The Influence of Molecular Weight on Drug Release from Ethylcellulose Barrier Membrane Multiparticulates

ABSTRACT SUMMARY

The influence of ETHOCEL™, premium ethylcellulose polymers, molecular weight on chlorpheniramine maleate release from coated beads was investigated. Drug release is retarded with increasing molecular weight (viscosity) of ethylcellulose (EC). Lower molecular weight grades yield solutions of lower viscosity, allowing faster spray application, while higher molecular weight grades provide films of higher mechanical film properties. Slower drug release can be obtained from a lower molecular weight grade of EC by the addition of plasticizers.

INTRODUCTION

ETHOCEL premium ethylcellulose products, with an ethoxyl content of 48.0- 49.5% and a number of different viscosity grades, are commonly used in pharmaceutical applications. Different viscosity grades are achieved by control of chain length (degree of polymerization) or the number of anhydroglucose units during the production process. The apparent viscosity can thus be regarded as an indirect measure of the polymer molecular weight[1]. Statistical analysis on EC samples has demonstrated a relationship between the nominal viscosity of a 5% solution in toluene/ethanol (expressed as mPa.s) and its molecular weight[2]. The objective of this work was to investigate the influence of EC molecular weight (viscosity) on drug release from coated beads.

EXPERIMENTAL METHODS

Drug Layering of Sugar Spheres

Chlorpheniramine maleate (CPM) was coated onto 18/20 mesh (850 - 1000 µm) SureSpheres™, drug layering substrate (Colorcon, USA), to a target drug load of 30 mg/g using a Pam-Glatt fluidized bed coater (FBE-125 equipped with Würster column, 360 mm length), using Hypromellose 2910 (METHOCEL™ E6, The Dow Chemical Company, USA) as a binder. Drug layering was carried out at an inlet temperature of 65-70°C, fluid delivery rate of 100 g/minute, atomizing air pressure of 22 pounds per square inch (psi) and an air volume of 800 cubic feet per minute (cfm).

Ethylcellulose Coating of Drug-Layered SureSpheres

The ETHOCEL sample properties used in this study are recorded in Table 1. The viscosity (determined of a 5% solution in an 80:20 solvent mixture of toluene: ethanol) and the ethoxy content of each of the samples

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was obtained from the certificate of analysis of the manufacturer (the Dow Chemical Company, USA). Coating solutions were prepared by dissolving each of the viscosity grades of ETHOCEL in the solvent mixture, isopropanol: water (90:10). Dibutyl sebacate [DBS, Vertellus, USA] (10% w/w with respect to the polymer) was added as a plasticizer. ETHOCEL Standard 10 Premium was also plasticized at 20% w/w. The final coating solution solids content for each of the molecular weight (viscosity) grades of EC used is listed in Table 2. CPM beads were coated to a 10% final film weight gain for each of the molecular weight (viscosity) grades using a GPCG 1.1 fluid bed apparatus (Pam-Glatt Pharma Technologies, India). Coating process parameters that were used are listed in Table 2.

Dissolution Testing

Drug release was measured from 1 g of coated pellets using a USP compliant automated dissolution bath (Erweka DT 800, Germany) apparatus 1 at 100 rpm. The dissolution medium was 1000 mL of purified water at 37 ± 0.5^{o}C. An online dual beam spectrophotometer (Perkin-Elmer, USA) was used for the detection of CPM at a wavelength of 262 nm over a 24 hour period. Purified water was used as reference.

Table 1. ETHOCEL Sample Properties

ETHOCEL Viscosity Designation	Lot number	Viscosity, mPa.s (cP)	Ethoxyl content, %
4	VG30013T01	5.3	48.7
7	WB07013T01	6.6	49.1
10	WA25013T01	10.3	49.4
20	WD01013T01	20.0	48.8
45	UL22013T01	43.5	48.9

