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Short communication

Determination of Methocel A15-LV cellulose ether in blends with microcrystalline cellulose

Sergio S. Cutié*, Charles. G. Smith

Analytical Sciences, Materials Science Characterization, 1897D Building, The Dow Chemical Company, Midland, MI 48667, USA

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Abstract

Methocel (trademark of Dow Chemical) A15-LV cellulose ether is mixed with microcrystalline cellulose and used in pharmaceutical formulations to coat slow release drugs. An analysis was needed to monitor the efficiency of the mixing of Methocel cellulose ether with the microcrystalline cellulose. The similarities in chemical structure of Methocel cellulose ether and cellulose made it extremely difficult for some spectroscopy techniques to distinguish between them. An extraction technique followed by separation in a size-exclusion chromatography column with refractive index detector was developed and validated and successfully used to monitor Methocel cellulose ether in cellulose. Also developed was a direct pyrolysis–capillary gas chromatography technique with flame ionization detector that generates equivalent results to the extraction–size-exclusion chromatographic technique. Due to limitations imposed by the requirement for small samples, the pyrolysis–GC approach is not as reproducible as the extraction–size-exclusion chromatographic procedure.

1. Introduction

Methocel (trademark of Dow Chemical) cellulose ethers are increasingly being used [1–3] in pharmaceuticals applications. (Methocel A-15 LV, a low-molecular-mass polymer, is mixed with microcrystalline cellulose which is widely used in pharmaceutical applications [4–6] to make slow release drug formulations.) Microcrystalline cellulose is a non-fibrous form of cellulose in which the cell wall of plant fibers has been broken into fragments ranging in size from a few hundred micrometers to a few tenths of a micrometer in length. Cellulose is insoluble in water while Methocel A15-LV cellulose ether is soluble. Microcrystalline cellulose acts like a pressure-sensitive adhesive and when tablets containing this material are placed in water, there is rapid disintegration, but no dissolution. Approximately 5% of Methocel cellulose ether is added to microcrystalline cellulose and there exists a need to determine how accurate the mixing process is. After some minor modifications, an extraction procedure followed by size-exclusion chromatography (SEC), previously used to determine concentrations of polyacrylic acid in water at the ppm level [7], was used to determine the Methocel cellulose ether content of a blended sample SG-955. Pyrolysis–gas chromatography

* Corresponding author.

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(Py–GC) was evaluated as an alternate technique for this analysis.

2. Experimental

2.1. SEC

A series of standards containing from 1.7 to 7.4% Methocel A15-LV cellulose ether were prepared by shaking appropriate masses of this polymer and the microcrystalline cellulose overnight on a flatbed shaker. About 0.02 g of these standards and the blended sample were extracted for 2 h by placing samples vials with about 10 g of 0.05 *M* sodium chloride using a mechanical shaker for solution agitation. After removal from the shaker, the samples were held for about 10 min to allow for phase separation. Aliquots of each extract were filtered (0.45-μm filter) before injection into the SEC apparatus. Instrumental parameters for this analysis are summarized in Table 1.

2.2. Py–GC

Portions of Methocel A15-LV cellulose ether, microcrystalline cellulose, a blended sample (SG-955), and the standard mixtures were weighed (52–562 μg) into quartz tubes. These sample tubes were placed into a Pt coil and equilibrated 10 min in the 200°C interface connected to the injection port of an HP5890 gas chromatograph equipped with dual flame ionization detectors. The sample was subsequently pyrolyzed (CDS 120 Pyroprobe; ramp = Off, interval = 20 s) at a set temperature of 500°C. Pyrolysis products were split between a 60 m × 0.2 mm) capillary column (J & W DB WAX; 0.25 μm film) and a 6 ft. × 1/8 in. stainless-steel column (1 ft. = 30.48 cm; 1 in. = 2.54 cm), packed with 0.1% SP1000 on Carbopack C (80–100 mesh). These columns were simultaneously programmed from 50°C (4 min) to 220°C at 6°C/min and the dual column separations were monitored with PE Nelson Turbochrom 3.3 software.

