

# The molecular weight and molecular weight distribution of hydroxypropyl methylcellulose used in the film coating of tablets

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The molecular weight and molecular weight distributions of nine grades of hydroxypropyl methylcellulose used in the film coating of tablets have been measured using gel permeation chromatography. With the exception of Pharmacoat 603, there is a high molecular ( $>5 \times 10^5$ ) component present in all grades ranging from relatively small amounts in grades with low nominal viscosity to relatively large amounts in the 50 mPas grade. The peak molecular weight taken from the distribution curve—an indication of the molecular weight of the main component—could be calculated from the nominal viscosity using the equation. Peak molecular weight =  $23.54 \times 10^3 (\text{viscosity})^{0.45}$ . The relationship could also be expressed in the standard form  $[\eta] = KM^\alpha$  where  $M$  is the peak molecular weight  $[\eta]$  is the intrinsic viscosity and  $K$  and  $\alpha$  are constants (in this case  $9.94 \times 10^{-4}$  and 1.096 respectively). The wide molecular weight distribution of these samples and the presence of quite high proportions of very low molecular weight ( $<5 \times 10^3$ ) components especially in samples with nominal viscosity designations of less than 15 mPas appears to affect their mechanical properties.

Hydroxypropyl methylcellulose is now used extensively in the film coating of tablets. It is prepared by the alkaline degradation of cellulose fibres which are subsequently treated with methyl chloride and propylene oxide giving both methoxyl and hydroxypropoxyl substitution on the anhydroglucose units. The material used for film coating has a methoxyl and hydroxypropoxyl substitution of 28-30 and 7-12% w/w respectively. An advantage of these polymers is their availability in a wide range of grades with varying viscosity designations representing the viscosities of 2% aqueous solutions of the polymer at 20 °C. It is possible to convert these nominal viscosities to number average molecular weights using reference data as has been done by Rowe (1976), but these values are suspect being derived from data obtained for methylcellulose, and they also suffer from the disadvantage in that they give no information on the molecular weight distribution. In recent years a new technique—gel permeation chromatography—has become available for the determination of molecular weight distribution of polymers. In this a polymer solution passes down a series of columns packed with gels of varying pore sizes and separation is dependent on molecular size. As the fractions elute, changes in the refractive index are measured and a continuous chromatogram of detection response (number of polymer molecules) against retention volume (molecular weight) is produced. This paper reports the use of this tech-

nique in the measurement of the molecular weight and molecular weight distribution of various viscosity grades of hydroxypropyl methylcellulose and discusses the implications in film formulation.

## MATERIALS AND METHODS

Nine grades of hydroxypropyl methylcellulose U.S.P. were obtained from two manufacturers—Pharmacoat 603, 606, 615 and Metolose 60SH-50 with nominal viscosity designations of 3, 6, 15 and 50 mPas respectively were obtained from Shinetsu Chemical Co. Limited, Japan, and Methocel E5, E8, E10, E15 and E50 with nominal viscosity designations of 5, 8, 10, 15 and 50 mPas respectively were obtained from Dow Chemical Co., U.S.A. The viscosity of a 2% w/w solution of each sample was measured using the standard test (United States Pharmacopeia XIX 1975).

The molecular weights and molecular weight distributions of these samples were measured using gel permeation chromatography (model GPC 200—Waters Associates Inc., Massachusetts, U.S.A.) with a standard styragel packing calibrated using polystyrene standards. The sample to be analysed was dissolved in dimethylacetamide at a concentration of 0.4% w/w. The number average molecular weight ( $\bar{M}_n$ ) weight average molecular weight ( $\bar{M}_w$ ) and peak molecular weight (indicative of the molecular weight of the main component) were all computed from the chromatogram. The molecular weight

distribution or dispersity was assessed using the ratio  $\bar{M}_w : \bar{M}_n$ , the higher this ratio the wider the distribution. A typical chromatogram and calibration curve are shown in Figs 1 and 2.

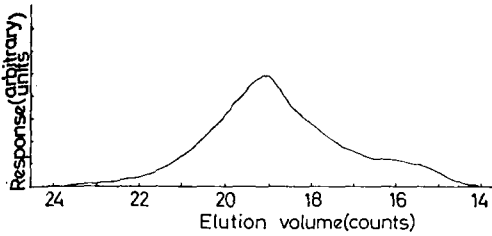


FIG. 1. A typical chromatogram for a sample of hydroxypropyl methylcellulose with a viscosity designation of 15 mPas.

