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Characterization of METHOCEL cellulose ethers by aqueous SEC with multiple detectors

C.M. Keary*

The Dow Chemical Company, Cellulosics R & D, Larkin Laboratory, Midland, MI 48674, USA

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Abstract

Initial evaluation of a multiple-detector, aqueous SEC technique has shown:

- that it is capable of high precision and accuracy;
- applicability to the analyses of METHOCEL cellulose ethers;
- ability to generate consistent values of R_{gW}, IV_W, $\bar{M}_W$, $\bar{M}_N$ and polydispersity;
- ability to generate dependable Mark–Houwink–Sakurada parameters.

Cellulose ethers in this study were commercial products, used ‘as received’, solutions were not dialyzed, corrections were not made for salt content or moisture content and batches were not specially selected. The robustness, convenience and reproducibility of the technique are impressive.

Keywords: Methylcellulose; Hydroxypropyl Methylcellulose; Aqueous size-exclusion chromatography; Intrinsic viscosity; Radius of gyration; Molecular weight; Mark–Houwink–Sakurada; Viscotek

1. Introduction

In common with most polymers, METHOCEL[1] cellulose ethers consist of a distribution of chain lengths. Within any homologous series of polymers, in the absence of branching, chain length defines the molecular weight of a polymer molecule. Within any of the conventional substitution ranges of cellulose ethers, nothing has a more profound influence on the physical, rheological and mechanical properties of the product than the length of the polymer chains. Industry has traditionally not specified commercially available cellulose ethers according to chain lengths or their distributions. Specification is mainly dependant upon the resultant viscosity of an aqueous solution of the polymer. Simplistically, cellulose ethers of high viscosity grades contain longer polymer chains than cellulose ethers of low viscosity grades. All grades contain a distribution of chain lengths which may or may not be similar.

Cellulose ethers are typically manufactured in a heterogeneous process in which a statistical distribution of substitution and sequence isomers is created; it is doubtful that we would ever require the technology to fully characterize every polymer chain with respect to isomerizations. It is much more likely that we will develop techniques to quantify compositional distributions. In the future, complete characterization of cellulose ether will involve both compositional and molecular weight distributions. Meanwhile, this report evaluates the use of multi-detector, size exclusion chromatography as a means to characterize cellulose ethers according to molecular weight and molecular weight distributions. The technique may also be used to provide intrinsic viscosity averages and distributions, and radius of gyration averages and distributions.

2. Chemistry of cellulose ethers

Commercially available products have evolved as a consequence of market demands. In theory, cellulose ethers may be manufactured with many different levels of substitution. Cellulose ethers are derivatives of cellulose in which some of the hydroxyl groups have been etherified. Alkali cellulose, formed by treating cellulose with sodium hydroxide, is further reacted with methyl chloride to yield methylcellulose, METHOCEL A products. For hydroxypropyl methylcelluloses, METHOCEL E, F and K products,

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* Fax: +1-517-638-9836.
E-mail address: cmkeary@dow.com (C.M. Keary).

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Table 1
Viscosity ranges and corresponding molecular weight ranges for METHOCEL cellulose ethers as published by Sarkar (1979)

Viscosity designation (mPa s)[a]	2% viscosity range (mPa s)	M_W range
5	4–6	18,000–22,000
25	20–30	48,000–60,000
50	40–60	65,000–80,000
100	80–120	85,000–100,000
400 = 4C	350–550	120,000–150,000
1500 = 15C	1200–1800	170,000–230,000
4000 = 4M	3500–5500	300,000–500,000

[a] Prefix with A, E, F or K.

propylene oxide is used in addition to methyl chloride to yield hydroxypropyl substitution on the anhydroglucose units.

The influence of methoxyl and hydroxypropyl substitutions may be attributed partially to the relative hydrophilicity of these substituent groups (Sarkar, 1979). On this basis, it may be predicted that METHOCEL A products will be more hydrophobic than the hydroxypropyl methylcelluloses, METHOCEL E, F and K products. This prediction is reflected, for example, in the response of dilute solutions of the cellulose ethers to heat; methylcellulose has a cloud point which is lower than that of the hydroxypropyl methylcelluloses and the cloud points of the hydroxypropyl methylcelluloses increase as the levels of methoxyl substitution decrease.

3. Historical perspective

Sarkar (1979) published a general listing of molecular weight ranges as they corresponded to viscosity ranges of METHOCEL cellulose ethers; Table 1 lists the ranges.

Sarkar and Cutié (1993) reported on an upgraded and optimized aqueous SEC/RI[2] method for the determination of molecular weight distributions of METHOCEL cellulose ethers. Their technique involved the use of a refractive index detector and calibration with pullulan polysaccharide standards. They evaluated many different cellulose ethers by the Mark–Houwink–Sakurada (M–H–S) relationship:

$$[\eta] = KM^a \tag{1}$$

where, $[\eta]$ = intrinsic viscosity in dl/g; they found that the factors were 1.47×10^{-4} and 0.78 for K and a, respectively. The authors did not consider the correlation coefficient of 0.97 as acceptable and postulated the main source of errors to reside in the determination of molecular weight.

Poché, Ribes and Tipton (1998) applied a combination of SEC and light-scattering techniques to the characterization of cellulose ethers. They concluded that the use of pullulan as a calibration standard in conventional SEC/RI resulted in an over-estimate of the molecular weight of cellulose ethers by as much as a factor of 3.2, over the range of molecular sizes which were studied. Additionally, it was concluded that a combined SEC/LALLS[3] technique was accurate but so labor-intensive as to be impractical for routine measurements. Efforts were made to develop correction factors, for each cellulose ether type, which could be easily applied to SEC/RI.

Multiple detection techniques for SEC analyses of polymers have been studied for several years (Bahary, Hogan, Jilani & Aronson, 1995; Gallot, 1980; Jackson & Barth, 1995) and commercially available systems (Beer, Wood & Weisz, 1999; Bosscher, Fruehauf, Rohlfs & Schweizer, 1998; Gillespie & Hammons, 1999; Haney, Gillespie & Yau, 1994) have come into routine use for characterization of various water-soluble polymers.

