International Journal of Pharmaceutics, 11 (1982) 175–179
Elsevier Biomedical Press

The molecular weight of methyl cellulose used in pharmaceutical formulation

R.C. Rowe

ICI Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire SK10 2TG (U.K.)

(Received January 10th, 1982)
(Accepted January 19th, 1982)

Methyl cellulose is used extensively in pharmacy as a thickener, emulsifier and stabilizer in liquid and semi-solid formulations and as a binder and film-former in tablet and film coating formulations. It is prepared by the alkaline degradation of cellulose fibres which are subsequently treated with methyl chloride. The basic repeating structure is one of the anydroglucose units with some of the hydroxyl groups substituted by methoxyl groups. The methyl cellulose used in pharmaceutical formulation has a degree of substitution (i.e. the average number of hydroxyl groups substituted per anhydroglucose unit) of between 1.64 and 1.92 corresponding to a methoxyl content of between 27.5 and 31.5% w/w. An advantage of this polymer is its availability in a wide range of grades with varying viscosity designations representing the viscosity of a 2% w/w aqueous solution of the polymer at 20°C. Since a knowledge of the molecular weight of these various viscosity grades is of importance to the pharmaceutical formulator, especially the one involved in film coating formulation where the molecular weight of the polymer used has an important effect on the mechanical properties of the resultant films (Rowe, 1976, 1980, 1982) and on the incidence of film cracking (Rowe and Forse, 1980), it is pertinent to review and compare the literature data on this polymer.

Data relating the molecular weight of a polymer to its viscosity in a solvent system are usually expressed in the form of the Mark-Houwink equation:

$$[\eta] = K \cdot M^{\alpha} \qquad (1)$$

where $[\eta]$ is the intrinsic viscosity of the polymer, M is its molecular weight and K and α are constants depending on the solvent and the solution temperature. These constants are usually calculated by regression analysis on intrinsic viscosity/molecular weight data on fractionated samples of polymer and hence will vary depending on the method used to determine the molecular weights of the samples, e.g. osmotic pressure, sedimentation, light scattering or gel permeation chromatography. In this respect methyl cellulose is no exception, there being 5 sets of constants for this

0378-5173/82/0000–0000/$02.75 © 1982 Elsevier Biomedical Press

TABLE 1

CONSTANTS FOR THE MARK-HOUWINK EQUATION FOR METHYL CELLULOSE IN AQUEOUS SOLUTION

Temperature (°C)	$K \times 10^4$ ($dl \cdot g^{-1}$)	α	Nominal viscosity range (mPas)	Method	Fraction-ation	Reference
25	3.16	0.55	10– 400	Light scattering	No	Neely (1963)[a]
25	4.75	0.55	10– 400	Light scattering	No	Neely (1963)[b]
20	2.80	0.63	50– 4,000	Sedimentation	Yes	Uda and Meyerhoff (1961)
20	3.21	0.89	10–10,000	Osmotic pressure	-	Savage (1965)
20	1.55	0.87	-	-	Yes	Vasileva and Petropavlovskii (1980)

[a] Data for number average molecular weight, $\overline{M}_n$.

[b] Data for weight average molecular weight, $\overline{M}_w$.

equation reported in the literature (Table 1). Unfortunately the data cannot be directly compared since that reported using a light scattering technique (Neely, 1963) has been based on a solution temperature of 25°C as opposed to 20°C used by the other workers. It is interesting to note that the values reported by Neely (1963) for α are somewhat lower than those reported by the other workers. This is only to be expected since α is indicative of the degree of polymer–solvent interaction and it is well known that methyl cellulose is 'less soluble', i.e. has a lower affinity for water, the higher the temperature.

