

Influence of electrolytes on the hydration of methylcellulose in solution

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Light-scattering techniques were used to obtain weight-average molecular weights for three grades of methylcellulose in water. On addition of electrolyte to the polymer solutions the molecular weight was not found to alter but the root-mean-square end-to-end length decreased. This contrasts with the results of Neely (1963). The exponent α of the Mark-Houwink viscosity equation was also found to decrease in the presence of electrolyte. Two stages of polymer dehydration are suggested for non-ionic cellulose ether derivatives.

The non-ionic cellulose ether derivatives methylcellulose (MC) and hydroxypropylmethylcellulose (HPMC) are often used as pharmaceutical suspending agents. The ethers differ in their effects on the addition of salts, the salt tolerance depending on the ions present (Savage, 1965; Dow Chemical Company, 1966).

Molecular studies on methylcellulose have previously been reported by Neely (1963) and Uda & Meyerhoff (1961). The molecular properties of other cellulose ethers, e.g. ethylhydroxyethylcellulose, sodium carboxymethylcellulose, have also been examined (Trap & Hermans, 1954; Schneider & Doty, 1954; Manley, 1956; Jullander, 1957; Öhman, 1969; Kassem & Mattha, 1970).

Heymann (1935) and Levy & Schwarz (1958) reported the effect of additives on the gel point depression of MC. Heymann considered the gel point depression to be due to polymer dehydration with subsequent association of the dehydrated chains with one another to form a gel.

In the present work the molecular properties of MC in aqueous solution have been determined by light scattering and viscometry, and the influence of various electrolytes on these properties have been observed. The aim was to seek relations between electrolytes and the degree of hydration of the MC molecules in solution.

MATERIALS AND METHODS

Materials

Methylcellulose: Methocel MC10 Premium, MC100 Premium and MC400 Standard supplied by the Dow Chemical Company. *Hydroxypropylmethylcellulose:* Methofas PM50 Powder supplied by ICI Limited, Nobel Division. *Distilled water*—freshly distilled and cooled; filtered through a 0.1 μm Millipore membrane. *Electrolytes*—sodium chloride, potassium chloride, lithium chloride, magnesium chloride, calcium chloride—laboratory reagent quality.

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Apparatus

A Brice Phoenix Model 2000 Universal Light-Scattering photometer was used in conjunction with readout on a Honeywell Brown Continuous Balance Potentiometer which was modified slightly to reduce the noise level (John, 1972). The photometer was used at a wavelength of 546 nm, and calibrated against the opal glass reference standard supplied by the manufacturer and against Bovine Serum Albumin. The refractive index increment dn/dc , was determined on a Brice Phoenix Model BP-2000-V differential refractometer.

Suspended level glass capillary viscometers with nominal constants of 0.01 cS s^{-1} were used to determine the viscosity ratio, η/η_0 , of solutions at $25^\circ \pm 0.1^\circ$.

Preparation of solutions

Stock solutions of the polymers were prepared by mechanically dispersing the required quantity of previously dried powder in about one third of the required volume of distilled water at 85 to 90° . When the powder was fully wetted, the remainder of the water was added as ice and the stirring continued until homogeneous. All diluted solutions were clarified either by filtration or centrifugation.

Determination of weight-average molecular weights

The basic light-scattering equation for the determination of weight-average molecular weight, \bar{M}_w , by the extrapolation method of Zimm (1948) is given by

$$\frac{K_m c}{R(\theta)} = \frac{1}{\bar{M}_w} + 2 A_2 c + \dots \dots \dots (1)$$

where c = concentration of solution in g of solute per ml of solution; $K_m = \frac{2 \pi^2 n^2 (dn/dc)^2}{N \lambda^4}$; $R(\theta)$ = reduced intensity at angle θ ; A_2 = second virial coefficient (higher order terms normally being neglected); N = Avogadro's number; λ = wavelength of light *in vacuo*; n = refractive index of solution; and π has its usual significance.

