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RESEARCH PAPER

Characterization of Cellulose Acetate Phthalate (CAP)

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ABSTRACT

Cellulose acetate phthalate (CAP) is a commonly used enteric coating polymer. CAP powder has been studied by various methods to determine characteristics that have an influence on its functionality. While some of the parameters are well known, such as free-acid content and substituent composition, new methods have been developed to examine them. Other characteristics, such as the molecular mass distribution, have not been reported earlier. Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), and thermal analysis have also been performed on fresh samples, as well as samples stored under various temperature and humidity conditions. Humidity is by far a more critical storage parameter than temperature, although the two act in conjunction; high humidity is more deleterious to the functionality of the polymer than high temperature. Functionality in this case is taken to be determined by the substituents and by the molecular mass distribution. Mass-average molecular mass of a number of batches of the polymer has been measured and ranges around 48 kg/mol with a degree of polydispersity of 1.6. A method to perform a rough estimation of the molecular mass of CAP has also been suggested based on knowledge of the substituent content. It may be possible to use the values of $<M_n>$ and $<M_m>$ obtained here for any other batch of the same viscosity grade of CAP. NMR has been employed to determine the fraction substituents in the polymer. However, an attempt to obtain the pattern of substitution of the CAP molecule by NMR was unsuccessful. Glass transition temperatures of CAP samples were measured. However, this characteristic of the polymer is judged not as sensitive to the loss of substituents as the molecular mass. Thermal treatment of the polymer in oxygen and inert atmospheres gave slightly different degradation products.

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Key Words: *Cellulose acetate phthalate; Humidity; Free acid; Substituent content; Phthalyl content; Acetyl content; Molecular mass distribution; SEC-MALLS; Thermal degradation; Glass transition temperature.*

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INTRODUCTION

Cellulose acetate phthalate is a commonly used tablet coating material employed to produce so-called enteric films, which resist prolonged contact with the strongly acidic gastric fluid, but soften, swell, and finally dissolve in the mildly acidic or neutral intestinal environment. This function of the polymer depends on a number of factors, such as structure, chemistry, molecular mass distribution, thermal behavior, and stability, along with the process (concentration, solvent/dispersion system, temperature, flow rate, pressure, humidity, etc.) and formulation (plasticizer, other additives, active substance, etc.) variables (1). In this work, we report an examination of some of the polymer characteristics, including the effect of storage. While a number of these characteristics have been studied earlier, others (such as the molecular mass distribution) have not been reported. Some new methods have also been developed to enable a more rapid examination of these characteristics than that allowed by the pharmacopoeia methods, for instance.

A search of the literature on CAP returns 977 listings in CAplus (1967–1997). However, the literature is very scattered, and it is difficult to get an overview of the behavior of this polymer. A number of studies have treated the film of the polymer (free film or as a tablet coating), but few studies can be found on the polymer itself. The most comprehensive study we could find is by Delporte (2) on the physicochemical properties of CAP films on storage.

MATERIALS

CAP was obtained from Eastman Chemical Company (Kingsport, TN), batches 50103 (51062-01), 50105 (51063-01), 50106 (51064-01), 50104 (41238-01), and 40706 (41240-01). These batches were received over a period of 10 months, between January 1995 and October 1995. All other reagents were used as received.

METHODS

Water Content

The water content of the polymer is used to correct the calculated free acids, phthalic, and acetic content and will also influence the measured viscosity.

Loss on Drying

Drying to constant weight at 105°C was performed on one batch of CAP.

Karl Fischer Titration

Karl Fischer titration was performed with a Metrohm 665 Dosimat and a Metrohm 682 Titroprocessor (Metrohm Ltd., Merisau, Switzerland). Titrator KF solution A (Merck 9247) and KF solution B (Merck 9246) (1:1) were used as the reagent, and MeOH and pyridine (1:1) were the solvents. Samples of 10–20 mg were analyzed.

Karl Fischer analysis was also performed on a Blending Volumetric KF Titrator, Turbo 2 from Orion (Boston, MA). The reagent used was Hydranal Composite 5 (Riedel de Haen).

Measurement of Free Acids

Free-acid (as phthalic acid) content is included in the pharmacopoeia specifications for CAP. While the USP-NF specifies extraction in MeOH:H_2O 50:50 for 2 hr, the Ph. Eur. specifies extraction in water for 5 min only. Total content of acids is determined by titration with 0.1 M NaOH to a phenolphthalein end point. Bauer (3) states that extraction in water alone is less efficient than in the MeOH/H_2O mixture, and that the extraction requires at least 30 min to reach equilibrium.

Extraction of Free Acids (Phthalic and Acetic Acid)

A water-based extraction procedure was examined. Free acetic acid was included in the test. An exact weight of CAP (approximately 10 mg) was suspended in 5 ml of CO_2-free water and shaken for various lengths of time, ranging from 10 to 120 min at room temperature. Samples were then centrifuged (10 min, 3000 rpm) and filtered (0.45 μm) prior to analysis. Recovery was tested by extracting a spiked CAP sample (CAP + 500 μl spiking solution = 18.1 μg/ml phthalic acid, 654.4 μg/ml acetic acid) and comparing with extraction from the same volume of the spiking solution itself.