Despite these technological developments, publications continue to report the difficulties of characterization of cellulose ethers (Jumel et al., 1996; Nilsson, Sundelöf & Porsch, 1995; Wittgren & Wahlund, 1997), especially involving determinations of molar mass and mass distribution. A further reflection of the intractable nature of the molar mass properties of cellulose ethers is the recent work of Lundqvist and Soubbotin (1997) who turned to classical techniques of osmometry and viscometry (Lundqvist, 1999) to characterize cellulose ethers.

4. Experimental

Connections between the various components of the SEC apparatus were made with PEEK tubing ($^1/_{16}'' \times 0.01''$ i.d.), where practical. Eluant was NaCl (0.05 M) prepared with de-ionized water containing 10 ppm of Dow Antimicrobial # 7287, flow rate was 1 ml/min. The eluant was filtered with a Whatman Aqueous IFD™ 0.2 μm in-line filter and was degassed by an Altech on-line degassing system. Pump was a model LC1120 from GBC Ltd., Australia, with a pulse dampener model LP-21 from Scientific Systems Inc. Samples were injected through 0.45 μm syringe filters (Gelman Nylon Acrodisc®, 13 mm) into a Rheodyne

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[2] Size exclusion chromatography with refractive index detector.

[3] Size exclusion chromatography with low angle, laser light-scattering detector.

model 9010 PEEK injector with a PEEK loop (100 μl). Two columns in series (TosoHaas, TSK GMPW$_{XL}$, 7.8 mm × 30 cm) and a guard column (TSK Column Guard PW$_{XL}$) were maintained at 45°C by an Eppendorf heater (CH-430) and controller (TC-50). At 45°C under chromatographic conditions, the cellulose ethers remained in solution. Eluted species passed through an in-line filter (0.2 μm, Whatman nylon, 13 mm) located immediately before the inlet to the LS detector.

The LS detector formed part of a Viscotek T60A dual detector with firstly a right-angle, laser light-scattering detector (LS) and secondly a four-capillary bridge viscometer detector (DP), modified by replacing all of the stainless steel capillaries with appropriately sized PEEK capillaries. The third detector in the system was a Viscotek LR40 laser refractometer (RI).

Analyses of the data were performed with Viscotek TriSEC software, version 3.0.

An average value for differential refractive index, d*n*/d*c*(670 nm), of cellulose ether solutions was taken as 0.129 following the work of Poché et al. (1998); the slight error due to wavelength difference was considered negligible. It was fully appreciated that the use of a single value for d*n*/d*c* across such a broad range of chemistries and polydispersities was a definite source of error.

Analyses of light-scattering data by the Viscotek software assumed that the second virial coefficient was zero at the concentrations encountered in chromatographic elution of nonionic cellulose ethers in aqueous solution.

An integral component of the viscometer detector is the delay volume which was made from a stainless steel column (approximately $8'' \times {}^{1}/_{4}''$) packed with coated glass beads. The nature of the coating was proprietary and it was found that cellulose ethers were being retained within the delay volume. Viscotek had previously determined that the coating also retained polyethylene oxide. It was found that 4 or 5 injections of polyethylene oxide solution (PEO MW = 200, 000; 2 mg/ml) were necessary before release of PEO from the delay volume could be seen in the chromatogram. Once this stage had been achieved, the delay column released subsequently injected cellulose ethers. Treatments with PEO solution were performed at least once per day when the system was in active use.

Solutions for chromatographic analyses were prepared quantitatively by adding eluant to METHOCEL powder and allowing the well-dispersed powder to hydrate overnight in a refrigerator. Solutions were prepared at 2–4 mg/ml for low molecular weight samples and at 1–2 mg/ml for the highest molecular weights which were encountered.

Intrinsic viscosities of bulk solutions were measured at 20°C using capillary viscometers (Schott Gerate, Type 52510/I) with a semi-automated ViscoSystem AVS500 equipped with water bath (CT42) and circulator/thermostat (CT1450). All cellulose ether solutions for bulk intrinsic viscosity measurements were prepared by dispersing the cellulose ether powder into hot, de-ionized water and then allowing hydration to take place, over-night in a refrigerator. For intrinsic viscosity studies, a stock solution was prepared from which dilutions were made such that the maximum concentration which was studied was approximately 1/5[η], where [η] is in dl/g. Intrinsic viscosity was calculated by extrapolation of reduced viscosity, η_{red}, to zero concentration.

5. Theory of combined LS-DP-RI detection

A very succinct description of the Viscotek procedure has already been published (Beer et al., 1999) and it will not be repeated fully here.

SEC recovery of less than 100% of injected polymer will influence the calculations of eluted concentrations from the RI detector response; for this reason significant effort was expended to assure reproducible release of cellulose ethers. As has already been mentioned within the experimental section, the system was conditioned by repeated injections of polyethylene oxide. In all cases, it was assumed that the calibrant pullulan was quantitatively recovered from the system and its RI response was used to determine a 'mass constant' for the instrument. Use of the mass constant to determine the concentration of eluted species in subsequent injections of pullulans or cellulose ethers of known concentrations enabled calculation of percent polymer recovered. Analyses were considered unacceptable if calculated percent recovery of injected polymer was below 80%; see Tables 6–9.

In conventional SEC/RI, molecular weight is typically determined upon the basis of a calibration procedure involving the measurement of retention volumes of narrow-distribution, molecular weight standards. For cellulose ethers, narrow molecular weight standards are not available and calibrations have commonly been performed with polyethylene oxide or pullulan standards. One of the advantages of Viscotek's approach is that no chromatographic calibration is necessary; molecular weight is determined from the light-scattering technique alone.

Viscotek's light-scattering detector operates at a wavelength of 670 nm and measures scattering at 90° from the incident light. A significant portion of the TriSEC software is dedicated to correcting the 90° signal to 0°.