For large particles of high molecular weight, the radius of gyration, R_g , can be determined from the slope of the zero concentration line of the Zimm plot. The root-mean-square end-to-end length, \bar{h} , is readily obtained from the radius of gyration. The limiting slope of the zero angle line of the Zimm plot is used to calculate the second virial coefficient, A_2 , a function of the polymer-solvent interaction (Stacey, 1956). Experimentally values of $K_m c/R(\theta)$ are required for each angle θ and concentration, c . To simplify the collection and interpretation of experimental data it is convenient (Evans, Huglin & Lindley, 1967; John, 1972) to subdivide the Rayleigh Ratio $R(\theta)$, in the form

$$R(\theta) = WYZ \dots \dots \dots (2)$$

where W = the sum of all the constants in $R(\theta)$; Y = a constant for each angle; Z = the experimentally determined portion of $R(\theta)$. Equation (1) can then be written in the form

$$\frac{K_m}{W} \cdot \frac{c}{YZ} = \frac{1}{\bar{M}_w} + 2 A_2 c + \dots \dots \dots (3)$$

The Zimm plot can now be drawn in the form c/YZ vs $\sin^2(\theta/2) + kc$, where k is an arbitrary constant scale factor. The intercept at $c = \theta = 0$ yields the value $(W/K_m)(\bar{M}_w)^{-1}$ from which \bar{M}_w can be calculated. The second virial coefficient and the radius of gyration are also calculated from the Zimm plot.

Determination of limiting viscosity numbers

The viscosity number, $(\eta - \eta_0)/\eta_0 c$, expresses the average contribution of the solute molecules at concentration, c , to the viscosity, where η , and η_0 are the viscosities of the solute and solvent respectively. The limiting viscosity number (LVN), $[\eta]$, is the value of the viscosity number at infinite dilution and is a measure of the capacity of a polymer molecule to enhance the viscosity. When equations (4) and (5) (Huggins, 1942; Kraemar, 1938) are used to obtain the LVN both equations have a common intercept at $c = 0$.

$$\frac{\eta - \eta_0}{\eta_0 c} = [\eta] + k_1 [\eta]^2 c + k_2 [\eta]^3 c^2 + \dots \quad (4)$$

$$\frac{\ln(\eta/\eta_0)}{c} = [\eta] - k_1' [\eta]^2 c - k_2' [\eta]^3 c^2 - \dots \quad (5)$$

It has been shown (Maron & Reznik, 1969) that $k_1 + k_1' = 0.5$ and $k_2 + k_2' = k_1 - 0.33$.

Mark and Houwink (Huggins, 1958) proposed the relation

$$[\eta] = K_v \bar{M}_v^\alpha \quad (6)$$

where K_v and α depend on the properties of the solute and solvent molecules and their interactions; \bar{M}_v = viscosity-average molecular weight. At the theta temperature or in a theta solvent equation (6) for a randomly coiled molecule becomes

$$[\eta]_\theta = K_v \theta_v^{0.5}$$

As α varies from 0.5 to 1.0, the molecule becomes more perturbed until finally when $\alpha = 1$, $\bar{M}_v = \bar{M}_w$.

RESULTS AND DISCUSSION

Neely (1963) in his study on HPMC and MC, found that the method of preparation and storage of MC solutions was critical. He found that a freshly prepared MC solution which had not been refrigerated exhibited a \bar{M}_w of 200 000 but a solution which had been refrigerated at 4° for 48 h had a \bar{M}_w of 122 000. Further periods of refrigeration had no detectable effect. In this work a MC '400' preparation was subjected to various storage conditions and it was found that there was no appreciable alteration in the limiting viscosity number of the macromolecule whether stored at laboratory temperatures or at 4° (Table 1). However, in line with the findings of Neely, it was decided that all MC solutions would be refrigerated until immediately before use. This also had the added advantage of precluding the use of a preservative.

Neely found that MC and HPMC formed aggregates in the presence of sodium chloride, although he did not study the effects of other salts on MC or HPMC. He obtained curved Zimm plots and assuming the curvature was due to polydispersity he

Table 1. *Effect of storage of MC '400' on viscosity data.*

	Storage after preparation				
	2 h R.T.	24 h R.T.	24 h 4°C	48 h 4°C	12 days 4°C
$[\eta]$	4.50	4.50	4.60	4.40	4.45
k_1	0.444	0.494	0.491	0.475	0.460
$k_1 + k_1'$	0.493	0.524	0.519	0.516	0.521

R.T. = Room Temperature = 21°.

obtained \bar{M}_n values from equation (7) which is the limiting case at higher angles, according to Schneider & Doty (1954).

$$K_{mc}/R(\theta) = (1/\bar{M}_n) [1/2 + N_n(U/2) + \dots \dots \dots] \quad (7)$$

where N_n = number average degree of polymerization; \bar{M}_n = number-average molecular weight; $U = [(4\pi/\lambda')\sin(\theta/2)]^2(b^2/6)$; b = effective bond length = $(h_n^2)^{1/2}/(N_n)^{1/2}$; and λ' = wavelength of light in the medium.