From the results of chromatographic analysis (data not shown), it was found that equilibrium was not reached at 120 min in all cases, in agreement with the comments by Bauer (3). Measurements showed not only high recov-

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eries (~100%), but also large standard deviations (~30% and ~10% for phthalic and acetic acids, respectively) at an extraction time of 30 min.

A new extraction procedure was developed based on CAP precipitation. An exact weight of CAP (approximately 10 mg) was dissolved in 250 µl THF with stirring. A total of 5 ml of water was added dropwise with vigorous stirring, allowing the polymer to precipitate out. The samples were centrifuged and the supernatant filtered before analysis by chromatography. Recovery was checked with spiked samples as described above.

The results of the chromatographic analysis showed high recovery (~100%) and lower standard deviations (<1% for phthalic acid and ~10% for acetic acid at quantification limit). The relative standard deviation (RSD) of the process was 4.1% for phthalic acid and 4.4% for acetic acid. This extraction procedure was then used in all subsequent tests.

Chromatographic Analysis of Free Acids

Bodmeier and Chen (4) have developed an isocratic reversed-phase high-performance liquid chromatography (RP-HPLC) method to quantify the organic acids (acetic, propionic, butyric, and phthalic acids) formed as a result of ester hydrolysis in aqueous pseudolatexes of cellulosic esters. A Beckman-Ultrasphere C_{18}, 5 µm, 250 × 4.6 mm column was used with a mobile phase consisting of 0.025 M phosphate buffer–methanol (80:20 v/v, pH 3.0), with detection at 210 nm. Linear response was obtained over the studied range of 2–10 mM for the aliphatic acids and 0.02–0.1 mM for phthalic acid. Minimum detectable concentrations were 0.02 mM, 0.05 mM, 0.1 mM, and 0.0005 mM for acetic, propionic, butyric, and phthalic acids, respectively.

When applied in our laboratory, the best results were obtained with a Waters C_{18} Nova-Pak®, 150 × 3.9 mm column using 10% MeOH in 0.025 mM phosphate buffer of pH 3 at 1 ml/min, injection volume 20 µl. (Other columns tested were HiChrom C_{18} 200 × 4 mm; C_{18} RP-18 Superspher® 100, 125 × 4 mm; C_{18} Endcapped RP-18 Superspher® 100, 125 × 4 mm). Retention time for acetic acid was 1.7 min, compared to 8.4 min for phthalic acid. These correspond fairly well with retention times obtained by Bodmeier and Chen (4) with a 20% MeOH eluent. The acetic acid was eluting close to the void in our system, which could only be improved at the cost of total analysis time; increasing retention time for acetic acid slightly caused a large increase in phthalic acid elution time. While gradient elution could be used to get around the retention time problem, the need for equilibration times between runs made this solution impractical. Instead of further optimizing the HPLC method, an ion exclusion chromatography (IEC) method was developed.

The IEC method was run on a Dionex Ion Pac® HPICE® ASI column, 250 × 9 mm, using a 2% acetonitrile in 0.5 mM H_2SO_4 eluent. Phthalic acid gives a broad peak in this system. Increasing the acid concentration from 0.1 to 0.5 mM reversed the elution order of acetic and phthalic acid, with phthalic acid eluting later. Acetonitrile in the mobile phase helped to reduce the hydrophobic interactions between this acid and the column and reduce peak width. Best results were obtained with 2% CH_3CN, above which resolution is affected negatively. Final retention times were 9.3 min for acetic acid and 10.6 min for phthalic acid. Formic acid eluted at 8.2 min in this system. 10% THF in water was also injected into the system to ensure that elution of THF did not interfere with any of the acids. This IEC method was then used to analyze the above precipitated and extracted samples. Limits of detection were 2 µg/ml (0.04 mM) and 0.05 µg/ml (0.0003 mM) for acetic and phthalic acid, respectively. The linear detection range studied extended to 1.1 mM for acetic acid and to 0.15 mM for phthalic acid. The relative standard deviation for acetic acid determination was 1.0% and for phthalic acid was 1.0% at 50 µg/ml.

Total Phthalic and Acetic Content

The USP/NF method for phthalyl content specifies dissolution of CAP in a mixture of EtOH:CH_2Cl_2, addition of EtOH and phenolphthalein, and titration with 0.1 M NaOH. For acetyl content, the sample is hydrolyzed in a mixture of water and 0.5 N NaOH, refluxed for 60 min, and titrated with 0.5 M HCl. The Ph. Eur. method for phthalyl content involves dissolution of CAP in ethylene glycol monomethylether and subsequent titration with 0.1 M NaOH. The acetyl content method is essentially similar to the USP/NF method except for a shorter reflux time (30 min) and the use of 0.1 M NaOH in the hydrolysis. Bauer (3) recommends elimination of ethylene glycol monomethylether since it has a hazard rating similar to ethylene glycol monoethylether, which is a suspected carcinogen.