It would appear that the only way of comparing molecular weight data for this polymer is by using a relationship which includes the nominal viscosity of the various grades or fractions of the polymer since this is always measured at a fixed concentration of 2% w/w and at a fixed temperature of 20°C. Such a relationship is of greater significance to the pharmaceutical formulator since the nominal viscosity is the standard used to control this polymer. Fig. 1 shows the data presented in this form and Table 2 shows the constants for the equation:

$$\text{Molecular weight} = K \cdot (\text{nominal viscosity})^n \qquad (2)$$

Unfortunately Vasileva and Petropavlovskii (1980) did not report nominal viscosities from the fractions used in their work and in this case the nominal viscosities were calculated using the equation:

$$\text{Nominal viscosity} = 3.06 \cdot (\text{intrinsic viscosity})^{3.58} \qquad (3)$$

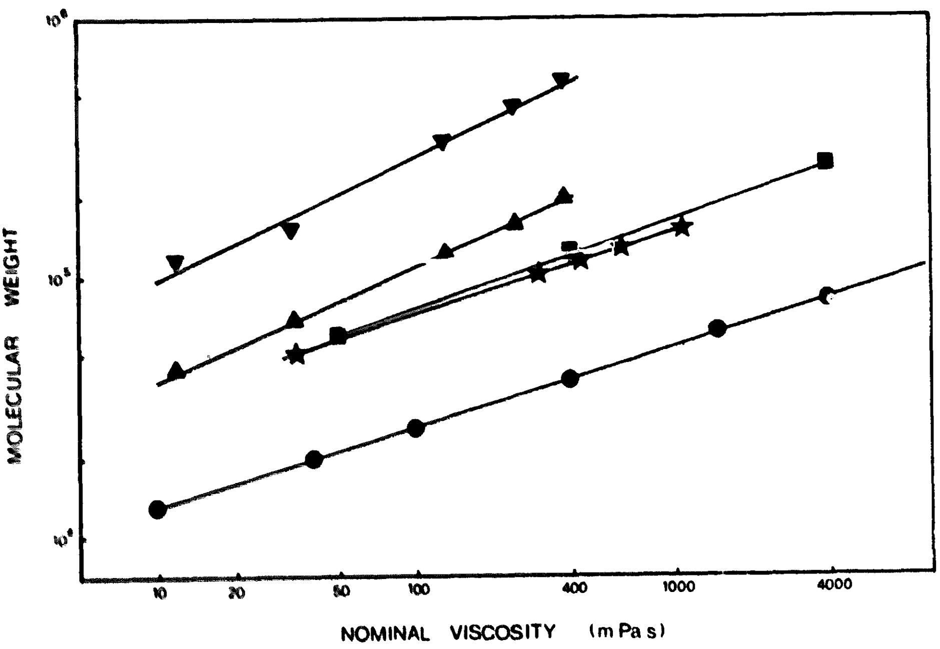

Fig. 1. Nominal viscosity/molecular weight data for methylcellulose. ▼, $\bar{M}_w$; ▲, $\bar{M}_n$ (Neely, 1963); ■, (Uda and Meyerhoff (1961); ★, (Vasileva and Petropavlovskii, 1980); ●, (Savage 1965).

TABLE 2

CONSTANTS FOR EQN. 2. CALCULATED BY REGRESSION ANALYSIS

Data	$K \times 10^{-3}$	n
Neely (1963)	13.84	0.447 [a]
Neely (1963)	32.49	0.478 [b]
Uda and Meyerhoff (1961)	15.10	0.351
Savage (1965)	6.27	0.314
Vasileva and Petropavlovskii (1980)	16.56	0.319

[a] Data for number average molecular weight, $\overline{M}_n$.

[b] Data for weight average molecular weight, $\overline{M}_w$.

This is an empirical equation determined by regression analysis on 19 samples of methyl cellulose where both the intrinsic viscosity and nominal viscosity had been measured. (Greminger and Savage, 1959; Savage, 1965). It differes from that reported previously by Greminger and Savage (1959) in the value of the intercept constant—3.06 as opposed to 3.4. However, such a small difference will have little effect on the calculated nominal viscosity.