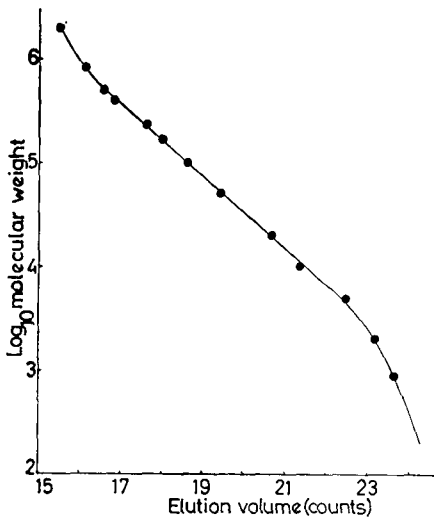


FIG. 2. A typical calibration curve for gel permeation chromatography using polystyrene standards.

RESULTS AND DISCUSSION

Results on samples of all nine grades of polymer are shown in Table 1 and Figs 3 and 4. It can be seen that with the exception of the sample of Pharmacoat 603 there is a high molecular weight ( $>5.0 \times 10^5$ ) component present in all grades varying from a relatively small amount in Methocel E5 to very high proportions in Methocel E50 and Metolose 60SH-50. The  $\bar{M}_w$  values reflect this component. In general the dispersity function increases with viscosity as does the peak molecular weight but no such trend can be seen for the  $\bar{M}_n$  values. Although there is quite a scatter in the  $\bar{M}_n$  results they are of the same order of

Table 1. Gel permeation chromatographic analysis of various hydroxypropyl methylcellulose samples.

Sample	Visc. of 2% aq. sol. mPas	Wt av. $\bar{M}_w \times 10^6$	No av. $\bar{M}_n \times 10^4$	Dispersity $\bar{M}_w/\bar{M}_n$	Peak M. Wt $\times 10^4$
Pharmacoat 603	3.4	0.54	0.55	9.7	3.45
Methocel E5	5.0	3.29	2.79	11.8	5.07
Pharmacoat 606	5.9	1.35	0.45	29.8	5.31
Methocel E8	8.5	8.03	2.94	27.3	5.55
Methocel E10	10.5	3.00	3.17	9.5	5.55
Pharmacoat 615	13.7	6.03	0.81	75.0	7.03
Methocel E15	15.0	22.90	3.20	71.5	6.56
Methocel E50	52.3	18.40	10.20	18.1	17.80
Metolose 60SH50	52.8	74.70	2.19	341.0	15.00

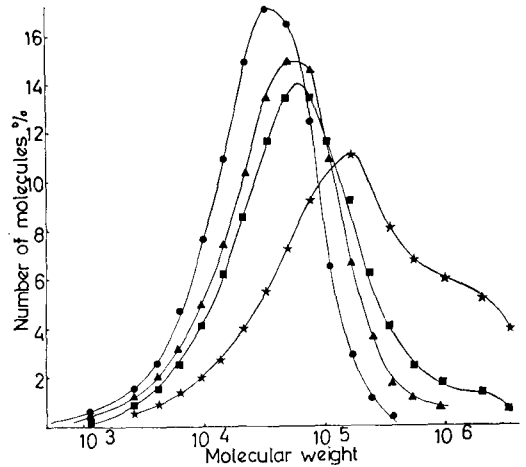


FIG. 3. Molecular weight distribution curves for Pharmacoat 603 (●) Pharmacoat 606 (▲) Pharmacoat 615 (■) and Metolose 60SH-50 (★).

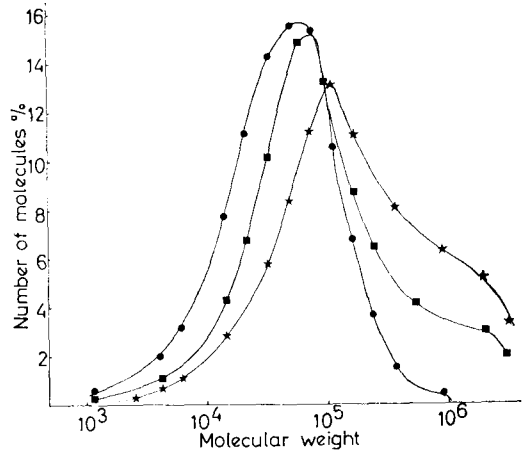


FIG. 4. Molecular weight distribution curves for Methocel E5 (●), Methocel E15 (■) and Methocel E50 (★).

magnitude as those calculated from viscosity data on methylcellulose (Rowe 1976). The wide distribution with the presence of a high molecular weight component has also been found in studies on hydroxypropyl cellulose (Wirick & Waldman 1970). Results on different batches of polymer with the same nominal viscosity designation shows the batchwise variation (Table 2.) Most variation appears in the samples with a nominal viscosity designation of 15 mPas.