Determination of molecular weight by classical light-scattering depends on the ability to measure the excess scattering intensity, due to the presence of polymer molecules, above the scattering due to the solvent. The Rayleigh equation relates the particle scattering function, $P(\theta)$, and the excess Rayleigh ratio, R_θ, to the weight-average molecular weight of the scattering polymer.

$$\frac{Kc}{R_\theta} = \frac{1}{M_W P(\theta)} + 2A_2c \qquad (2)$$

where, A_2 is the second virial coefficient which may be ignored for the present purposes and c is the sample

Table 2
Precision study using pullulan as light-scattering calibrant and replicant (LS constant = 6.73×10^{-6})

Injection	M_W	M_N	Pd	IV_W (dl/g)[a]	R_{gW} (nm)[b]	R_{hW} (nm)[c]
Calibrant	100,000	84,500	1.18	0.456	11.54	16.08
Unknown	101,100	84,700	1.19	0.469	11.67	16.26
Unknown	100,000	84,500	1.18	0.462	11.59	16.13
Unknown	100,700	84,700	1.19	0.458	11.58	16.12
Unknown	99,700	83,600	1.19	0.461	11.56	16.10
Average	100,300	84,400	1.19	0.461	11.59	16.14
St Dev	518	410	0.01	0.004	0.04	0.06
St Dev %	0.52	0.49	0.45	0.96	0.38	0.39

[a] IV_W is the weight-average intrinsic viscosity.
[b] R_{gW} is the weight-average radius of gyration.
[c] R_{hW} is the weight-average hydrodynamic radius.

concentration. $P(\theta)$ is assumed to equal 1 at 90°, therefor Eq. (2) reduces to:

$$\frac{Kc}{R_\theta} = \frac{1}{M_W^{\mathrm{est}}} \tag{3}$$

by this process, an initial estimate of the molecular weight of each chromatographic slice is obtained.

The Flory–Fox equation is then used to calculate an estimated radius of gyration, R_g, for a linear, flexible chain molecule, based upon the estimated M_W from Eq. (3) and the measured intrinsic viscosity, $[\eta]$:

$$R_g^{\mathrm{est}} = \frac{1}{\sqrt{6}}\left(\frac{[\eta]M_W^{\mathrm{est}}}{\Phi}\right)^{1/3} \tag{4}$$

where, Φ is the Flory viscosity constant. Application of a linear, flexible chain model to cellulose ethers may not be fully valid in view of the relative rigidity of the backbone of the polymers (Lapasin & Pricl, 1995).

Radii of gyration, from Eq. (4), for each elution slice are used to re-estimate $P(\theta)$ and, ultimately, a new estimate of the molecular weight is calculated from:

$$M_{New}^{\mathrm{est}} = \frac{M_W^{\mathrm{est}}}{P(\theta = 90^\circ)} \tag{5}$$

An iterative process is created by repeating the procedure, from Eq. (4), until molecular weights and radii of gyration values no longer change significantly.

6. Results and discussions

6.1. Triple detection technique: accuracy and precision

Pullulan ($\bar{M}_W = 100,000$) was used as a light-scattering calibration standard and as the "unknown" for replicate injections; Viscotek's operating procedures were followed. Table 2 lists results and statistical analysis of the injections. Clearly, a high level of precision was achieved, however it was noted that the estimated polydispersity of the pullulan was higher than reported by the supplier (Polymer Laboratories, Amherst, MA.) who reported $M_W/M_N = 1.10$, based upon an ultracentifugal sedimentation equilibrium method. The present high values of polydispersity were due to an under-estimate of M_N rather than an over-estimate of M_W.

A more relevant precision study was performed by replicate injections of cellulose ether K4MP; once again pullulan ($\bar{M}_W = 100,000$) was used as the light-scattering calibrant. Results are listed in Table 3. Again, a high level of precision was achieved, and additionally, with the increased polydispersity of the samples, it was valid to present the M–H–S parameters. Comparison of the $\bar{M}_W$ values in Table 3 with corresponding ranges in Table 1 shows agreement.

Accuracy of the technique was evaluated by characterization of pullulan standards alone and blended together. Six pullulan standards were evaluated separately and the results are listed in Table 4. Pullulan ($\bar{M}_W = 100,000$) was used as a light-scattering calibration standard. Accuracy of the technique is further illustrated in Fig. 1, by the correlation coefficient of the fit to the experimental values. This plot has

Table 3
Precision study using K4MP as replicant (K and a are the M–H–S parameters. LS constant = 6.77×10^{-6})

Injection	M_W	M_N	Pd	IV_W (dl/g)	R_{gW} (nm)	R_{hW} (nm)	a	K (dl/g)$^{-a}$
K4MP	378,800	70,700	5.36	8.490	42.94	59.88	0.726	9.35×10^{-4}
K4MP	357,600	66,900	5.35	8.438	42.48	59.23	0.735	8.32×10^{-4}
K4MP	380,400	71,000	5.36	8.523	43.01	59.98	0.724	9.57×10^{-4}
K4MP	390,300	84,300	4.63	8.665	43.77	61.04	0.718	1.03×10^{-3}
Average	376,775	73,225	5.18	8.529	43.05	60.03	0.726	9.37×10^{-4}
St Dev	11915	6595	0.31	0.0842	0.46	0.65	0.0061	6.95×10^{-5}
St Dev %	3.16	9.01	6.08	0.99	1.08	1.08	0.84	7.42

Table 4
Accuracy by comparison with known pullulans (LS constant = 6.77×10^{-6})

Injection	Pullulan identity	M_W	M_N	Pd[a]	IV_W (dl/g)	R_{gW} (nm)	R_{hW} (nm)
ACCUR2	12,200	10,700	8,700	1.23	0.108	3.39	4.72
ACCUR3	23,700	20,700	17,400	1.19	0.162	4.84	6.73
ACCUR4	48,000	46,300	39,400	1.18	0.277	7.56	10.53
ACCUR1	100,000	100,000	87,600	1.14	0.455	11.56	16.10
ACCUR5	186,000	185,100	154,700	1.20	0.695	16.29	22.70
ACCUR6	380,000	412,500	337,700	1.22	1.189	25.42	35.42

[a] Polydispersity values in brackets were manufacturer's data from ultracentrifugal sedimentation equilibrium method.

