Molecular Weight Determination of Hypromellose Acetate Succinate (HPMCAS) Using Size Exclusion Chromatography with a Multi-Angle Laser Light Scattering Detector

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The molecular weight of hypromellose acetate succinate (HPMCAS), a polymer used for enteric coating, was determined by means of size exclusion chromatography with a multi-angle laser light scattering detector. The weight-average molecular weight (Mw) of several lots and grades ranged approximately from 17000 to 20000, and the number-average molecular weight (Mn) was around 13000. The inter-day precision of measurement, in terms of the coefficient of variation, was less than 5%.

Key words hypromellose acetate succinate; molecular weight; SEC-MALLS; hydroxypropyl methylcellulose acetate succinate; laser light scattering

Hypromellose acetate succinate (HPMCAS, also known as hydroxypropyl methylcellulose acetate succinate) is a cellulose ester, which is typically used as an enteric coating agent for solid dosage forms in the pharmaceutical industry.[1] It contains methyl, hydroxypropyl, acetyl and succinoyl groups on a cellulose backbone. This polymer has been listed in a compendial publication, *Japanese Pharmaceutical Excipients*, since 1993. Molecular weight is generally an important parameter for a polymer, but detailed studies on the molecular weight of HPMCAS have not been reported. The objective of this study was to determine the absolute molecular weight of commercially available HPMCAS using a modern analytical method.

Experimental

Samples Six commercial grades of hypromellose acetate succinate (Shin-Etsu AQOAT®, Shin-Etsu Chemical Co., Ltd., Japan) were used. The grades were AS-LG, AS-MG, AS-HG, AS-LF, AS-MF, and AS-HF. The letters L, M, and H distinguish the contents of acetyl and succinoyl groups. The Letter G represents granular grade, and F represents fine particle grade. Three lots of each grade were tested. The analytical data for the samples used in this study are shown in Table 1.

Preparation of Sample Solutions The sample solutions for the molecular weight measurement were prepared as follows. First, HPMCAS powder or granules were dissolved in 0.03 mol/l NaOH. Then the same volume of 0.1 mol/l potassium hydrogen phthalate was added and mixed. The final polymer concentration was 0.2 w/v %. The pH of the solution was approximately 4.8, but the polymer was not precipitated with this preparation method. The solution was then filtered through a 0.45-μm membrane filter (DISMIC-13cp, ADVANTEC, Tokyo, Japan) prior to injection.

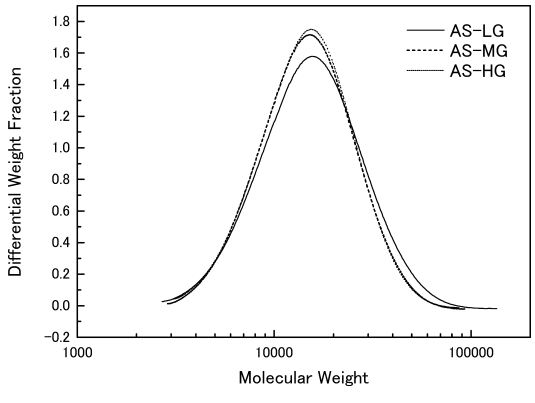

Fig. 1. Typical Molecular Weight Distributions of HPMCAS

Determination of Molecular Weight Molecular weight of the polymer was measured by means of size exclusion chromatography with a multi-angle laser light scattering system (SEC-MALLS). The system 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, USA), 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 same as the sample solvent, which was a mixture of 0.03 mol/l NaOH and 0.1 mol/l potassium hydrogen phthalate (1 : 1 v/v), at a flow rate of 1.0 ml/min. A 100-μl aliquot of sample solution was injected *via* an injection valve (Rheodyne Model 7125, U.S.A.). The refractive index increments of the sample solutions were 0.128 ml/g for AS-LG and AS-LF, 0.132 ml/g for AS-MG and AS-MF and 0.124 ml/g for AS-HG and HF, as measured with a refraction meter (DRM-1021, Otsuka Electronics, Japan). Data were collected and analyzed on a computer using appropriate software (ASTRA, Wyatt Technology, U.S.A.). For each measurement run, calibration was carried out using standard pullulan samples (Shodex, Japan).

