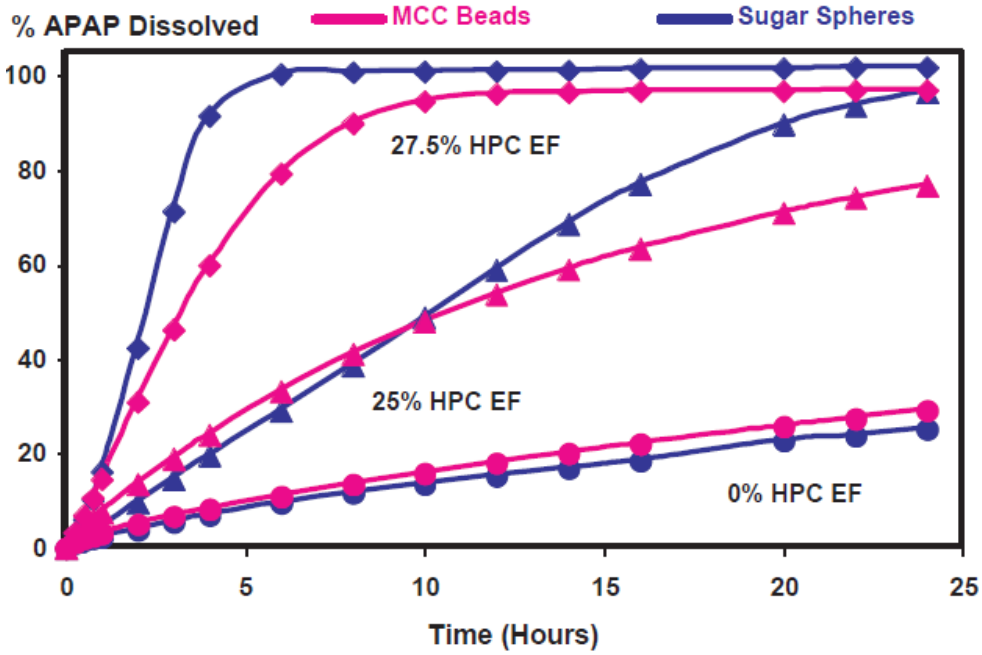


Figure 5.
Effect of Water Soluble Cellulose Ether Type on PROP release from spheronized, MCC based beads. 7.5% coating comprises N22 EC, HPC EF or HPMC 5 cps, Diethyl Phthalate, Magnesium Stearate and Talc in Ethanol: Water (90:10).

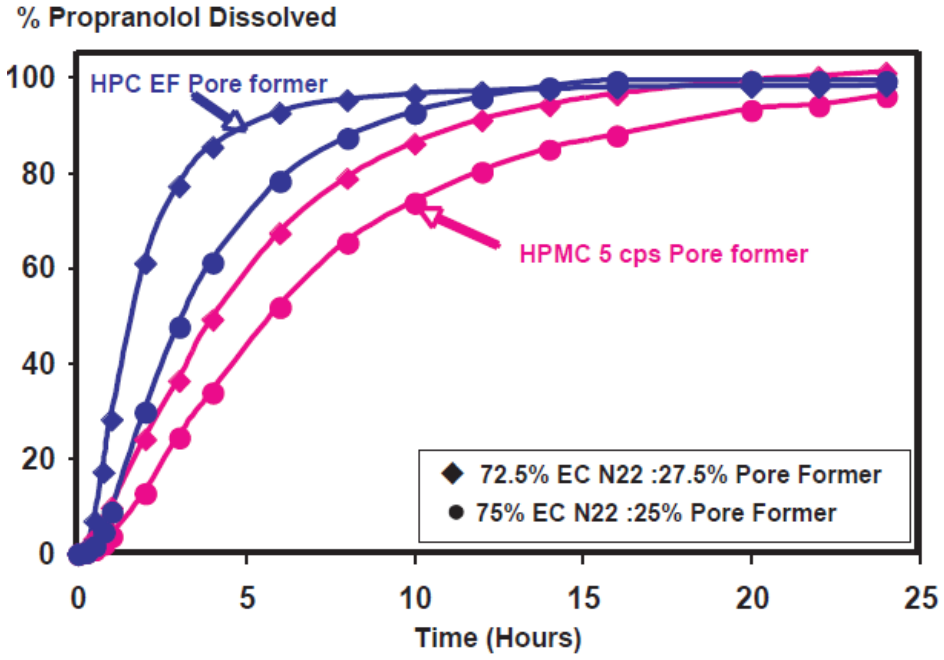


Figure 6.
Effect of EC and HPC molecular weight on APAP release from drug-layered sugar spheres. 7.5% coating comprises N22 EC or N10 EC, HPC EF or LF, Diethyl Phthalate, Magnesium Stearate and Talc in Ethanol:Water (90:10).

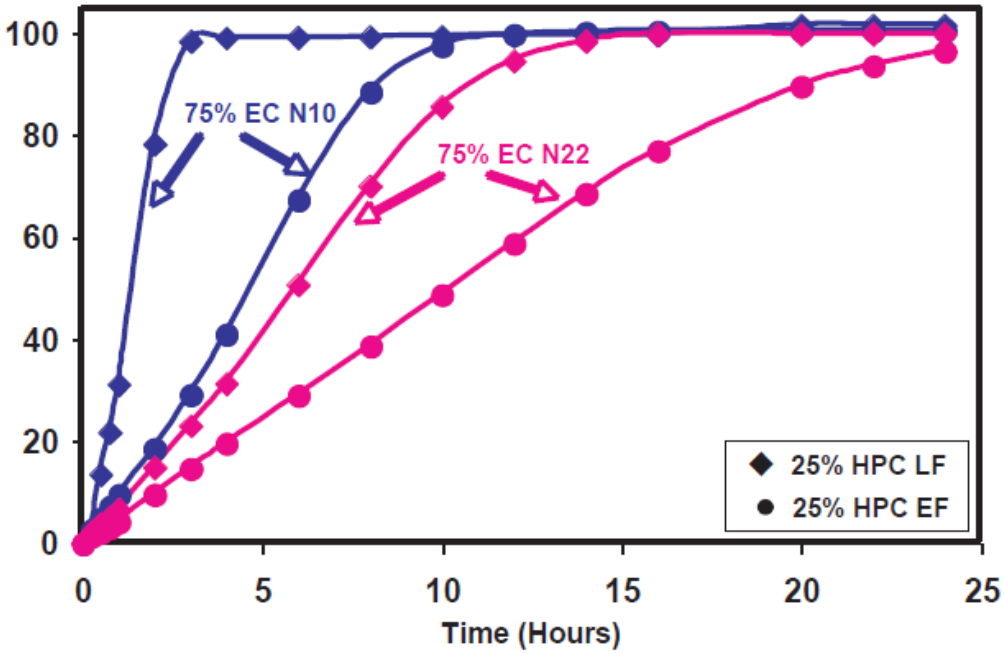


Figure 7.
Effect of HPC molecular weight on APAP release from drug-layered sugar spheres. 7.5% coating comprises, N22 EC, HPC EF, LF or JF, Diethyl Phthalate, Magnesium Stearate and Talc in Ethanol:Water (90:10).