Hydrolysis of Phthalic and Acetic Groups

A method more suitable for rapid analysis of phthalic and acetic groups was developed based on the total hydrolytic release of these groups as free acids by NaOH. A factorial experimental design was used to optimize the hydrolysis procedure with respect to temperature, con-

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centration of NaOH, and time. The measured levels of acetic acid and phthalic acid were found to reach a steady level after 2 hr at 105°C in 2 M NaOH. The final method involved dissolution of an exact weight (approximately 10 mg) of CAP in 2 ml of 2 M NaOH. The solution was then placed in an oven at 105°C for 2 hr, neutralized with 3 ml of 1 M H_2SO_4 dropwise with stirring, subjected to filtration (0.45 μm), and analyzed by the IEC method above.

Molecular Mass Distribution

CAP is supplied along with a viscosity specification. Viscosity blending is often used by manufacturers to obtain the desired in-specification viscosity. Since the same viscosity can be obtained using different blends, a better measure of the actual chain characteristics of the polymer is its molecular mass distribution (MMD). No reports on the molecular mass determination of CAP were found in the literature, although there are several articles dealing with MMD analysis of cellulose derivatives by size exclusion chromatography (SEC) (see, e.g., Refs. 5 and 6). We developed a system based on SEC-MALLS-RI to perform an absolute characterization and another SEC-UV-RI system more suitable for routine use. Normally, dual detection is not required when running traditional SEC-UV or SEC-RI, but one of the aims of this method development was to compare and contrast light-scattering detection with traditional SEC and also compare UV (ultraviolet) detection with RI detection.

Size Exclusion Chromatography

Molecular-volume-based separation was carried out on two PLgel 5 μm Mixed-C 300 × 7.5 mm columns (Polymer Labs Ltd., Shropshire, UK) connected in series. The columns are rated for separation in the range 0.2–3000 kg/mol (polystyrene). The SEC-UV-RI system was equipped with a Waters System Interface Module, Waters 616 pump (1 ml/min), Waters 712 WISP (injection volume 50 μl), Waters 490 multiwavelength detector (280 nm), and a Waters 410 differential refractometer. The SEC-MALLS-RI system was set up similarly, except that the UV detector was replaced by a DAWN multiangle laser light scattering (MALLS) detector (Wyatt Technology Corp., Santa Barbara, CA). Both systems were equipped with a Millenium 2010 Chromatography Data System.

The columns were calibrated with polystyrene standards (10 standards in the range 0.5–3000 kg/mol; Polymer Labs Ltd., Shropshire, UK) and saturated with CAP using a 0.5% w/w solution of CAP in THF in order to prevent further unspecific adsorption of polymer to the column during the analyses. Samples for measurement were also dissolved in THF at a concentration of 0.5% w/w. All samples were filtered through a 0.45-μm filter prior to injection.

The number-average molecular mass $<M_n>$, mass-average molecular mass $<M_m>$, and polydispersity index were all evaluated from the chromatograms. The standard deviations for $<M_n>$ and $<M_m>$ by MALLS were 2.8 and 1.5 kg/mol, respectively; by UV they were 2.0 and 1.6 kg/mol, respectively; and by RI they were 2.1 and 1.0 kg/mol, respectively.

Specific Refractive Index Increment *dn/dc*

CAP solutions in THF were dialyzed against THF to remove low molecular mass fraction. The concentration of CAP in the dialyzed solutions was measured by UV spectrophotometry as given below. The refractive indices were then measured on these dialyzed solutions on a Chromatix KMX-16 differential refractometer at 632.8 nm and 25°C. The *dn/dc* for CAP in THF was calculated to be 0.1038 ml/g.

Ultraviolet Spectrophotometry

An HP 8452A diode array spectrophotometer was used to find the UV absorption maximum for CAP in THF. A strong peak exists at 280 nm. This peak was then used to construct a standard curve for measuring concentrations in unknown solutions. The standard curve was corrected for water content of the CAP powder.

Spectroscopic Characterization

Spectroscopy can be used as a fingerprint for the structure of the material at a molecular level. Small differences in the spectra can be used to detect differences in the material, either between batches or as a result of storage.

Fourier Transform Infrared Spectroscopy

CAP powder samples were analyzed by Fourier transform infrared spectroscopy (FTIR) on a Nicolet 60 SXB using a PAS detector Model 200 from MTEC Photoacoustics.

Nuclear Magnetic Resonance Spectrometry

CAP samples consisting of approximately 15 mg powder were prepared in 0.7 ml deuterated dimethyl sulfoxide (DMSO). ^{1}H-NMR (nuclear magnetic resonance) and ^{13}C-NMR spectra were recorded on a Bruker DRX 500 spectrometer at 30°C. The residual solvent signal of DMSO-d_6 was used as an internal reference (2.50 ppm

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Table 1

Storage Conditions Used in the Study

No.	Temperature (°C)	Salt Used	p_{water} (mbar)	Relative Humidity (%)
1	20	KNO_3	22.1	94.6
2	40	$MgBr_2$	22.1	30.0
3	40	NaCl	55.1	74.7
4	40	KNO_3	65.6	89.0
5	60	LiCl	22.1	11.0

for ^{1}H-NMR and 39.50 ppm for ^{13}C-NMR) for identity. Trimethylbenzene (TMB) was used as an internal standard for concentration; an amount in the range of 5 mg TMB was accurately weighed and added to the sample solutions. Both one- and two-dimensional spectra were recorded. However, only the results from the ^{1}H-NMR spectra are presented here since information from the ^{13}C-NMR and two-dimensional spectra was very limited. The spectra were used in the quantification of the degree of substitution of the polymer.