Table 2. Coating Parameters used for EC Coating

Parameter	Response GPCG 1.1					
	4 cP	7 cP	10 cP		20 cP	45 cP
Charge (g)	600	600	600	600	600	600
Air volume (m/s)	11-12	11-12	11-12	10-11	11- 12	11-12
Inlet air temperature (^{o}C)	35- 36	34- 35	34- 35	35-39	34- 35	30- 33
Exhaust air temperature (^{o}C)	31- 33	32- 33	32- 33	34-36	32- 33	30- 32
Product temperature (^{o}C)	32- 34	33- 34	32- 33	33-35	33- 34	30- 32
Fluid delivery rate (g/min)	6- 7	7	5- 6	6-7	7	6- 7
Atomization pressure (bar)	0.9	1.0	0.8- 1	0.8-1	1.0	1.0-1.2
Solids content (%)	7	7	7	7	7	5
Plasticizer (% wrt polymer)	10	10	10	20	10	10

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RESULTS AND DISCUSSION

The dissolution profiles of CPM beads coated with formulations containing various molecular weight (viscosity) grades of ETHOCEL are shown in Figure 1. It is observed that samples coated with the lower molecular weight (viscosity) grades had faster release rates than samples coated using higher viscosity grades of ETHOCEL. This is consistent with other literature reports[3-5].

Rowe reported that films prepared from low molecular weight polymers with short chains are relatively weak and that as the chain length, and hence molecular weight increases, the mechanical properties of the films improve until at some critical molecular weight there is no further improvement[4]. Similar effect was also observed on comparisons of release profiles of formulations comprising various viscosity grades of ETHOCEL (Table 3). Slowest release was obtained where the highest molecular weight grade was used (45 cP) and fastest release was obtained where the lowest molecular weight was used (4 cP).

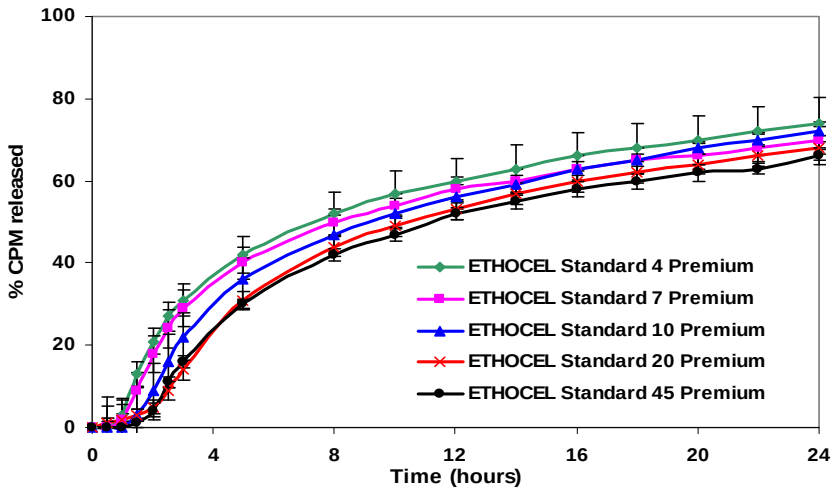

Figure 1. The Effect of Molecular Weight of Ethylcellulose on Drug Release

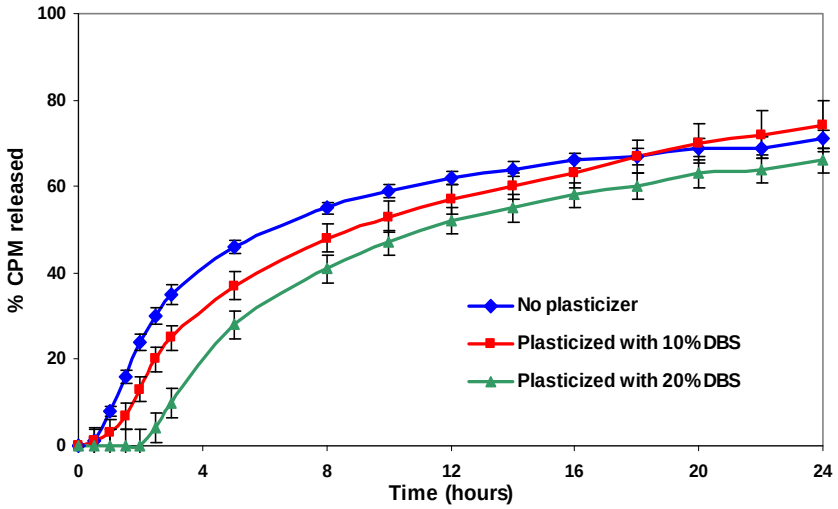

Figure 2. The Effect of Plasticizer Content on Drug Release from Ethylcellulose Films