This technique has been questioned (Banks, Greenwood & Sloss, 1969) as the curvature could be due to dust in the solutions. In contrast to Neely, we obtained rectilinear Zimm plots for MC in water (Table 2, and Fig. 1) and in various concentrations of sodium chloride solutions (Table 3). We found that the addition of electrolyte did not alter the weight-average molecular weight, and the mean square end-to-end distance was found to depend on the concentration of sodium chloride added. We found a decrease in the mean square end-to-end length with increasing salt concentration, and attribute this to the removal of water from the macromolecule, more water being removed by an increased sodium chloride concentration. This has the effect of causing the macromolecules to become more coiled until ultimately sufficient salt would be present to form the theta condition. This is also supported by the general decrease in the second virial coefficient as the sodium chloride concentration is decreased.

From the data given by Savage (1965), the Dow Chemical Company (1966), and us, a log-log plot of $[\eta]$ against \bar{M}_n was constructed and number average molecular weights of 1.7×10^4 , 3.06×10^4 and 4.72×10^4 obtained for MC'10', MC'100' and

Table 2. *Light-scattering results for methylcellulose in water.*

MC Grade	400	100	10
Intercept, $c = \theta = 0$	0.01	0.02	0.035
Slope, $c = 0$	1.43	0.77	0.76
} $\left. \begin{array}{l} \text{Slope, } c = 0 \\ \text{Intercept, } c = \theta = 0 \end{array} \right\}$	143	38.5	21.71
	$\bar{M}_w, \times 10^{-6}$	8.08	4.02
$(R_g)^2, \times 10^{-6}, (\text{\AA})^2$	45.512	12.253	6.911
$(\bar{h})^2, \times 10^{-8}, (\text{\AA})^2$	273.072	73.518	41.466
$(\bar{h}), \times 10^{-3}, \text{\AA}$	16.53	8.574	6.439
Slope, $\theta = 0$	17.50	7.95	-0.167
$A_2, \times 10^5$	10.83	4.94	-0.104

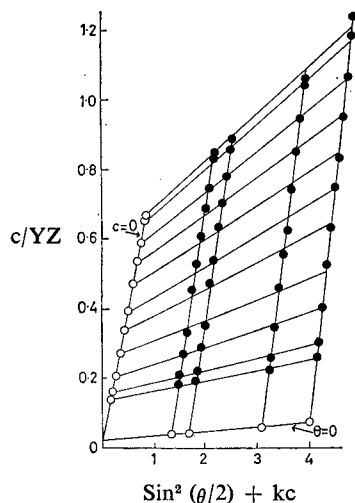


FIG. 1. Zimm plot of MC '100' in water. Closed circles represent experimental data; open circles represent extrapolated data.

Table 3. Light-scattering results for MC '100' in sodium chloride solutions

Solvent	Sodium chloride			
	0.500M	0.375M	0.250M	0.125M
Intercept, $c = \theta = 0$	0.02	0.02	0.02	0.02
Slope, $c = 0$	0.27	0.27	0.40	0.56
$\left. \begin{array}{l} \text{Slope, } c = 0 \\ \text{Intercept, } c = \theta = 0 \end{array} \right\}$	13.5	13.5	20.0	28.0
$\bar{M}_w, \times 10^{-6}$	4.02	4.02	4.02	4.02
$(R_g)^2, \times 10^{-6}, (\text{\AA})^2$	4.297	4.297	6.365	8.912
$(\bar{h})^2, \times 10^{-6}, (\text{\AA})^2$	25.782	25.782	38.190	53.472
$(\bar{h}), \times 10^{-3}, \text{\AA}$	5.078	5.078	6.180	7.313
Slope, $\theta = 0$	2.22	2.53	5.97	17.25
$A_2, \times 10^8$	1.38	1.57	3.71	10.72

Table 4. Effect of added electrolyte on the viscosity data for the three grades of methylcellulose.

MC Type	Salt added (All 0.2M)	LVN (dl/g)	k_1	k_1'	$k_1 + k_1'$
10	MgCl ₂	1.508	0.243	0.231	0.474
	LiCl	1.404	0.453	0.075	0.528
	KCl	1.410	0.423	0.101	0.524
	CaCl ₂	1.560	0.156	0.321	0.477
100	MgCl ₂	3.15	0.431	0.085	0.516
	LiCl	2.65	0.598	-0.091	0.507
	KCl	2.70	0.658	-0.176	0.482
	CaCl ₂	3.30	0.356	0.118	0.474
400	MgCl ₂	4.30	0.502	0.013	0.515
	LiCl	4.20	0.717	-0.181	0.536
	KCl	4.10	0.571	-0.071	0.500
	CaCl ₂	4.40	0.434	0.062	0.496