X-ray Diffraction

X-ray diffraction (XRD) was performed with a Guiner-Hägg camera, CuKα_1-radiation (λ = 1.5405981 Å) on CAP powder.

Thermal Characterization

Thermogravimetric Analysis

CAP powder samples were subject to thermogravimetric analysis (TGA) on a Mettler TA4000 system using a TGA50 analyzer. Sample masses of approximately 20 mg were placed in Al_2O_3 crucibles. The heating rate was 5°C/min, and the temperature interval was 50°C–600°C. Nitrogen atmosphere was used in the temperature range 50°C–500°C, and oxygen was used over 500°C.

Differential Scanning Calorimetry

CAP powder samples were subject to differential scanning calorimetry (DSC) on a Mettler TA4000 system using a DSC30 analyzer. Sample masses of approximately 10 mg were placed in aluminum pans with crimped lids and also lids with pinholes. The scanning rate was 10°C/min over the range 50°C–300°C. Nitrogen flow rate was 50 ml/min.

Storage Studies

In order to study the hydrolytic stability of CAP, samples of the polymer were stored for 15 weeks in open vials in desiccators containing saturated salt solutions (Table 1). The storage conditions were chosen to obtain three conditions with the same temperature and three conditions with the same partial pressure p_w (i.e., activity) of water (7).

Products Formed by Heat

Olaru et al. (8) have studied the thermal degradation of CAP films by exposing solvent-cast films to heat between 120°C and 220°C for various times. Heating was performed in an air atmosphere, and the film samples were extracted for analysis of the degradation products by

Table 2

Results of Water Content Measurements by Different Techniques

Batch No.	Loss on Drying (%)	Karl Fischer (%)	Karl Fischer Orion Turbo II (%)	TGA (%)	DSG (%)	Certificate (%)
50103		2.03		3.19	1.57	1.5
50105		1.87		2.04	1.58	2.2
50106		1.75		1.57	1.66	1.3
50104		2.41		2.24	1.87	2.0
40706	2.38	2.35	2.35	2.43	2.01	1.2

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HPLC. Phthalic anhydride was the principal degradation product.

We have repeated these studies, but with CAP powder placed in gas chromatography (GC) headspace vials in which the atmosphere was changed to either oxygen or nitrogen. The vials were heated in an oven at 105°C for 24 hr before analysis of the headspace for evolved gas products.

The products were analyzed on various systems to ensure that all products were picked up: a Perkin-Elmer HS-GC/MS with an ion trap detector and a DB-225 column (medium polarity, 30 m, 0.32 mm, 0.25 μm) with settings 40°C (8 min) to 200°C at 5°C/min; a 5890 Hewlett Packard GC with an FID detector and a DB-WAX column (polar, 30 m, 0.32 mm, 0.5 μm) with settings 40°C (8 min) to 200°C at 5°C/min; a Finnigan quadrupole headspace-GC/MS equipped with a DB-5MS column (nonpolar, 30 m, 0.32 mm, 0.5 μm); with settings 40°C (10 min) to 200°C (2 min) at 5°C/min; manual injection with solid-phase microextraction (SPME) technique and Supelco Carbowax.

RESULTS AND DISCUSSION

Water Content

The water contents of the different batches analyzed by various techniques are given in Table 2 along with the value specified in the certificate of the manufacturer. All the samples contained comparable water levels. Some small variations in the batches are seen.

All the methods give comparable results. The standard deviation is somewhat higher in the thermogravimetric analyses. For rapid determination during developmental work, the Karl Fischer (Orion Turbo) is the fastest; the DSC is also quite convenient, but slower. The difference in the measured values as compared to the values from manufacturers is probably a consequence of the storage/exposure history of the sample.

Measurement of Free Acids

The concentrations of free acetic and phthalic acids in the CAP samples are given in Table 3. The values are averages of two replicates of material drawn from each batch. When calculated as total acid, the values correspond to approximately 1.5%, which falls well in the specification range in the pharmacopoeias (USP-NF maximum 6%; Ph. Eur. maximum 3%). The amount of free phthalic acid does not seem to vary as much as that of the free acetic acid, probably due to the latter being volatile.

Table 3

Free Acetic Acid and Phthalic Acid in Fresh CAP Samples

Batch No.	μg Acetic Acid/mg CAP	μg Phthalic Acid/mg CAP
50103	6.6	9.6
50105	1.5	9.8
50106	2.1	10.6
50104	3.2	10.8
40706	3.3	10.6

When stored at various conditions, the free phthalic acid concentration rises, while the acetic acid concentration apparently falls below detection levels (see Table 4). The absence of acetic acid in these samples may be explained by the fact that acetic acid is volatile. Increasing water partial pressure p_w (at a constant temperature of 40°C) causes an increase in the phthalic acid concentration, while higher temperatures (at constant vapor pressure of water, i.e., constant activity of water) seem to result in lower phthalic acid content, although still much higher than in fresh material. This can be explained on the basis of the adsorption isotherm for water. At higher temperatures, the CAP powder absorbs less water (for the same water activity), and therefor there is a lower level of hydrolysis, resulting in less free acid. (The relative