Precision Study Repeatability (intra-day variation) and intermediate precision (inter-day variation) of the molecular weight measurement were tested and evaluated as coefficient of variation (relative standard deviation).[2] The measurement was repeated five times in a day to test the intra-day variation, and also repeated on six different days to test the inter-day variation. On each day, sample solutions and the eluent were freshly prepared, and calibration was performed individually.

Results and Discussion

Figure 1 shows typical molecular weight distributions, derived from the chromatograms, of three substitution grades of HPMCAS (AS-LG, AS-MG, AS-HG). Every sample showed one broad peak. Table 2 shows the weight-average molecular weight (Mw), weight-average degree of polymerization (DPw), number-average molecular weight (Mn) and polydispersity (Mw/Mn) of each sample. DPw was calculated by dividing Mw by the mean formula weight of the monomer ring unit (see Table 1). Mw was found to be approximately 20000 for AS-LG, and approximately 18000 for AS-MG and AS-HG. The Mw of AS-LF was approximately 18000, and that of AS-MF and AS-HF was approximately 17000. Mn was around 13000 for all grades.

Table 3 shows the results of the precision study for Mw, Mn, and Mw/Mn. The intra-day precision, represented by coefficient of variation (CV), was 2% or less. The inter-day

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Table 1. Sample Data of HPMCAS

Grade	Lot No.	Viscosity[a] (mm^2/s)	Methoxyl		Hydroxypropoxyl		Acetyl		Succinoyl		Mean formula weight of monomer ring unit[c]
			wt%	MS[b]	wt%	MS	wt%	MS	wt%	MS	
AS-LG	002002	2.73	22.3	1.89	7.0	0.25	7.7	0.47	15.6	0.41	263.5
	102016	2.60	22.3	1.89	7.1	0.25	7.8	0.48	15.4	0.40	263.4
	207045	2.79	22.8	1.92	7.1	0.25	7.5	0.46	15.1	0.39	261.8
AS-MG	903031	2.73	23.2	1.90	7.2	0.24	9.0	0.53	11.3	0.28	253.5
	102010	2.77	23.2	1.91	7.5	0.26	9.4	0.56	11.0	0.28	255.0
	306067	2.71	23.3	1.91	7.4	0.25	8.8	0.52	11.5	0.29	254.3
AS-HG	901014	2.75	23.8	1.89	7.3	0.24	11.8	0.68	6.3	0.15	246.3
	102006	2.69	23.7	1.88	7.6	0.25	12.0	0.69	5.8	0.14	245.9
	204016	2.71	24.0	1.91	7.7	0.25	11.7	0.67	6.0	0.15	246.3
AS-LF	108061	2.51	22.2	1.88	7.1	0.25	7.7	0.47	15.4	0.41	262.8
	210055	2.58	22.8	1.93	7.1	0.25	7.5	0.46	15.4	0.40	262.8
	304042	2.65	22.5	1.90	7.1	0.25	7.2	0.44	15.5	0.40	261.7
AS-MF	204027	2.62	23.3	1.89	7.0	0.24	9.2	0.54	10.8	0.27	251.9
	207037	2.69	23.7	1.93	7.3	0.25	8.9	0.52	11.0	0.28	253.1
	207040	2.75	23.5	1.91	7.3	0.25	8.9	0.52	11.0	0.28	252.8
AS-HF	112074	2.70	23.6	1.89	7.3	0.24	11.3	0.65	7.3	0.18	247.8
	204013	2.65	23.9	1.92	7.6	0.25	11.0	0.64	7.5	0.19	248.9
	204024	2.60	24.0	1.92	7.4	0.24	11.0	0.63	7.3	0.18	247.7

Viscosity and substituent contents were determined according to the monograph in "Japanese Pharmaceutical Excipients." *a*) Ubbelohde viscometer, 20 °C, sample concentration: 2 w/w% in 0.1 mol/l-NaOH. *b*) MS=molar substitution, which represents the mean number of substituent group per glucose ring unit. *c*) This was calculated from the weight percentage of the substituents.