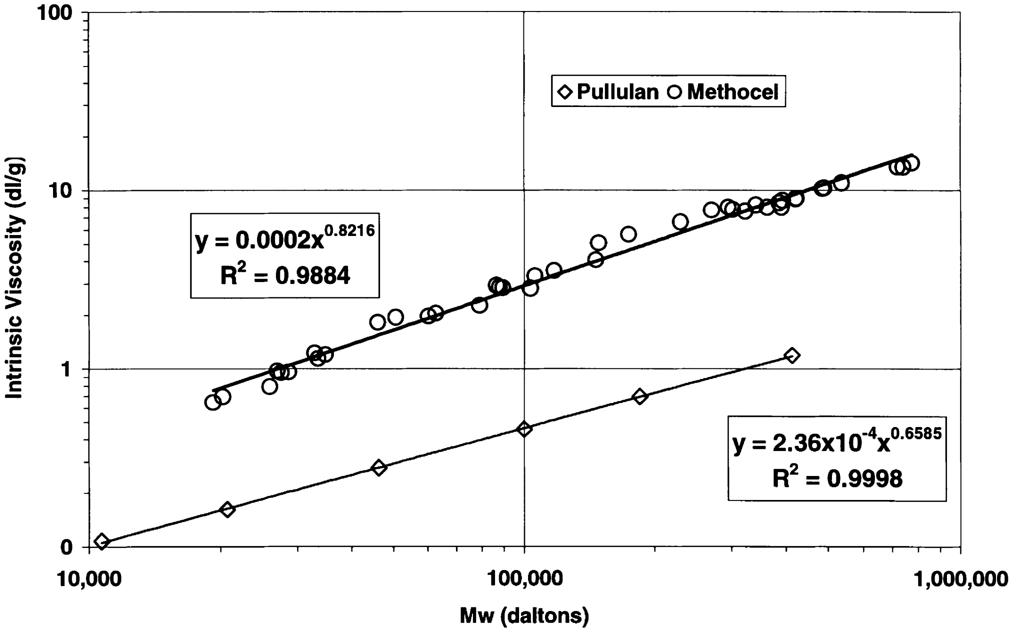

Fig. 1. Comparison of pullulan and cellulose ether.

also generated M–H–S parameters $a = 0.658$ and $K = 2.36 \times 10^{-4}$ $(\mathrm{dl/g})^{-a}$ for pullulans, which are in excellent agreement with $a = 0.635 \pm 5\%$ and $K = 3.6 \times 10^{-4} \pm 10\%$ dl/g (Poché et al., 1998).

A final measure of accuracy was provided by an evaluation of replicate injections of a blend of four pullulan standards as shown in Table 5. The blend comprised[4] P380K(0.0155 g), P186K (0.0214 g), P48K (0.0136 g) and P12.2K (0.0156 g); if we assume that the individual components of the blend are monodisperse, it is readily calculated that the blend should have the following characteristics:

$$\bar{M}_W = 162{,}000 \quad \bar{M}_N = 38{,}500 \quad \textit{and} \quad \mathrm{Pd} = 4.21.$$

Agreement between measured molecular weights and theoretical values is excellent. Standard deviations of all terms are acceptably low apart from the value of K which exhibited a standard deviation percentage = 23.13. Absolute average values for a and K were in almost perfect agreement with values obtained for the individual pullulans, as illustrated in Fig. 1.

7. M–H–S parameters and the Huggins parameter

M–H–S parameters are ubiquitously associated with polymer characterization. Eq. (1):

$$[\eta] = KM^a$$

contains parameters K and a which are complex functions of the polymer, solvent, co-solutes and temperature. Parameter a does not depend on the molecular weight of flexible-chain polymers but is reported (Lapasin & Pricl, 1995) to become a decreasing function of M for semi-flexible chains above a critical molecular weight. Both parameters are related to stiffness of the polymer and almost any a value from 0.4 to >1.2 has been reported for cellulosic derivatives (Brandrup & Immergut, 1989) in aqueous solution. K reflects the stereochemistry of the intra-molecular species and cellulosic derivatives are typically described (Lapasin & Pricl, 1995) as comprised of highly expanded coils,

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[4] For example, P100K = pullulan, $\bar{M}_W = 100{,}000$ daltons.

Table 5
Accuracy study by characterization of blended pullulan standards (LS constant = 6.77×10^{-6})

	M_W	M_N	Pd	IV_W (dl/g)	R_{gW} (nm)	R_{hW} (nm)	a	K (dl/g)$^{-a}$
Blend	179,800	42,800	4.20	0.609	14.27	19.88	0.683	1.76×10^{-4}
Blend	179,000	42,200	4.24	0.624	14.37	20.02	0.648	2.76×10^{-4}
Blend	179,700	43,000	4.18	0.594	14.15	19.71	0.688	1.60×10^{-4}
Blend	179,100	40,700	4.40	0.614	14.28	19.89	0.652	2.59×10^{-4}
Average	179,400	42,175	4.26	0.610	14.27	19.88	0.67	2.18×10^{-4}
St Dev	353.55	901.04	0.0865	0.0108	0.0782	0.1101	0.0179	5.04×10^{-5}
St Dev %	0.20	2.14	2.03	1.77	0.55	0.55	2.68	23.13

leading to high values of K, as a consequence of the 1,4-linkage within the backbone of the polymer chains.

The Huggins equation describes the relationship between reduced viscosity and concentration for dilute polymer solutions:

$$\frac{\eta_{sp}}{c} = [\eta] + k'[\eta]^2 c \tag{6}$$

If we plot reduced viscosity versus concentration for a series of dilute polymer solutions and extrapolate to zero concentration, the intercept with the viscosity axis gives the intrinsic viscosity. Further, if we divide the slope of the line by the square of the intrinsic viscosity, we obtain k'_H, the dimensionless Huggins parameter, which has commonly been observed to have a value between 0.3 and 0.4 in good solvents and 0.5–0.8 in θ-solvents (Lapasin & Pricl, 1995). The Huggins parameter is considered to be an indicator of pair-wise hydrodynamic interaction between polymer chains in a given solvent. There is a wide scatter of values of k'_H for cellulosic derivatives in the literature (Brandrup & Immergut, 1989).