It can be seen (Fig. 1, Table 3) that in all cases the molecular weights determined by light scattering are much higher than those determined by either sedimentation or osmotic pressure. This trend has also been reported for a similar water-soluble cellulose ether-hydroxyethyl cellulose— and is thought to be due to the heterogeneity in the molecular weight distribution of such polymers (Brown, 1961). The differences reported, however, were not so large as seen with methyl cellulose and the question arises as to which molecular weight is the best indication of film properties for this polymer. Recent work on two other cellulose ethers used in film coating, viz. hydroxypropyl methylcellulose and ethylcellulose, has shown that the

TABLE 3

COMPARISON OF CALCULATED VALUES FOR THE MOLECULAR WEIGHTS OF SEVERAL VISCOSITY GRADES OF METHYLCELLULOSE

Nominal viscosity (mPas)	Calculated values for the molecular weights ($\times 10^{-4}$)					
	Rowe (1980) M_p	Neely (1963) $\overline{M}_n$	Neely (1963) $\overline{M}_w$	Uda and Meyerhoff (1961) $\overline{M}_w$	Savage (1965) $\overline{M}_n$	Vasileva and Petropavlovskii (1980)
10	6.08	3.87	9.76	3.39	1.29	3.45
20	8.28	5.37	13.61	4.32	1.61	4.30
50	12.48	7.95	21.07	5.96	2.14	5.77
100	16.98	10.84	29.36	7.60	2.60	7.20

peak molecular weight (M_p) determined from gel permeation chromatography (indicative of the molecular weight of the major component within the molecular weight distribution) is a very important characteristic in defining the mechanical properties of cast films prepared from such polymers (Rowe, 1980, 1982). Since hydroxypropyl methylcellulose has a similar structure to methylcellulose it is possible, knowing the molecular weight of the former, to estimate the molecular weight of a methylcellulose of the same nominal viscosity. This can be done by first calculating the numerical degree of polymerization (i.e. the number of anhydroglucose units) of the former by dividing its molecular weight by its unit molecular weight (i.e. the molecular weight of a single substituted anhydroglucose unit—201 for the hydroxypropyl methylcellulose used by Rowe (1980)) and then multiplying the result by the unit molecular weight of methyl cellulose—196. If this is done (Table 3), then estimations of peak molecular weights for various viscosity grades of methyl cellulose are intermediate between the number average and weight average molecular weights determined by light scattering. In the absence of data from gel permeation chromatography, therefore, it would appear logical to use the light scattering data (Neely, 1963) to calculate molecular weights of the various grades of methylcellulose instead of using that determined from osmotic measurements (Savage, 1965) as is normally presented in manufacturers' literature. Use of the latter will tend to under-estimate the molecular weight and hence is unlikely to be useful in a predictive assessment of the effect of various viscosity grades of this polymer on the mechanical properties of films cast from them.

References

Brown, W., Hydroxyethyl cellulose. A study of its macromolecular properties in solution. Arkiv. Chem., 18 (1961) 227–284.

Greminger, G.K. and Savage, A.B., Methylcellulose and its derivatives. In Whistler, R.L. (Ed.), Industrial Gums. Polysaccharides and their Derivatives, Academic Press, 1959, pp. 565–596.

Neely, W.B., Solution properties of polysaccharides. IV. Molecular weight and aggregate formation in methylcellulose solutions. J. Polym. Sci., Part A 1 (1963) 311–320.

Rowe, R.C., The effect of molecular weight on the properties of films prepared from hydroxypropyl methylcellulose. Pharm. Acta Helv., 51 (1976) 330–334.

Rowe, R.C., The molecular weight and molecular weight distribution of hydroxypropyl methylcellulose used in the film coating of tablets. J. Pharm. Pharmacol., 32 (1980) 116–119.

Rowe, R.C., Molecular weight studies on ethyl cellulose used in film coating. Acta Pharm. Suec., 19 (1982) 157–160.

Rowe, R.C. and Forse, S.F., The effect of polymer molecular weight on the incidence of film cracking and splitting on film coated tablets. J. Pharm. Pharmacol., 32 (1980) 583–584.

Savage, A.B., Methylcellulose and Hydroxypropyl methylcellulose. In Mark, H.F., Gaylord, N.G. and Bikales, N.M. (Eds.), Encyclopedia of Polymer Science and Technology, Interscience, Vol. 3, New York 1965, pp. 492–510.

Uda, V.K. and Meyerhoff, G., Hydrodynamische eigenschaften von methylcellulosen in lösung. Mackromol. Chem., 47 (1961) 168–184.

Vasileva, G.G. and Petropavlovskii, G.A., Influence of the molecular weight of methylcellulose on its cross-linking and on the properties of spatially structured films. J. Appl. Chem. U.S.S.R., (English translation) 53 (1980) 1944–1948.