Molecular Weight Determination of Hypromellose Phthalate (HPMCP) Using Size Exclusion Chromatography with a Multi-angle Laser Light Scattering Detector

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The molecular weight of hypromellose phthalate (HPMCP), a polymer used for enteric coating, was determined using size exclusion chromatography with a multi-angle laser light scattering detector. The values of weight-average molecular weight (Mw) of commercially available grades (HP-55, HP-55S, and HP-50) were 45600, 60200, and 37900, respectively. Their inter-day precisions expressed in terms of the coefficient of variation were less than 3%. A correlation curve between Mw and solution viscosity was prepared so that Mw could be easily estimated from the solution viscosity measured by the compendial method.

Key words hypromellose phthalate; hydroxypropyl methylcellulose phthalate; molecular weight; size exclusion chromatography

Hypromellose phthalate (HPMCP, formerly named Hydroxypropyl Methylcellulose Phthalate) is a cellulose ester which is typically used as an enteric coating agent for solid dosage forms in the pharmaceutical industry. It contains methyl, hydroxypropyl, and phthalyl groups on its cellulose backbone. This polymer has been listed in pharmacopeias for many years. Generally, molecular weight is a key parameter of a polymer, but only a few studies have been reported on the molecular weight of HPMCP.[1,2] In quality control of cellulose derivatives, molecular weight is not routinely measured. This is probably because the direct measurement of molecular weight generally requires an expensive and complicated analytical system. Instead, solution viscosity, which is related to molecular weight, is usually employed to monitor quality because it is a simple, easy and reproducible method. Thus, it would be useful if one could easily calculate the molecular weight from the solution viscosity. The objectives of the present study are to measure the molecular weight of HPMCP using a modern analytical method, and to obtain a correlation curve relating molecular weight to solution viscosity.

Experimental

Samples Three commercially available grades of hypromellose phthalate (HPMCP, type HP-50, HP-55 and HP-55S, Shin-Etsu Chemical Co., Ltd., Japan) were used. HP-55 and HP-55S have the same phthalyl contents, but different viscosities, and HP-50 has a different phthalyl content. In addition, three other samples with the same phthalyl contents as those of HP-55 and 55S, but having different viscosities, were specially prepared in our laboratory. These samples were used to obtain the molecular weight-viscosity relationship curve. Chemical data for the six samples are shown in Table 1.

Table 1. Chemistry of HPMCP Samples

Grade	Viscosity (mm^2/s)	Hydroxypropoxyl contnt (%)	Methoxyl content (%)	Phthalyl content (%)
HP-50	51	7.1	22.3	22.5
HP-55	42	6.2	19.3	33.3
Sample A	78	6.2	19.2	33.2
HP-55S	147	6.2	19.1	33.0
Sample B	545	6.2	19.1	34.1
Sample C	1640	6.2	19.1	33.2

HP-50, HP-55, and HP-55S are commercially available products. Samples A, B and C were prepared in laboratory for the present study. Their specifications are the same as those of HP-55 and 55S, except for viscosity.

Measurement of Molecular Weight Molecular weight of the polymer was measured by means of size exclusion chromatography (SEC) with a multi-angle laser light scattering detector. The sample was dissolved in a mixture of the acetate-chloride buffer (pH 5.6, I=0.10) and *N*,*N*-dimethylformamide (9 : 1 v/v). The composition of the buffer was as follows; 2.46 g of CH_3COONa, 0.10 g of CH_3COOH, and 5.84 g of NaCl in a liter of distilled water. Polymer solutions were prepared by adding the samples directly to the mixed solution and stirring at room temperature. The polymer concentration was 0.1 w/w %. Prior to injection, the sample solutions were filtered through a 0.45-μm membrane filter (DISMIC-13cp, ADVANTEC, Japan).