Table 2. Molecular Weight of HPMCAS

AS-LG

Lot No.	Mw	DPw	Mn	Mw/Mn
002002	20400	77	13200	1.55
102016	18800	71	12800	1.46
207045	21200	81	13800	1.54
Mean±S.D.	20133±1222	77±5	13267±503	1.52±0.05

AS-LF

Lot No.	Mw	DPw	Mn	Mw/Mn
108061	17700	67	12600	1.41
210055	17900	68	13700	1.39
304042	18900	72	12500	1.39
Mean±S.D.	18167±643	69±3	12933±666	1.40±0.01

AS-MG

Lot No.	Mw	DPw	Mn	Mw/Mn
903031	18400	73	13000	1.42
102010	17700	69	12700	1.40
306067	17700	70	13400	1.33
Mean±S.D.	17933±404	71±2	13033±351	1.38±0.05

AS-MF

Lot No.	Mw	DPw	Mn	Mw/Mn
204027	16700	66	12500	1.24
207037	17500	69	12800	1.37
207040	17100	68	12900	1.33
Mean±S.D.	17100±400	68±1	12733±208	1.31±0.07

AS-HG

Lot No.	Mw	DPw	Mn	Mw/Mn
901014	17700	72	12900	1.37
102006	18300	74	13000	1.41
204016	17300	70	13000	1.32
Mean±S.D.	17767±503	72±2	12967±58	1.37±0.05

AS-HF

Lot No.	Mw	DPw	Mn	Mw/Mn
112074	17700	71	13300	1.33
204013	17100	69	13100	1.31
204024	17300	70	12700	1.35
Mean±S.D.	17367±306	70±1	13033±306	1.33±0.02

Mw:weight-average molecular weight. DPw: weight-average degree of polymerization. Mn: number-average molecular weight. Data of each lot represents mean of 3—5 experiments.

precision was less than 5%. The present method is concluded to be acceptable for measurement of the molecular weight of HPMCAS.

HPMCAS is manufactured from hypromellose (HPMC, also known as hydroxypropyl methylcellulose). Generally, cellulose compounds are partially degraded after a chemical reaction.[3] We had measured the molecular weight of the particular grade of Hypromellose used as the starting material for HPMCAS manufacture. Its DPw was slightly higher than that of HPMCAS. This suggests that the values measured in this study are reasonable, being consistent with the idea that the polymer was slightly degraded during the chemical processing. We had also tried the molecular weight determination of HPMCAS dissolved in organic solvents, but the resulting DPw values were significantly greater than that of the starting hypromellose. This indicates that HPMCAS may

Table 3. Precision Study (AS-MG lot 102010)

Repeatability (intra-day variation)

	Mw	Mn	Mw/Mn
Individual data	17000	12400	1.37
	17000	12700	1.34
	17100	12600	1.36
	17200	12300	1.40
	17300	12900	1.34
Mean±S.D.	17150±129	12625±250	1.36±0.028
CV (%)	0.8	2.0	2.0

Intermediate precision (inter-day variation)

	Mw	Mn	Mw/Mn
Individual data	17100	12600	1.36
	17100	12400	1.38
	17300	12800	1.35
	17600	12800	1.38
	18400	12100	1.52
	18400	13200	1.39
Mean±S.D.	17650±609	12650±378	1.40±0.063
CV (%)	3.5	3.0	4.5

exist in an aggregated form in organic solvents, and therefore the organic solvent system is not regarded as an appropriate method for accurate measurement of the molecular weight of this polymer. Similar results were observed when we measured the molecular weight of hypromellose phthalate, another widely-used enteric coating agent.[4)]

The molecular weight of AS-LG and AS-LF seemed to be slightly higher than those of the other two substitution grades. The three grades have different contents of acetyl and succinoyl groups (Table 1), and therefore their manufacturing conditions are not exactly the same. The slight difference in the molecular weight of AS-LG and AS-LF may therefore be due to differences in its reaction history during processing. It was also apparent that the molecular weight of F grades was slightly lower than that of G grades. F grades are produced by pulverization of G grades, and so a slight reduction of the polymeric chain length owing to mechanical shear would be considered.

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