Table 1
Instrument parameters for SEC analysis

Column	1 TSK G1000 PW
Detector	Refractive index; Waters Model 410
Eluent	0.05 *M* Sodium chloride
Integration	PE Nelson Turbochrom 3.3
Flow	1 ml/min
Injection	100 μl

3. Results and discussion

3.1. SEC

The response of the refractive index detector was found to be linear for Methocel A15-LV cellulose ether from 30 to 340 ppm as shown in the plot of Fig. 1. Fig. 2 compares the SEC chromatograms for extracts from the microcrystalline cellulose blend, microcrystalline cellulose, and the Methocel A15-LV cellulose ether. The cellulose ether is distinctly apparent as a positive peak response at a retention time of about 5.3 min.

3.2. Accuracy study

To determine the recovery of known amounts of Methocel A15-LV cellulose ether from blends with microcrystalline cellulose, fourteen replicate portions of the blended standards were extracted and the extracts were analyzed by SEC. Results

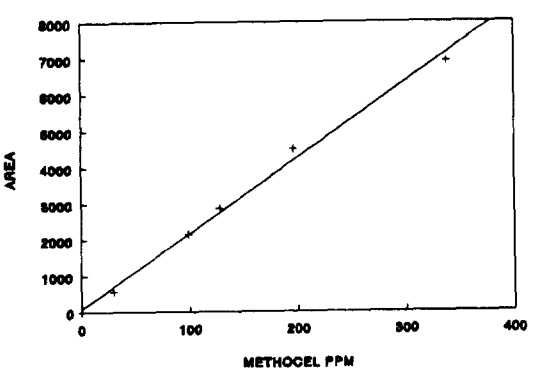

Fig. 1. Linearity curve for the refractive index detector. $y = 20.8791x + 88.0173$.