Table 4

Free Acetic Acid and Phthalic Acid in CAP Samples from Batch 50103 After Storage for 15 Weeks Under Various Conditions

	Free Acids Content (μg Acid/mg CAP)		
Storage p_w	Stored at 20°C	Stored at 40°C	Stored at 60°C
22.1 mbar			
Acetic acid	<0.1	<0.1	<0.1
Phthalic acid	41.0	33.0	27.3
55.1 mbar			
Acetic acid		<0.1	
Phthalic acid		137.9	
65.6 mbar			
Acetic acid		<0.1	
Phthalic acid		174.3	

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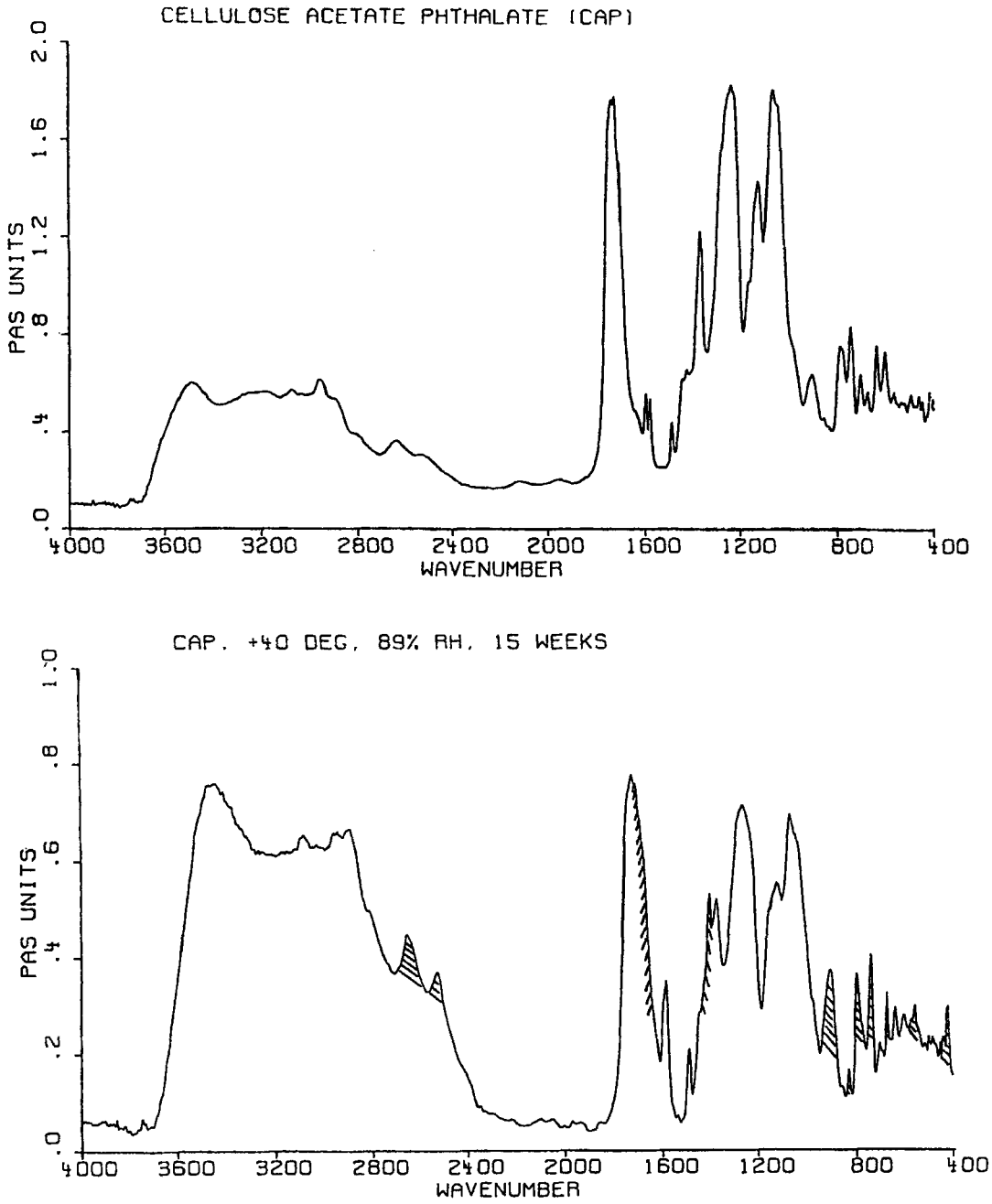

Figure 1. Infrared spectra of CAP powder and CAP after storage at 40°C with p_w = 65.6 mbar (89% RH) for 15 weeks. The shaded regions represent phthalic acid.

humidity percentage decreases with increasing temperature for the same p_w.) Thus, humidity or moisture has a greater effect on the storage stability of CAP powder than temperature does. These results suggest that, when evaluating CAP film (e.g., see Refs. 2 and 9), tablet coating (e.g., see Ref. 10), or powder stability data, both these factors must be taken into account simultaneously.