Table 2. Batchwise variation in the molecular weights of hydroxypropyl methylcellulose.

Sample	Visc. of 20% aq. sol. mPas	Wt av. M. Wt	No av. M. Wt	Dispersity $\overline{Mw}/\overline{Mn}$	Peak M. Wt $\times 10^4$
		$\overline{Mw} \times 10^4$	$\overline{Mn} \times 10^4$		
Pharmacoat 606	5.9	1.35	0.45	29.8	5.31
	5.9	1.52	3.40	4.5	6.97
	6.3	1.20	1.74	6.9	6.31
	6.7	1.16	2.95	3.9	6.97
Pharmacoat 615	13.7	6.03	0.81	75.0	7.03
	14.2	15.80	4.25	33.1	10.80
	15.3	4.51	0.46	99.0	4.31
Methocel E5	5.0	3.29	2.79	11.8	5.07
	5.1	2.58	1.11	23.2	4.79
Methocel E50	40.8	15.80	6.60	24.0	11.10
	52.3	18.40	10.20	18.1	17.80

Statistical analysis on the full sixteen samples shows that there is a relationship between the viscosity (expressed as mPas) and the peak molecular weight (Fig. 5) of the form.

$$\text{Peak molecular weight} = K (\text{viscosity})^n \quad (1)$$

where  $K$  and  $n$  have the values  $23.54 \times 10^3$  and 0.45 respectively.

If the intrinsic viscosity ( $[\eta]$  expressed as  $\text{dl g}^{-1}$ ) of each sample is calculated from the viscosity values using the equations of Rudin & Wagner (1975) then

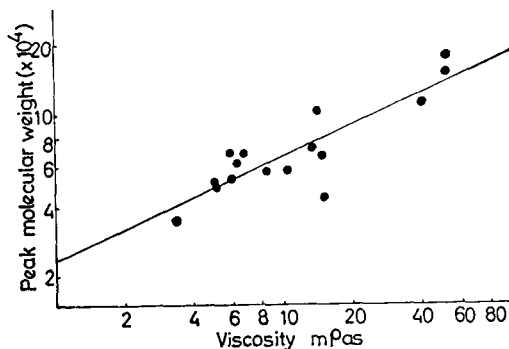


Fig. 5. The relationship between nominal viscosity and peak molecular weight.

the relationship can be expressed in the form of the standard Mark-Houwink equation

$$[\eta] = KM^\alpha \quad (2)$$

where  $M$  is the molecular weight and  $K$  and  $\alpha$  are constant—in this case  $9.94 \times 10^{-4}$  and 1.096 respectively. Normally such relationships are determined from measurements on samples where the dispersity functions are below 10. In this work the dispersity functions are much higher but in both equations statistical analysis shows high significance— $P < 0.001$ .

The exponential factor  $\alpha$  in the Mark-Houwink equation is ultimately connected with the general form of the molecule in solution. If the polymer molecule in solution is coiled tightly into a spheroid form the constant should have the value zero but if it is rigidly extended in the form of a rod and value is two. If, however, the molecule is extended at random, as in the case of a good solvent, the value is unity. The value for hydroxypropyl methylcellulose calculated in this work (1.096) implies that the molecule is extended at random when dissolved in water and hence water is a very good solvent for the polymer—a conclusion which fits the observation that all the grades used for film coating form completely clear aqueous solutions free of gel particles.

It is possible to prepare polymer samples of intermediate viscosity by blending high and low viscosity grades using the formula.

$$\log \eta_s = \frac{N \log \eta_1 + (100 - N) \log \eta_2}{100} \quad (3)$$

where  $\eta_s$  is the viscosity sought,  $\eta_1$  and  $\eta_2$  are the viscosities of the first and second components of the blend and  $N$  is the percentage by weight of the component with viscosity  $\eta_1$ . Results on two blends having a nominal viscosity designation of 15 mPas prepared in this way are shown in Table 3. Although the  $\overline{Mw}$  and dispersity functions are very high, as

Table 3. Gel permeation chromatographic analysis of blends of hydroxypropyl methylcellulose blends. (Blend equivalent to a 15 mPas viscosity grade).