Size Exclusion Chromatography with Multi-angle Laser Light Scattering System (SEC-MALLS) The SEC-MALLS system used in this study included a pump (DS-4, Shodex, Japan), a degasser (ERC-3115, ERC Inc., Japan), columns (OHpak SB-806MHQ, protected by a OHpak SB-G guard column, Shodex, Japan), a multi-angle laser light scattering detector (DAWN, Wyatt Technology, U.S.A.), equipped with a 5 mW He–Ne laser (632.18 nm) capable of measuring the intensity of the scattered light at 18 angles, and a refractive index detector (RI-71, Shodex, Japan). The eluent was the mixture of acetate-chloride buffer and *N*,*N*-dimethylformamide (9 : 1 v/v), at a flow rate of 1.0 ml/min. A 100-μl sample was injected *via* an injection valve (Rheodyne Model 7125, U.S.A.). The refractive index increments of the sample solutions were 0.146 ml/g for HP-50, and 0.152 ml/g for HP-55 and the other same chemical types, as measured with a refraction meter (DRM-1021, Otsuka Electronics, Japan). Data were collected and analyzed on a computer using the ASTRA software (Wyatt Technology, U.S.A.). For each measurement run, calibration was carried out using standard pullulan samples (Shodex, Japan).

Precision Study Inter-day precision[3] for the molecular weight measurement was determined and expressed as coefficient of variation (relative standard deviation). The measurement was repeated on five different days. On each day, sample solutions and eluent were freshly prepared, and calibration was performed individually.

Viscometry The solution viscosity of HPMCP was measured in accordance with USP 26/NF 21, except for the expression of the unit. Each sample was dissolved in a mixture of methanol and methylene chloride (50 : 50 w/w). The sample concentration was 10 w/w % and its viscosity was measured using a Ubbelohde viscometer (Canon Instrument, U.S.A.) at 20 °C. In the current USP-NF method the Ubbelohde viscosity is expressed in the unit of cSt (centistokes), but in this study, we use mm^2/s (square millimeters per second) according to the International System of Units.

Data Analysis To obtain an equation for an estimation curve, a regression analysis was applied to the molecular weight-viscosity plots using a software (ORIGIN, OriginLab, U.S.A.).

Results and Discussion

Typical molecular weight distributions of the three com-

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mercial grades of HPMCP (HP-50, HP-55 and HP-55S) are shown in Fig. 1. A precision study was also conducted to determine the inter-day variation. The results are shown in Table 2. The inter-day precision, represented by coefficient of variation (CV), was less than 3% for the weight-average molecular weight (Mw). For the number-average molecular weight (Mn), the CV was less than 6%. In our other studies using the same system, we also obtained higher CV for Mn compared to Mw in many cases. Thus Mn seems to be less reproducible than Mw in this system. We therefore used only Mw for further studies.

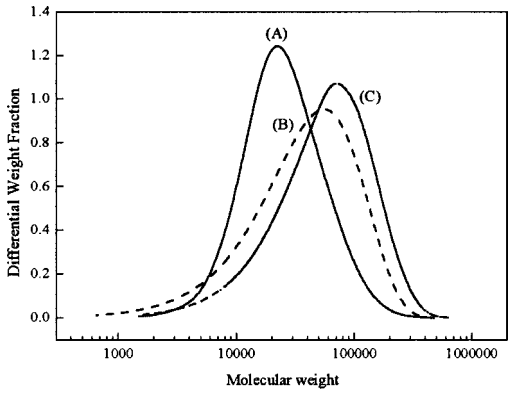

Fig. 1. Typical Molecular Weight Distribution of Commercial Grades of HPMCP

Sample: (A) HP-50, (B) HP-55, (C) HP-55S.

Table 2. Inter-day Precision Study

HP-50

	Mw	Mn	Mw/Mn
Individual data	36900	13600	2.71
	38900	15700	2.48
	38300	14700	2.61
	37800	14400	2.63
	37400	15100	2.48
Mean±S.D.	37860±777	14700±784	2.58±0.10
CV (%)	2.1	5.3	4.0

HP-55

	Mw	Mn	Mw/Mn
Individual data	44800	19100	2.35
	47200	19600	2.41
	45400	18900	2.40
	44300	18900	2.34
	46200	18800	2.46
Mean±S.D.	45580±1150	19060±321	2.39±0.05
CV (%)	2.5	1.7	2.0