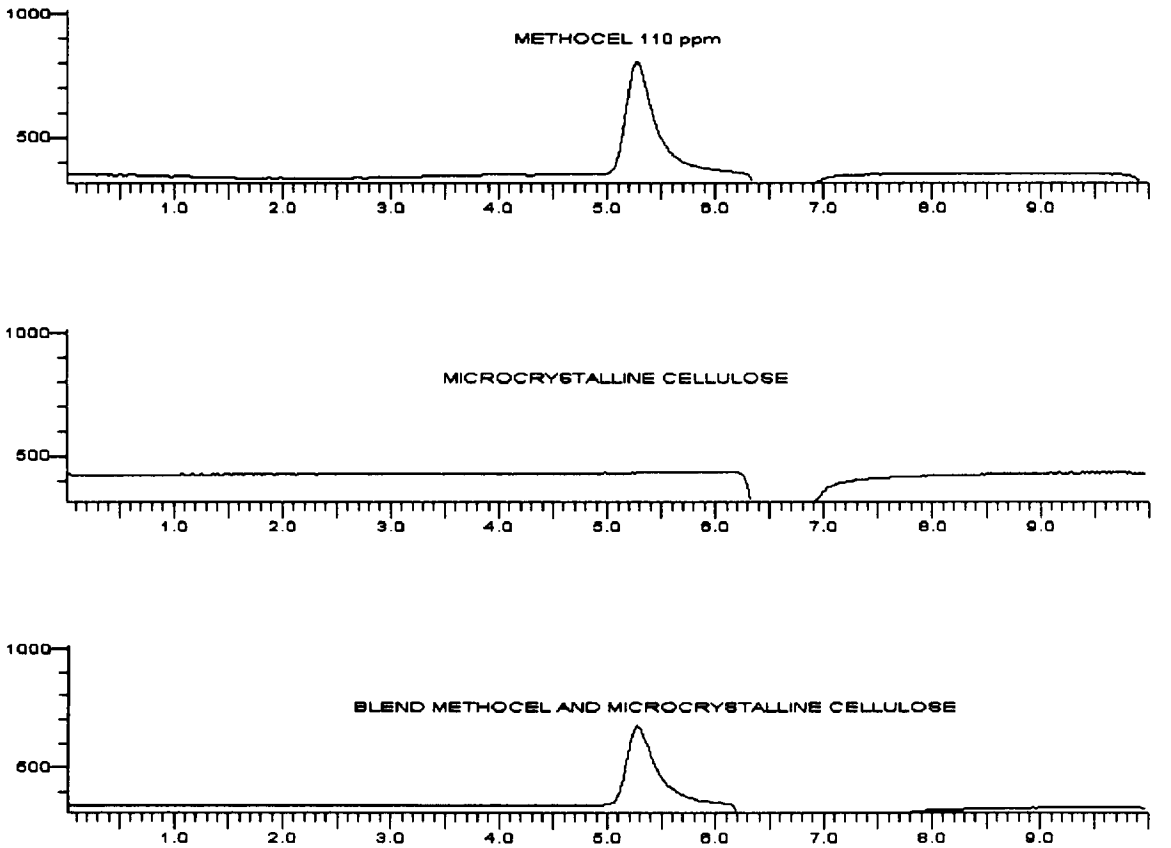

Fig. 2. Comparison of size-exclusion chromatograms.

showed average recoveries of 96% with a standard deviation of 6.9% and a range of 88 to 110%.

3.3. Precision study

To estimate the precision of the extraction–SEC procedure, eleven portions of a standard blend (5.9% Methocel A15-LV cellulose ether) were extracted and analyzed over a two day period. Results showed a relative standard deviation of ± 14.2% at the 95% confidence level.

3.4. Py–GC

Initially, samples of the Methocel A15-LV cellulose ether, microcrystalline cellulose, and blended standards were pyrolyzed at a set temperature of 700°C. Pyrograms for these runs contained several peaks from the microcrystalline cellulose that interfered with the major peak from pyrolysis of the cellulose ether. Using a lower set pyrolysis temperature (500°C), however, resulted in pyrograms with fewer interferences from the microcrystalline cellulose as shown in the comparison of Fig. 3.

Portions (454–562 μg) of the powdered standard blends (1.7–7.4% Methocel A15-LV cellulose ether) and microcrystalline cellulose, were pyrolyzed at a set temperature of 500°C. Pyrolysis products were split and separated using the dual-column system, then the area of a unique Methocel A15-LV cellulose ether pyrolysis product (9.1 min on the capillary DB WAX column) was plotted against the mass of cellulose ether pyrolyzed for each standard blend. The resulting curve (Fig. 4) showed a linear correla-

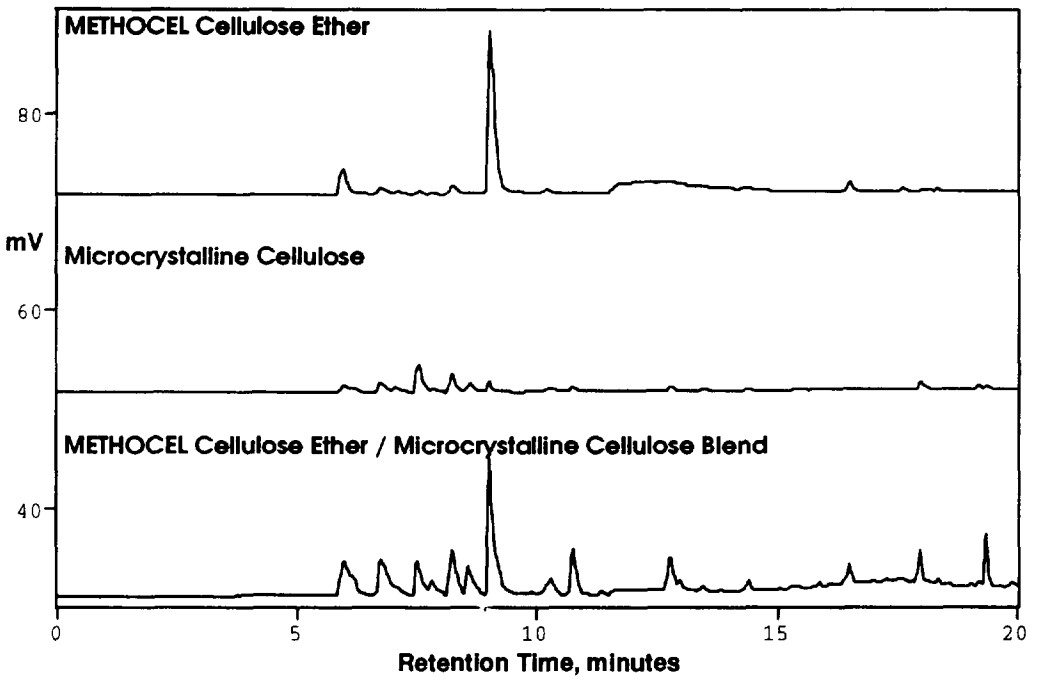

Fig. 3. Comparison of partial 500°C pyrograms for Methocel A15-LV, microcrystalline cellulose, and a blended sample.

tion over the range of the prepared standard blends.