In Tables 6–9, cellulose ethers from different batches were used in replicate experiments unless it is stated otherwise. The symbol $[\eta]$ has been reserved for intrinsic viscosity as measured by Ubbelohde tubes and bulk solutions. Intrinsic viscosity as measured by the chromatographic technique has been given the symbol IV.

7.1. A-chemistry, methylcellulose

A selection of A-chemistry METHOCEL products was examined and the results are summarized in Table 6. A log–log plot of IV_W versus M_W, from the TriSEC evaluations, gave K_A and a_A values for the selection of cellulose ethers which were analyzed; correlation coefficient $R^2 = 0.9968$, Table 10. Huggins parameter exhibited a significant scatter of values.

Molecular weights according to Ubbelohde tube measurements of the bulk solution were calculated by equation:

$$M_V = \left(\frac{[\eta]}{K_x}\right)^{\frac{1}{a_x}} \tag{7}$$

where, x designates the METHOCEL chemistry. The sole purpose of using Eq. (7) was to illustrate the level of agreement that might be expected between chromatographic and bulk experiments when reliable M–H–S parameters were available.

Molecular weights by both methods are in relatively good agreement but were not consistent with those ranges shown in Table 1. Molecular weight, from Ubbelohde tube measurements of bulk solution, is viscosity-averaged, $\bar{M}_V$, and would be expected to be less than $\bar{M}_W$ from SEC. Another source of difference between bulk, Ubbelohde tube measurements and the SEC technique was that bulk measurements were performed in deionized water.

An alternative form of the M–H–S equation relates intrinsic viscosity to the degree of polymerization, DP, a term which is commonly encountered in the literature of cellulose and its derivatives:

$$[\eta] = K'(\mathrm{DP})^{a'}$$

a log–log plot gave $R^2 = 0.9969$, $K' = 2.06 \times 10^{-2}$ and $a' = 0.815$.

7.2. E-chemistry, hydroxypropyl methylcellulose

A selection of E-chemistry METHOCEL products was examined and the results are summarized in Table 7. A log–log plot of IV_W versus M_W, from the TriSEC evaluations, gave K_E and a_E values for the selection of cellulose ethers which were analyzed; correlation coefficient $R^2 = 0.9958$, Table 10. Huggins parameter exhibited a significantly narrower scatter of values than was found with A-chemistry. Comparing the Huggins parameters for A and E chemistries reveals no clear difference in the magnitude of their values. It had been anticipated that A-chemistry, as a consequence of its more-hydrophobic nature, would exhibit Huggins values which reflected an enhanced polymer–polymer interaction in comparison with the more-hydrophilic E-chemistry; this was not observed.

Molecular weights according to Ubbelohde tube measurements of the bulk solution were calculated by Eq. (7). M_W by both methods are in relatively good agreement, were not consistent with those ranges shown in Table 1 but were consistent with the values which were presented in Table 6 for A-chemistry.

Table 6
METHOCEL A; characterization by SEC with LS-DP-RI detectors

Methocel	Ubbelohde					TriSEC							
					Huggins							M–H–S	
	R[a]	DP[b]	$[\eta]$ (dl/g)	M_V	k'_H	M_W	M_N	Pd	DP[c]	%rec[d]	IV$_W$ (dl/g)	a	K (dl/g)$^{-a}$
A15	187	237	1.7064	44,300	0.6413	46,000	21,300	2.2	246	96.5	1.82	0.902	1.24×10^{-4}
A15						50,600	14,700	3.4	271	92.9	1.93	0.886	1.43×10^{-4}
A4C FG	187	643	3.8282	120,200	1.4300	174,500	76,700	2.3	933	98.8	5.63	0.744	8.09×10^{-4}
A4C FG						148,900	50,600	2.9	796	94.6	5.04	0.809	3.66×10^{-4}
A15C	187	965	5.3165	180,300	1.0449	229,700	59,300	3.9	1,230	89.5	6.59	0.770	5.81×10^{-4}
A4M	188	1,379	7.1344	259,200	0.7993	270,800	70,500	3.8	1,440	87.1	7.72	0.777	5.52×10^{-4}
A4M						295,400	69,800	4.2	1,571	96.4	8.00	0.745	7.91×10^{-4}

[a] Average formula weight of the repeat unit of the molecule.
[b] Degree of polymerization = (M_v)/R.
[c] Degree of polymerization = (M_W from SEC)/R.
[d] Calculated weight-percent recovered of injected sample.

Table 7
METHOCEL E; characterization by SEC with LS-DP-RI detectors

Methocel	Ubbelohde					TriSEC							
					Huggins							M–H–S	
	R[a]	DP[b]	$[\eta]$ (dl/g)	M_V	k'_H	M_W	M_N	Pd	DP[c]	%Rec[d]	IV$_W$ (dl/g)	a	K (dl/g)$^{-a}$
E3P	203	77	0.5422	15,600	0.9788	20,300	8,080	2.5	100	95.3	0.69	0.965	5.02×10^{-5}
E5P	203	125	0.8097	25,300	0.8674	28,700	11,100	2.6	141	94.8	0.96	0.948	5.98×10^{-5}
E6P	200	170	1.0321	34,000	0.6513	34,800	12,300	2.8	174	98.6	1.20	0.931	7.56×10^{-5}
E15P	203	296	1.6533	60,000	0.8177	60,300	24,800	2.4	297	94.8	1.97	0.846	1.93×10^{-4}
E50P	199	485	2.4454	96,500	0.8052	86,700	33,800	2.6	436	82.7	2.91	0.894	1.23×10^{-4}
E4MP	203	1,792	7.3244	363,700	0.7184	323,200	78,700	4.1	1,592	87.6	7.55	0.741	7.26×10^{-4}
E4MP						363,100	61,800	5.9	1,789	92.3	7.98	0.765	5.54×10^{-4}
E10MP CR	201	1,986	7.9107	399,200	0.9060	394,200	65,200	6.1	1,961	88.5	8.69	0.712	1.07×10^{-3}
E10MP CR						423,000	73,500	5.8	2,104	87.9	8.96	0.731	8.47×10^{-4}
E10MP CR						421,900	68,400	6.2	2,099	90.9	8.90	0.732	8.38×10^{-4}

[a] Average formula weight of the repeat unit of the molecule.
[b] Degree of polymerization = (M_v)/R.
[c] Degree of polymerization = (M_W from SEC)/R.
[d] Calculated weight-percent recovered of injected sample.