HP-55S

	Mw	Mn	Mw/Mn
Individual data	58900	26400	2.23
	62000	23800	2.61
	59700	25600	2.33
	60500	26900	2.25
	59900	26000	2.30
Mean±S.D.	60200±1158	25740±1187	2.34±0.15
CV (%)	1.9	4.6	6.5

Table 3 shows the viscosity, Mw, and weight-average degree of polymerization (DPw) of the six samples examined. DPw was calculated by dividing Mw by the mean formula weight of the glucose-ring unit. Fig. 2 shows the correlation plot between molecular weight and viscosity. Regression analysis for the HP-55 series gave the following equation;

$$Mw = 18663 \cdot \eta^{0.239}$$

where η is the solution viscosity. The correlation coefficient was 0.9991. This relationship should allow easy estimation of molecular weight from solution viscosity measured on a routine basis. HP-50 did not fit on the same curve, presumably because of the difference in chemical composition. This means that the equation applies only to polymer samples with the same substitution level as HP-55. Probably a similar linearity applies to different substitution grades like HP-50, although this has not been confirmed because different viscosity grades are not commercially available.

Figure 3 shows the relationship between DPw and viscos-

Table 3. Viscosity, Mw, and DPw of HPMCP

Sample	Viscosity (mm^2/s)	Mw	DPw
HP-50	51.3	37900	145
HP-55	42.4	45600	150
Sample A	78.3	53700	177
HP-55S	146.7	60200	198
Sample B	544.7	85200	281
Sample C	1639.0	109000	359

The values represent mean of 3—5 replicates.

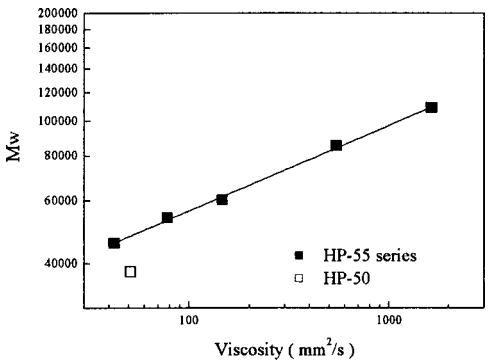

Fig. 2. Weight-Average Molecular Weight *versus* Viscosity of HPMCP

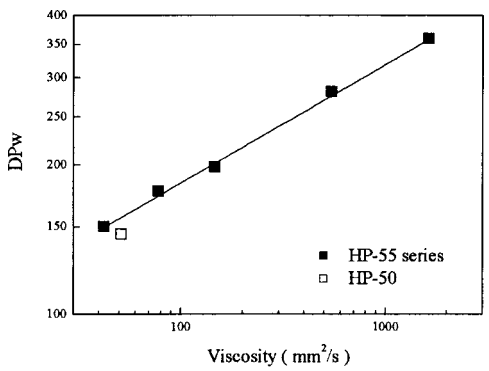

Fig. 3. Weight-Average Degree of Polymerization *versus* Viscosity of HPMCP

ity. The following equation was obtained;

$$DPw = 61.3 \cdot \eta^{0.239}$$

The correlation coefficient was 0.9990. HP-50 deviated less from the HP-55 line, as compared to the case of the Mw plot. This may suggest that the solution viscosity depends more on the length, rather than the weight of the polymer.

Kato *et al.*[1] reported that the Mw of HP-55 was 45000 and that of HP-55S was 76200, which are similar to our results, although they did not report solution viscosities. They also used a laser scattering detector, but it was a single-angle device, and their column and eluent were different from ours. Rowe[2] reported that the Mw of HP-55 was 139000—205200, and that of HP-55S was 134800—208200. These values are significantly higher than ours, and there was no dependency on viscosity. Rowe used an SEC system, but the molecular weight was measured only as a relative value using polystyrene standards. With light scattering method, molecular weight is obtained as an absolute value. This could account for the difference from our results.

The present study has provided the absolute molecular weight of the three commercial grades of HPMCP and afforded a simple equation by which a molecular weight can be easily calculated from the solution viscosity. The same system can be applied to other cellulosic polymers, and we are continuously studying on it.

References

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