The infrared (IR) spectra of the stored CAP sample also show peaks characteristic of phthalic acid that are not present in the fresh sample (Fig. 1). The peaks agree

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with the assignments made by Olaru et al. (8) after analyzing heat-treated CAP films.

Total Phthalic and Acetic Content

The amount of acetic and phthalic acids present as substituents in the CAP powders is reported in Table 5 along with the results on the batch certificates. (These values have been corrected for free acids.) The calculated acetyl and phthalyl contents then correspond to the specification requirements in the pharmacopoeias. There is good consistency among the batches.

When stored at various conditions, a loss in the degree of substitution as measured by the acetyl and phthalyl contents is seen (Table 6). It is apparent that storage humidity is again a major parameter influencing the rate of hydrolysis of the CAP polymer. No significant differences were observed among batches.

An attempt was made in this work to determine by NMR the relative amount of substituent in the three possible positions in the six-member hemiacetal rings in CAP. Goodlett et al. (11) have used NMR to similarly determine the distribution of acetyl groups in cellulose acetates. It is likely that materials with the same overall degree of substitution but a different pattern of substitution will have different functional characteristics. Unfortunately, this quantitative distribution determination did not work with CAP due to the more complicated structure. The two substituents in the three possible positions affect the shifts so that no specific pattern is conceived; there is severe overlap in the proton signals from cellulose. Changing the temperature up to 90°C was not useful to resolve this.

Specific shifts from acetyl and phthalyl groups are, however, obtained at 2.2–1.8 ppm and 7.9–7.2 ppm, respectively; this can be used to quantitate the amount of these groups in relation to the polymer. Results from NMR measurements of two batches are also included in Table 5; the standard deviation of the NMR results is 0.2%. It can be seen that the agreement between the val-

Table 6

Amounts of Bound Acetyl and Phthalyl Groups in CAP Batch 50103 After Storage for 15 Weeks Under Various Conditions

	Substituent Content in CAP (% w/w)		
Storage p_w	Stored at 20°C	Stored at 40°C	Stored at 60°C
22.1 mbar			
Acetyl content	19.8	20.8	19.1
Phthalyl content	32.4	33.5	31.0
55.1 mbar			
Acetyl content		17.6	
Phthalyl content		25.0	
65.6 mbar			
Acetyl content		9.2	
Phthalyl content		19.6	

Table 5

Measured Amounts of Bound Acetic and Phthalic Acid in Fresh CAP Samples and Their Calculated Acetyl and Phthalyl Content

Batch No.	µg Bound Acetic Acid/mg CAP	Acetyl Content (% w/w)	µg Bound Phthalic Acid/mg CAP	Phthalyl Content (% w/w)
50103	293	21.0	396	35.5
		19.4 (NMR)		33.5 (NMR)
		23.5 (certif.)		34.8 (certif.)
50105	305	21.9	403	36.2
		19.5 (NMR)		33.8 (NMR)
		23.3 (certif.)		34.5 (certif.)
50106	293	21.0	393	35.3
		22.7 (certif.)		34.7 (certif.)
50104	291	20.9	389	34.9
		22.8 (certif.)		34.3 (certif.)
40706	269	19.3	360	32.3
		24.4 (certif.)		34.4 (certif.)