Table 8
METHOCEL F; characterization by SEC with LS-DP-RI detectors

Methocel	Ubbelohde					TriSEC							
					Huggins							M–H–S	
	R[a]	DP[b]	$[\eta]$ (dl/g)	M_V	k'_H	M_W	M_N	Pd	DP[c]	%Rec[d]	IV$_W$ (dl/g)	a	K(dl/g)$^{-a}$
F4P	198	100	0.7484	19,700	1.0697	27,000	14,900	1.8	136	95.4	0.97	0.951	6.22×10^{-5}
F4P						27,600	8,950	3.1	139	98.2	0.95	0.973	4.80×10^{-5}
F7						32,900	13,000	2.5		101.5	1.23	0.861	1.70×10^{-4}
F7						33,500	11,300	3.0		89.5	1.13	0.931	7.48×10^{-5}
F17						79,200	25,800	3.1		94.1	2.27	0.880	1.24×10^{-4}
F17						62,600	16,000	3.9		103.9	2.03	0.889	1.23×10^{-4}
F50P	196	371	2.2726	72,700	1.3067	89,400	29,300	3.1	456	99.4	2.83	0.824	2.61×10^{-4}
F50P						87,800	27,800	3.2	448	103.1	2.84	0.816	2.90×10^{-4}
F50P						103,600	53,700	1.9	529	96.9	2.80	0.841	1.91×10^{-4}
F50P						106,200	50,300	2.1	542	100.1	3.30	0.812	3.03×10^{-4}
F4MP	196	1,286	6.5557	252,000	1.1936	341,500	65,600	5.2	1,742	96.1	8.21	0.769	5.56×10^{-4}
F4MP						302,300	85,200	3.6	1,542	90.8	7.73	0.756	6.41×10^{-4}

[a] Average formula weight of the repeat unit of the molecule.
[b] Degree of polymerization = (Mv)/R
[c] Degree of polymerization = (Mw from SEC)/R.
[d] Calculated weight-percent recovered of injected sample.

Table 9
METHOCEL K; characterization by SEC with LS-DP-RI detectors

Methocel	Ubbelohde					TriSEC							
					Huggins							M–H–S	
	R^{a}	DP[b]	$[\eta]$ (dl/g)	M_V	k'_H	M_W	M_N	Pd	DP[c]	%Rec[d]	IV_W (dl/g)	a	$K(\text{dl/g})^{-a}$
K3P	198	85	0.5931	16,700	0.7353	26,000	10,900	2.4	131	102.1	0.79	0.964	4.72×10^{-5}
K3P						19,300	6,480	3.0	97	94.1	0.64	0.928	7.24×10^{-5}
K100P	195	512	2.6445	99,800	0.7700	146,500	61,700	2.4	751	103.2	4.06	0.791	3.88×10^{-4}
K100P						117,500	28,800	4.1	603	99.6	3.54	0.799	3.62×10^{-4}
K4MP	195	1,668	7.1164	325,400	0.8714	390,700	66,900	5.8	2,004	90.5	7.96	0.737	8.00×10^{-4}
K4MP						386,700	97,200	4.0	1,983	83.6	8.46	0.723	9.66×10^{-4}
K15MP	196	2,154	8.8534	422,200	0.7356	485,000	75,300	6.4	2,474	99.0	10.18	0.730	9.08×10^{-4}
K15MP						537,300	106,000	5.1	2,741	93.1	10.92	0.683	1.65×10^{-3}
K15MP						489,500	83,000	5.9	2,497	98.2	10.25	0.729	9.18×10^{-4}
K100MP	199	2,939	11.63	584,800	1.03	720,200	150,600	4.8	3,674	96.4	13.43	0.674	1.89×10^{-3}
K100MP						775,700	125,200	6.2	3,958	93.1	14.11	0.643	2.79×10^{-3}
K100MP						742,600	97,700	7.6	3,789	96.1	13.40	0.680	1.73×10^{-3}

[a] Average formula weight of the repeat unit of the molecule.
[b] Degree of polymerization = (Mv)/R.
[c] Degree of polymerization = (M_W from SEC)/R.
[d] Calculated weight-percent recovered of injected sample.

An alternative form of the M–H–S equation relates intrinsic viscosity and degree of polymerization:

$$[\eta] = K'(\mathrm{DP})^{a'}$$

a log–log plot gave $R^2 = 0.9962$, $K' = 1.67\times10^{-2}$ and $a' = 0.826$.

7.3. F-chemistry, hydroxypropyl methylcellulose

A selection of F-chemistry METHOCEL products was examined and the results are summarized in Table 8. A log–log plot of IV_W versus M_W, from the TriSEC evaluations, gave K_F and a_F values for the selection of cellulose ethers which were analyzed; correlation coefficient $R^2 = 0.9945$, Table 10. The limited number of Huggins parameter values were closely grouped around an approximate average value of 1.2.

Molecular weights according to Ubbelohde tube measurements of the bulk solution were calculated by Eq. (7). M_W by both methods are in relatively good agreement, were consistent with the values which were presented for A and E chemistries, but agreed poorly with those ranges shown in Table 1.

An alternative form of the M–H–S equation relates intrinsic viscosity and degree of polymerization:

$$[\eta] = K'(\mathrm{DP})^{a'}$$

a log–log plot gave $R^2 = 0.9955$, $K' = 1.46\times10^{-2}$ and $a' = 0.853$.