To estimate the reproducibility of pyrolysis data, duplicate portions of the 5.9% Methocel cellulose ether standard blend and three portions of the SG-955 blend, were weighed, pyrolyzed and chromatographed using the dual-column system. Using the average response factor (μg Methocel cellulose ether per area at 9.1 min) from capillary chromatography of the standard

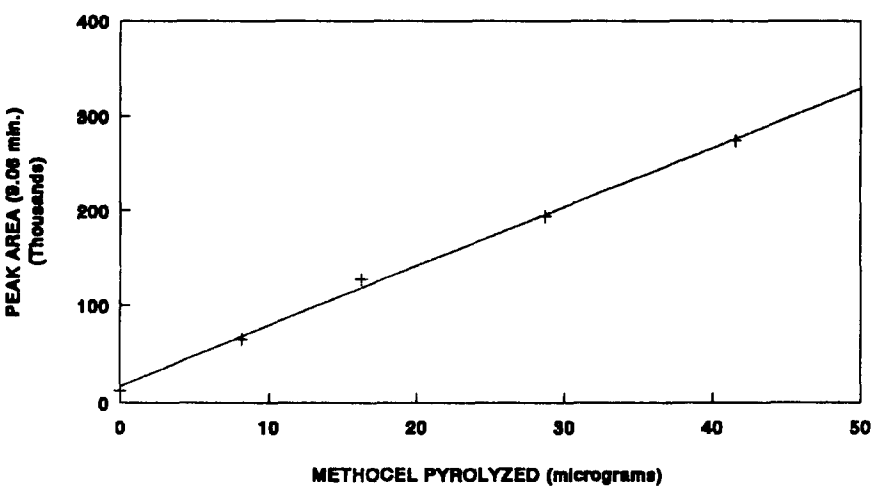

Fig. 4. Correlation curve for Methocel A15-LV cellulose ether concentration and pyrolysis response at 9.1 min. $y = 6245.836x + 16\,430.2497$.

blend, the Methocel cellulose ether content of the SG-955 blend was calculated at 4.0, 5.4, 5.8% (average = 5.1%). These data highlight a flaw in the Py–GC technique for quantitative analysis of this type of insoluble sample. The technique is not as reproducible as the extraction–SEC approach because of (1) errors in weighing small samples and (2) possible non-uniform distribution of components in the sample. Consequently, the extraction–SEC procedure is preferred for the determination of Methocel A15-LV cellulose ether in blends with microcrystalline cellulose.

References

[1] I. Lichnerov, J. Heinrich and J. Rak, *Ceska Slov. Farm.*, 43 (1994) 22–25.
[2] K. Mitchell, J.L. Ford, D.J. Armstrong, P.N. Elliott, C. Rostron and J.E. Hogan, *Int. J. Pharm.*, 100 (1993) 155–163.
[3] G. Agoes, U. Maru and R. Setiadi, *Acta Pharm. Indones.*, 14 (1989) 1–10.
[4] H. Miyamoto, *Pharm. Tech. Jpn.*, 10 (1994) 321–330.
[5] L.S. Wan, Prasad and P.P. Kanneganti, *Int. J. Pharm.*, 41 (1988) 159–167.
[6] M. Landin, R. Martinez-Pacheco, J.L. Gomez-Amoza, C. Souto, A. Concheiro and R.C. Rowe, *Int. J. Pharm.*, 91 (1993) 143–149.
[7] S.S. Cutié, W.C. Buzanowski and J.W. Berdasco, *J. Chromatogr.*, 513 (1990) 93–105.