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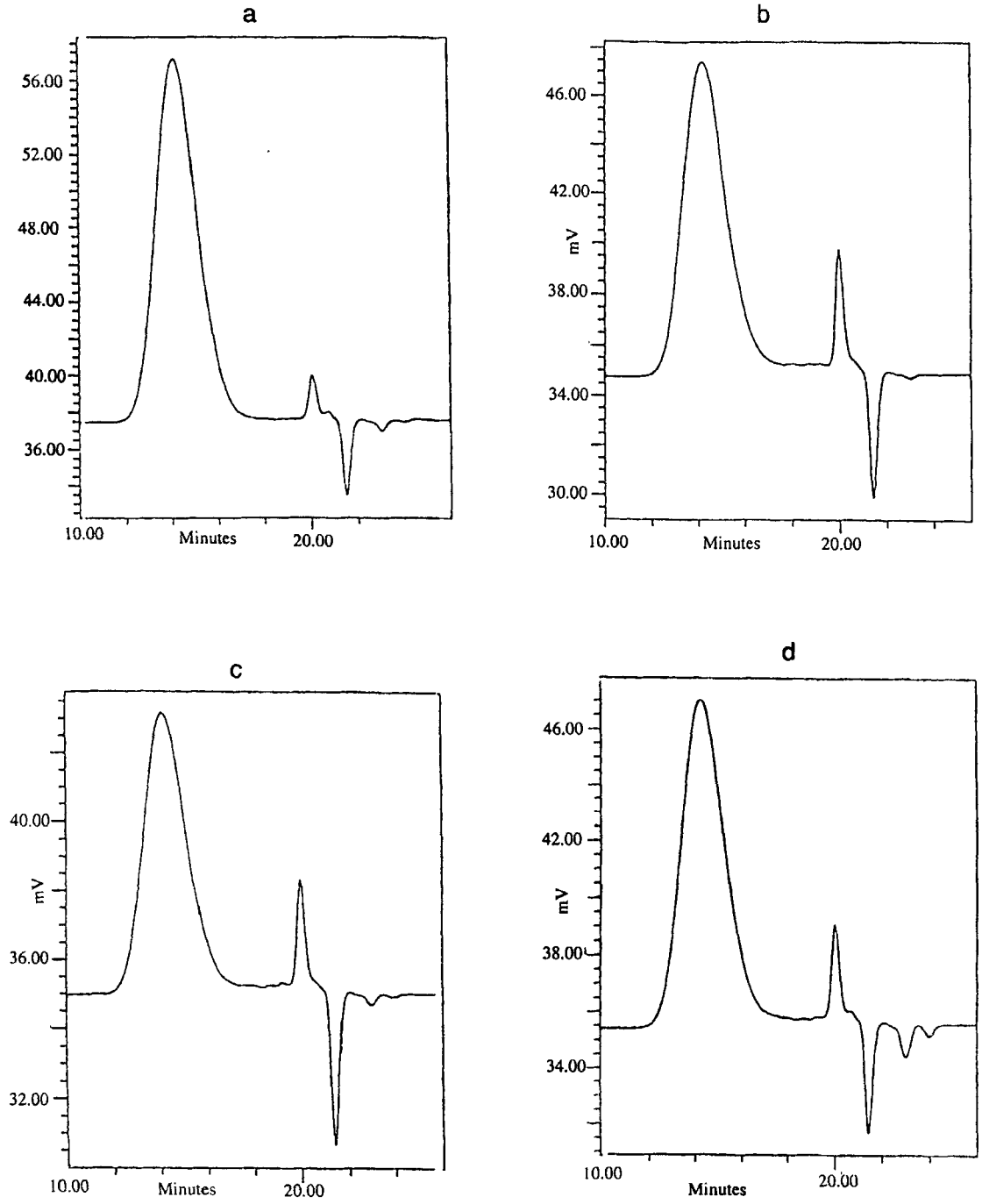

Figure 2. SEC-RI chromatograms of (a) CAP powder and CAP powder after storage for 15 weeks at (b) 20°C, p_w = 22.1 mbar (94.6% RH); (c) 40°C, p_w = 22.1 mbar (30% RH); (d) 60°C, p_w = 22.1 mbar (11% RH); (e) 40°C, p_w = 55.1 mbar (74.7% RH); (f) 40°C, p_w = 65.6 mbar (89% RH). The peak at 20 min is free phthalic acid.

(continued)

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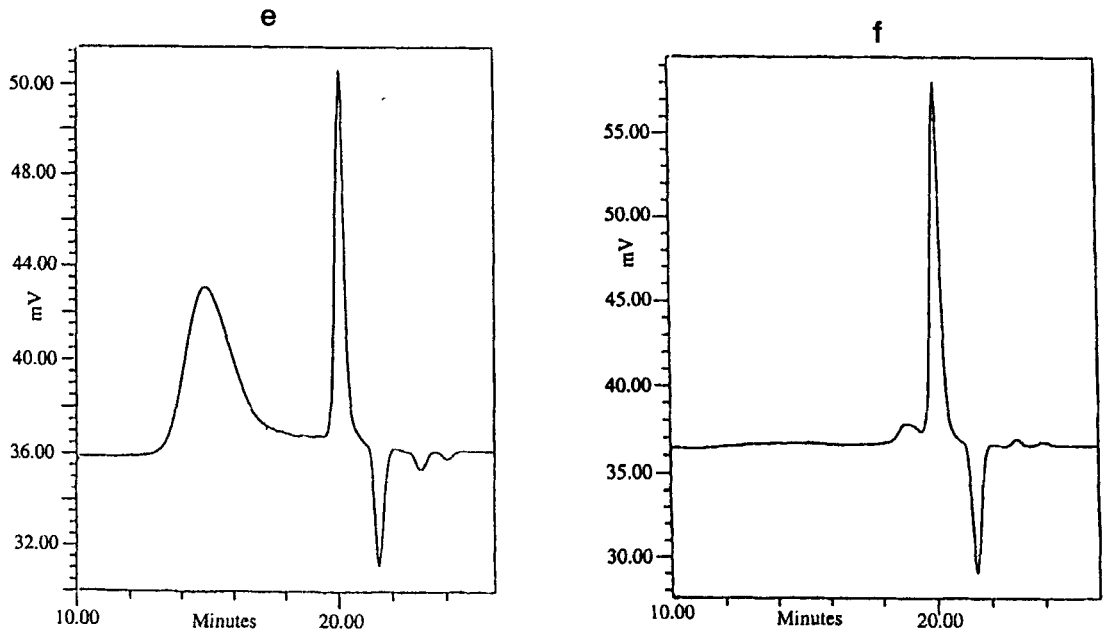

Figure 2. Continued

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ues obtained by hydrolysis of the substituent groups in NaOH followed by IEC and the values obtained by NMR is good.

Molecular Mass Distribution

The molecular masses of the CAP batches were measured in both absolute detection mode (MALLS) and relative to polystyrene standards (UV, RI) in this work. Example SEC-RI chromatograms are shown in Fig. 2. The results are compiled in Table 7, with a number of extra batches, including one from WAKO, have been added to the study.