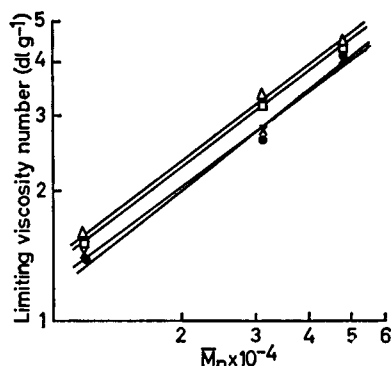


FIG. 2. Log-log plot of limiting viscosity number against \bar{M}_n for MC in the presence of 0.2M magnesium chloride (\square , $\alpha = 0.76$), 0.2M lithium chloride (\bullet , $\alpha = 0.81$), 0.2M potassium chloride (\times , $\alpha = 0.76$), and 0.2M calcium chloride (Δ , $\alpha = 0.75$). In the absence of electrolytes α was found to be 0.89.

MC'400' respectively. Using the viscometric data we obtained (Table 4) and constructing a similar log plot of $[\eta]$ against \bar{M}_n (Fig. 2) shows that the Mark-Houwink exponent, α , which is related to the degree of extension of the macromolecule, is decreased in the presence of salt solutions. Thus the end-to-end length is reduced by the addition of salt solutions, and this serves to confirm the light-scattering results for MC in the presence of sodium chloride solutions. The effect of salt solutions on the viscometric properties for HPMC'50' was not as marked as that for MC (John, 1972).

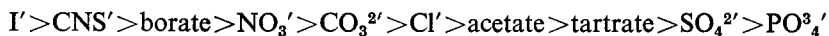
In a theta solvent, the exponent α becomes equal to 0.5 and these results show that the addition of small amounts of salt solutions cause a decrease in this exponent. Increasing the concentration of the salts would lead to further decreases in α until it became equal to 0.5. Theta conditions would then exist and the salt concentration would be very near to that required to 'salt-out' the macromolecule. This contrasts with Neely (1963) who suggested that as the salt removed the enmeshed water from the macromolecule it lowered the temperature at which aggregation becomes possible. The results obtained in this work indicate no more aggregation in the presence of salts than in their absence.

The mechanism of sol-gel transformation of MC has been studied by Heymann (1935) who reported that the gel point depression by electrolytes is primarily related to the concentration and kind of anions present. Savage (1965), generally agreeing with the results of Heymann, stated that the gelation temperature of MC and HPMC may be lowered by the addition of either cations or anions, the tolerance for ions generally following the classic order of Hofmeister's lyotropic series:

for cations:



for anions:



A shift to the left will raise the gel-point whereas a shift to the right will lower it.

Bringing the work of Heymann and Neely to bear on these results, it would seem possible to envisage a partial dehydration of MC with low concentrations of electrolytes. This would account for these results; the r.m.s. end-to-end length decreased but with no alteration in molecular weight. As the concentration of electrolyte is raised a

more complete dehydration occurs which allows molecular association to take place leading up to the sol-gel transformation. This would account for the results of Neely; the r.m.s. end-to-end length was fairly constant but molecular weight increased.

The two dehydration aspects might well be linked with Heymann's results for the viscosity ratio of MC plotted against temperature. The initial fall of (η/η_0) against temperature was quite shallow (first aspect) but about 10° below the gelation temperature the viscosity curve falls more steeply (second aspect) to the gelation temperature. This view might also be supported by Savage who suggested that a MC'400' solution shows little tendency to associate until it has been warmed to near 30°.

The decreased viscosity of methylcellulose solutions on storage (Davies & Rowson, 1958) might well be explained in terms of hydration and dehydration. Since the preparation of methylcellulose solutions appears to be very important (Neely), earlier work on methylcellulose might well be in doubt. It is possible that the initial solution, which is also used as the control for storage studies, might not have been fully hydrated and could well have contained aggregates. Aggregates appear to be formed by molecules building up side by side and if on subsequent storage deaggregation and further hydration occurred, then a viscosity drop must result.

A decreased polymer length, which would result in a decrease in viscosity, has been shown to result from dehydration of the polymer by addition of electrolytes. Other additives could well have a similar or opposite effect (Levy & Schwarz, 1958). It is also possible that microbial contamination of methylcellulose solutions in the past has resulted in a viscosity loss being reported on storage. In some cases complexation of the preservative may have caused such a situation, insufficient preservative remaining uncomplexed to be effective.

Acknowledgements

One of us (E. G. John) gratefully acknowledges the receipt of a research assistantship from Liverpool Corporation.

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