Table 10
M–H–S parameters for A, E, F and K chemistry METHOCEL products

Methocel	a	$K\ (\text{dl/g})^{-a}$
A	0.813	0.000294
E	0.827	0.000186
F	0.852	0.000164
K	0.838	0.000172

7.4. K-chemistry, hydroxypropyl methylcellulose

A selection of K-chemistry METHOCEL products was examined and the results are summarized in Table 9. A log–log plot of IV_W versus M_W, from the TriSEC evaluations, gave K_K and a_K values for the selection of cellulose ethers which were analyzed; correlation coefficient $R^2 = 0.977$, Table 10. Huggins parameter exhibited the least scatter in comparison to all other chemistries which were examined; it is not certain that this reflects the fact that the K-substitution region is the least hydrophobic of all systems studied in this program. Comparing the Huggins parameters for A, E and F chemistries reveals no clear difference in absolute values.

Molecular weights according to Ubbelohde tube measurements of the bulk solution were calculated by Eq. (7). M_W by both methods are in relatively good agreement, were not consistent with those ranges shown in Table 1, but were consistent with the present values for A, E and F chemistries.

An alternative form of the M–H–S equation relates intrinsic viscosity and degree of polymerization:

$$[\eta] = K'(\mathrm{DP})^{a'}$$

a log–log plot gave $R^2 = 0.9961$, $K' = 1.46\times10^{-2}$ and $a' = 0.836$.

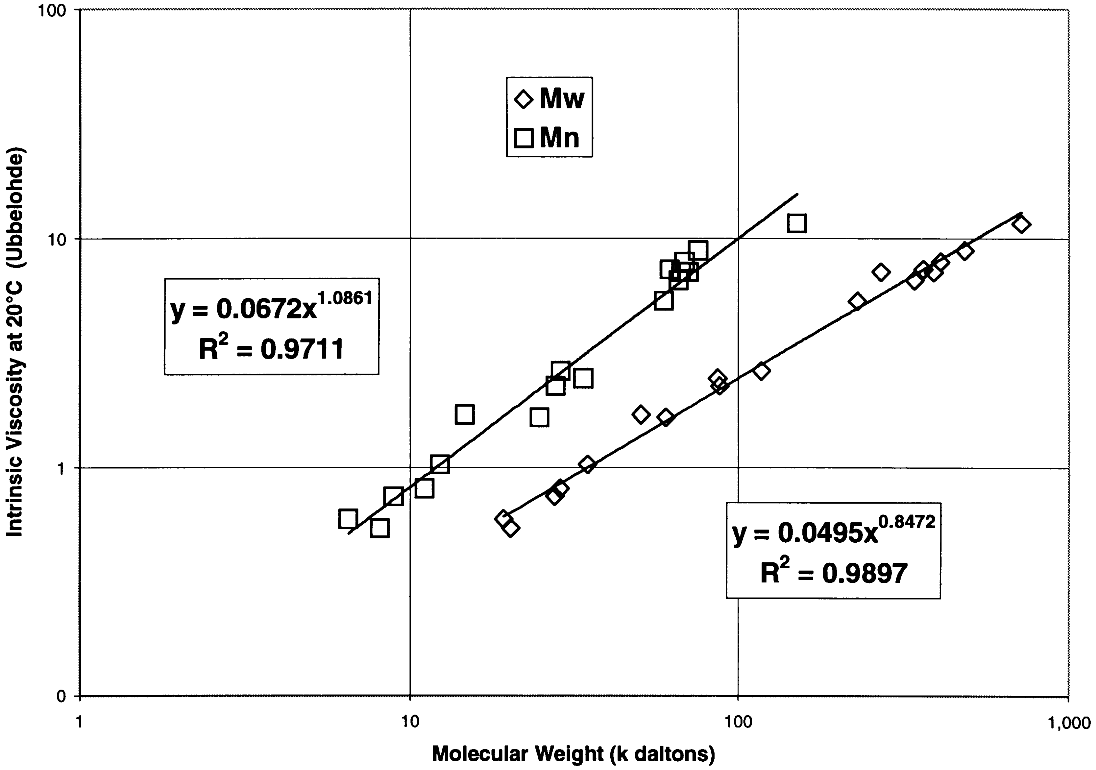

Fig. 2. Molecular weight / Intrinsic Viscosity (Ubbelohde) correlation.

8. Cellulose ethers summary

Combining all of the METHOCEL and pullulan results into one M–H–S plot, Fig. 1, provides a convenient comparison of the influence of polymer chain stiffness. The overall M–H–S parameters for METHOCEL products were derived from data with a low correlation coefficient; for this reason, it is recommended that *a* and *K* values be applied from the individual chemistries as listed in Table 10.

In Fig. 1, we plot values of IV_W versus $\bar{M}_W$, the plot not only reflects the influence of Eq. (1) but also illustrates that, for similar molecular weights, cellulose ethers exhibit intrinsic viscosities which are approximately one order of magnitude greater than those of pullulans.

Fig. 2 clearly confirms that there are significant correlations between intrinsic viscosity, as measured on bulk solutions by Ubbelohde tube, and molecular weight averages from TriSEC; this is merely a consequence of behaviors which may be

Table 11
Published results for identifiable cellulose ethers systems

Name	Viscosity grade	$[\eta]$ (dl/g)	k'_H	M_W (kDa)	M_N (kDa)	M_W/M_N	Technique[a]
E3P	3	0.69	0.45	15.0	9.3	1.6	IV, Os for M_N
E6P	6	0.92	0.56	21.0	12.0	1.8	IV, Os for M_N
Metolose 60SH-50[b]	50	2.65	0.63	63.0	31.0	2.0	IV, Os for M_N
Metolose 60SH-50	50			132.0	35.0	3.8	MALLS
F50	50			96.0	43.0	2.2	SEC/LALLS
F50	50			113.0			MALLS
E4MEP	4M	7.40		301.0	137.0	2.2	SEC/LALS/RI
E4MP	4M			170.0	100.0	1.7	IV, Os for M_N
E4MP	4M			225.0	117.0	1.9	MALLS
Metolose 60SH-10000	10M	9.4		220.0	120.0	1.8	IV, Os for M_N
E10MP	10M			309.0	158.0	2.0	MALLS
K15M	15M	9.20		770.0	400.0	1.9	SEC/MALLS
K15M	15M			498.0	100.0	5.0	SEC/LALLS
E75M	75M			902.0	508.0	1.8	SEC/LALLS
J75M	75M			1,025.0	346.0	3.0	SEC/LALLS

[a] IV = intrinsic viscosity, MALLS = multi-angle, laser light scattering, LALLS = low-angle, laser light scattering, O_s = osmometry.