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Rowe demonstrated that interrelationships between dissolution, mechanical properties, and molecular weight of EC, support the concept that cracking occurs with low molecular weight grades of EC, and, defects decrease with increasing molecular weight, after which the films become coherent. In another study, Rowe quantified the dependence of permeability, release rate and incidence of cracking of film coatings on the molecular weight of EC. The data on mechanical properties, tensile strength and elongation to break indicated that mechanical properties increase with molecular weight[4].

Mechanical properties of films can also be increased by the addition of plasticizers. Plasticizers lower the internal stress within the coating, resulting in a more coherent film. Films formed from ETHOCEL Standard 10 Premium, showed slower drug release rates proportional to the amount of the plasticizer added (Figure 2). Decreased drug release from films plasticized at higher levels can be attributed to a more coherent EC film produced as a result of reduced residual internal stress within the coating[3].

EC of greater molecular weight yields more viscous solutions. The high viscosity of EC solutions (even at low concentrations) is the outcome of chain extension and immobilization of the solvated molecules[6]. Appropriate selection of the molecular weight (viscosity) grade of ETHOCEL to provide the desired drug release profile will need to be selected, while also giving due consideration to processing ease and productivity.

Table 3. f_2 Value Comparisons

ETHOCEL Formulation Comparisons	f_2 value
Std.4 Prem. X Std.7 Prem.	76.14
Std.4 Prem. X Std.10 Prem.	59.91
Std.4 Prem. X Std. 20 Prem.	52.60
Std.4 Prem. X Std. 45 Prem.	49.40
Std.7 Prem. X Std.10 Prem.	68.55
Std.7 Prem. X Std. 20 Prem.	59.42
Std.7 Prem. X Std. 45 Prem.	55.56
Std.10 Prem. X Std. 20 Prem.	73.22
Std.10 Prem. X Std. 45 Prem.	66.28
Std.20 Prem. X Std. 45 Prem.	84.95

CONCLUSIONS

The viscosity or molecular weight grade of EC can impact drug release rates. Drug release is retarded with increasing molecular weight (viscosity) of EC. The retardation in drug release can be attributed to an improvement in the mechanical properties of the film. Alternately, the addition of plasticizers to coating formulations can provide for slower drug release, due to a decreased residual internal stress within the coating, resulting in more coherent films. Lower molecular weight grades yield solutions of lower viscosity, allowing faster spray application, while higher molecular weight grades provide films of higher mechanical film properties. Coating formulations which yield the desired film properties, as well as afford a faster spray application, would be most advantageous. Future work will investigate the incorporation of pore formers into ethylcellulose polymers to improve % terminal drug release.

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REFERENCES

1. Rekhi G, Jambhekar S. Ethylcellulose- A polymer review. *Drug Dev Ind Pharm*. **1995;** 21(1):61-77.
2. Rowe RC. Molecular weight studies on ethylcellulose used in film coating. *Acta Pharm. Suec.* **1982**; 19:157-160.
3. Rowe RC. The effect of the molecular weight of ethyl cellulose on the drug release properties of mixed films of ethyl cellulose and hydroxypropyl methylcellulose. *Int. J. Pharm*. **1986**; 29:37-41.
4. Rowe RC. Molecular weight dependence of the properties of ethylcellulose and hydroxypropyl methylcellulose films. *Int. J. Pharm*. **1992**; 88:405-408.
5. Coppens KA, Dasbach TP, Frauchiger L. Ethylcellulose coating: Effects of viscosity grade, coating weight, and accelerated storage conditions. *31st Annual Meeting of the Controlled Release Society*, **2004**.
6. Onions A. Films from water-based colloidal dispersions. *Manuf. Chem*, March **1986**, 55-59 & April **1986**, 66-67.

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