Blend	Wt av. M. Wt	No av. M. Wt	Dispersity $\overline{Mw}/\overline{Mn}$	Peak M. Wt $\times 10^4$
	$\overline{Mw} \times 10^6$	$\overline{Mn} \times 10^4$		
Pharmacoat 603/ Metolose 60SH-50	22.20	3.81	584	5.65
Pharmacoat 606/ Metolose 60SH-50	4.35	3.76	116	7.82

would be expected when blending two extremes of the molecular weight range, the peak molecular weights are similar to that calculated from equation 1 for a 15 mPas grade namely  $7.88 \pm 1.28 \times 10^4$ .

A knowledge of the effect of molecular weight on the properties of films is very important in the formulation of film coatings for solid dosage forms. It has already been shown (Rowe 1976) that as the viscosity grade of hydroxypropyl methylcellulose is increased the films become harder, less elastic and more resistant to abrasion and the coated tablets have a longer disintegration time and higher crushing strength. The dependence of the mechanical properties (tensile strength, elongation), of polymers upon molecular weight is qualitatively the same for all polymers. As the molecular weight increases the strength also increases proportionately until at some critical molecular weight there is no further increase. This inflection in the curve occurs at a degree of polymerization of approximately 200–250 equivalent to a molecular weight of approximately  $4-5 \times 10^4$  for hydroxypropyl methylcellulose. It would be expected, therefore, that all grades with a viscosity designation above 6 mPas (equivalent to a molecular weight of  $5 \times 10^4$ ) would have the same mechanical properties. This is not the case in practice. Fig. 6 shows tensile strength data from manufacturer's literature and Hawes (1978)\* plotted against peak molecular weight where the inflection occurs at a molecular weight of  $7-8 \times 10^4$  (equivalent to a grade with a viscosity designation of approximately 12–15 mPas).

The discrepancy is probably due to the wide molecular weight distribution of this polymer and the presence of very low molecular weight components ( $<5 \times 10^3$ ) especially in the grades with nominal viscosities below 15 mPas. It is known that such components do have a deleterious effect on the mechanical properties of a polymer disproportionate to their concentration on a weight basis.

While it must be realized that the molecular weights measured in this work are not absolute, but calculated by reference to polystyrene having the

\* Hawes (1978) actually measured the tensile strength of films prepared from blends of Pharmacoat 606 and Methocel E15. The molecular weights of each of the blends were calculated firstly using equation 3 to obtain the nominal viscosity of the blend and secondly substituting this value in equation 1.

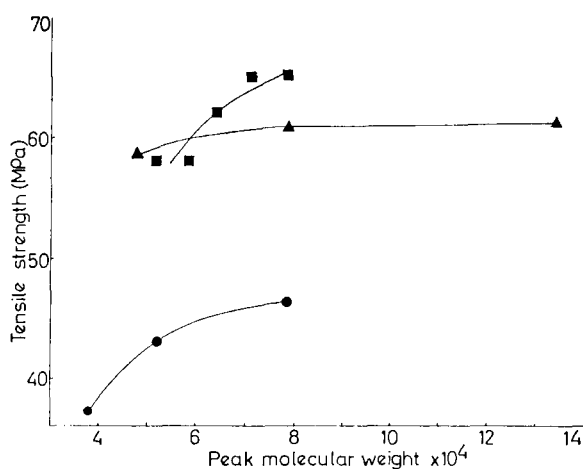


FIG. 6. The effect of peak molecular weight on the tensile strength of hydroxypropyl methylcellulose samples (■) data from Hawes (1978), (▲) data from Dow Chemical Co., U.S.A.—films cast from water (●) data from Shinetsu Chemical Co. Limited—films cast from a 50:50% solvent mixture of dichloromethane and methanol.

same hydrodynamic volumes as the polymer under test, the results correlate well with the standard theories of polymer behaviour. Such data are invaluable to the formulator in understanding the behaviour of the film former when applied to the surface of a solid dosage form and being able to rectify film defects and optimize film formulations.

#### Acknowledgement

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