[b] Trademark of Shin-Etsu Chemical Company, Japan.

Table 12
Summary of cellulose ether ranges

Methocel	Ubbelohde			TriSEC				
			Huggins					
	$[\eta]$ (dl/g)	M_v (kDa)	k'_H	M_W (kDa)	M_N (kDa)	M_W/M_N	IV_W (dl/g)	Rg_w (nm)
E3P	0.54	13.9	0.98	20.3	8.1	2.5	0.70	7.4
K3P	0.59	14.9	0.74	19.3	6.5	3.0	0.64	7.0
F4P	0.75	18.8	1.07	27.6	8.9	3.1	−0.95	8.8
E5P	0.81	22.3	0.87	28.7	11.1	2.6	0.96	9.2
E6P	1.03	29.7	0.65	34.8	12.3	2.8	1.20	10.5
E15P	1.65	51.8	0.82	60.3	24.8	2.4	1.97	15.1
A15	1.71	39.3	0.64	50.6	14.7	3.4	1.93	13.7
F50P	2.27	73.8	1.31	87.8	27.8	3.2	2.84	19.1
E50P	2.45	82.2	0.81	86.7	33.8	2.6	2.91	19.1
K100P	2.64	103.3	0.77	117.5	28.8	4.1	3.54	22.2
A15C	5.32	188.0	1.04	229.7	59.3	3.9	6.59	34.0
F4MP	6.56	252.0	1.19	341.5	65.6	5.2	8.21	41.3
K4MP	7.12	325.3	0.87	390.7	66.9	5.8	7.96	41.5
A4M	7.13	259.2	0.80	270.8	70.5	3.8	7.72	37.8
E4MP	7.32	363.7	0.72	363.1	61.8	5.9	7.98	41.3
E10MP CR	7.91	399.2	0.91	410.0	68.5	6.0	8.80	45.5
K15MP	8.85	422.2	0.74	485.0	75.3	6.4	10.18	49.2
K100MP	11.63	584.8	1.03	720.2	150.6	4.8	13.43	62.5

described by Eq. (7). It is doubtful if we would ever wish to sell cellulose ethers according to molecular weight; the convenience and familiarity of a simple viscosity measurement are significant. However, it appears from Fig. 2, that intrinsic viscosity may provide an accurate reflection of molecular weights of cellulose ethers. There are currently efforts underway within The Dow Chemical Company to evaluate measurement of intrinsic viscosity as an alternative to apparent viscosity.

Table 11 provides a summary of recently published results of independent analyses of cellulose ethers. Table 12 is a subjective summary of the main findings of the present study compiled from results of multiple experiments which were performed with cellulose ethers from multiple batches. Results are arranged in order of increasing $[\eta]$. In most cases, the same order is reflected in the TriSEC measurements of IV_W but discrepancies exist for 4 M mPa s viscosities. It is unclear if these occur due to non-exclusion interactions with the chromatographic columns or if they are simply reflections of normal, batch-to-batch variations. It is anticipated that experience with the technique will clarify this situation. $\bar{M}_V$, as expected, was less than $\bar{M}_W$ from SEC, however the difference between the two averages did not exhibit any obvious trend with chemistries or viscosity ranges.

As expected, any trends in the Huggins parameters were obscured by scatter of the values; it was interesting to note that their general magnitude was significantly greater than published values; Lundqvist (1999) has reported $k'_H = 0.45$ for E3P and 0.56 for E6P; and Nilsson et al. (1995) reported 0.54 for E4M. Reports of values of Huggins parameter >1.0 are not uncommon (Brandrup & Immergut, 1989; Nilsson et al., 1995) for cellulosic derivatives. $\bar{M}_W$ followed the intrinsic viscosity order almost perfectly but $\bar{M}_N$ exhibited many departures.

By comparing ranges from Table 1 with values in Tables 11 and 12, it may be concluded that:

- SEC/RI provided an over-estimate of $\bar{M}_W$, consequently Pd was frequently much higher than would be expected upon derivitization of cellulose;
- $\bar{M}_N$ by SEC/RI is especially unreliable;
- the TriSEC procedure provides values of $\bar{M}_W$ and $\bar{M}_N$ which are self-consistent across METHOCEL chemistry ranges;
- the TriSEC procedure provides values of $\bar{M}_W$ and $\bar{M}_N$ which generally agree with recently published results from independent researchers using various combined techniques;
- the TriSEC procedure provides values of $\bar{M}_N$ which tend to be greater than $\bar{M}_N$ values from osmometry.

9. Conclusions

Initial evaluation of the current multiple-detector SEC technique has shown:

- that it is capable of high precision and accuracy;
- applicability to the analyses of cellulose ethers;
- ability to generate consistent values of R_{gW}, IV_W, $\bar{M}_W$, $\bar{M}_N$ and polydispersity.

Additional capabilities, such as generation of various averages of intrinsic viscosity and radius of gyration, have not been fully evaluated but it is anticipated that these will provide further tools for characterization of cellulose ethers. Comparison of polydispersities based on molecular weight with polydispersities based on intrinsic viscosity or radius of gyration have the potential to characterize cellulose ethers as never before.

Cellulose ethers in this study were used 'as received', solutions were not dialyzed, corrections were not made for salt content or moisture content and batches were not specially selected. The robustness, convenience and reproducibility of this technique are impressive.

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