The results show very slight variation in the molecular masses between various batches measured by either technique. The average $<M_n>$ and $<M_m>$ for CAP from the five primary batches were estimated at 40.8 ± 2.0 kg/mol and 86.3 ± 2.5 kg/mol, respectively, based on UV and RI detection. The corresponding values from MALLS detection are 30 ± 1.7 kg/mol and 48 ± 0.5 kg/mol, respectively. The resulting polydispersity indices are different between the indirect and absolute detectors.

Both the number-average and mass-average molecular masses, $<M_n>$ and $<M_m>$, respectively, differ significantly between the two types of detectors, with the differences in corresponding $<M_m>$ values being much greater. The difference between the two types of detection may be ascribed to the calibration standards employed in the case of indirect detection. Since no commercial CAP standards for molecular masses are available, (almost) monodisperse fractions of polystyrene have been used. Separation in SEC is based not on molecular size, but on molecular volume in the solvent system in question. Any differences in the hydrodynamic volume of similar molecular mass polystyrene and CAP will cause systematic errors in the calibration curve. CAP apparently has a larger hydrodynamic volume than polystyrene for the same molecular weight, resulting in an overestimation of $<M_m>$ for CAP. THF is a medium hydrogen-bonding solvent and is likely to function as a better solvent for CAP than for polystyrene. The reason that this error is much more severe for $<M_m>$ than for $<M_n>$ is, however, unclear. It is expected that an error in the calibration will have a greater effect on the $<M_m>$; however, there may be some adsorption effects on the column that are not taken into accounted. An example MMD for a batch from the UV measurements is shown in Fig. 3.

The small variations in molecular masses among batches seem to suggest that the manufacturer uses one batch of cellulose for a number of batches of CAP. Re-

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Table 7

Molecular Masses of Fresh Samples of CAP Determined with Relative Detectors UV and RI and the Absolute Detector MALLS(-RI)

Batch No.	$<M_n>$ (kg/mol)	$<M_m>$ (kg/ng)	Polydispersity Index	Method
50103	37.6	84.6	2.3	UV
	41.6	86.7	2.2	RI
	31.0	49.2	1.6	MALLS(-RI)
50105	38.8	83.8	2.2	UV
	41.6	84.1	2.1	RI
	31.1	48.3	1.6	MALLS(-RI)
50106	38.7	83.8	2.2	UV
	41.3	85.1	2.2	RI
	31.4	48.8	1.6	MALLS(-RI)
40706	39.9	86.8	2.2	UV
	39.6	86.5	2.2	RI
	27.6	48.6	1.8	MALLS(-RI)
50104	39.4	84.8	2.2	UV
	41.2	85.0	2.1	RI
	32.0	48.4	1.5	MALLS(-RI)
211253-01	43.7	92.0	2.1	RI
	29.3	47.5	1.6	MALLS(-RI)
300461-00	43.0	89.6	2.1	RI
	30.7	48.3	1.6	MALLS(-RI)
311032-01	43.7	93.9	2.1	RI
	32.9	48.8	1.5	MALLS(-RI)
311081-01	44.3	93.2	2.1	RI
	30.2	47.9	1.6	MALLS(-RI)
WAKO	37.4	82.0	2.2	RI
	32.6	47.5	1.5	MALLS(-RI)

sults such as these can be used to correlate the functionality of these polymers since a number of film properties depend on the molecular weight. An example is the incidence of defects in films coated on tablets (12).

The effect of hydrolysis during storage on the molecular masses is very dramatic. Results from the analysis of one batch are given in Table 8. Again, the humidity seems to be the more critical parameter when compared to temperature. Looking at the MALLS data, storage at low p_w (= 22.1 mbar) at various temperatures causes only a slight lowering of the $<M_m>$ (from 49 initially to 49, 48, and 48 kg/mol for storage at 20°C, 40°C, and 60°C, respectively). The same holds for $<M_n>$, too. However, the effect of increasing humidity at 40°C is much greater. When stored at p_w = 55.1 mbar (40°C, 75% RH) for 15 weeks, the $<M_m>$ falls from 49 to 31 kg/mol. Increasing the humidity to a p_w of 65.6 mbar (40°C, 89% RH) results in hydrolysis that removes a large portion of the substituent groups (see Table 6). In this case, there is a complete absence of polymer peak in the SEC chromatograms (see Fig. 2). Note that with increasing levels of hydrolysis, CAP molecules begin to revert to cellulose, which is insoluble in THF. Thus, less and less of the sample dissolves in the SEC eluent/solvent; the low degree of substitution in the 40°C, 89% RH sample essentially makes it insoluble. This change in the nature of the polymer, from being CAP-like to cellulose-like, also induces an error in the MALLS measurement in that the refractive index increment also changes, which has not been taken into account.

The chromatograms in Fig. 2 also show a peak for phthalic acid at approximately 20 min that is seen to increase with storage at increasing humidity. This peak could conceivably be used to quantify free phthalic acid in these samples.

The primary reason for reduction in molecular mass of CAP on storage is the hydrolysis of substituent groups.

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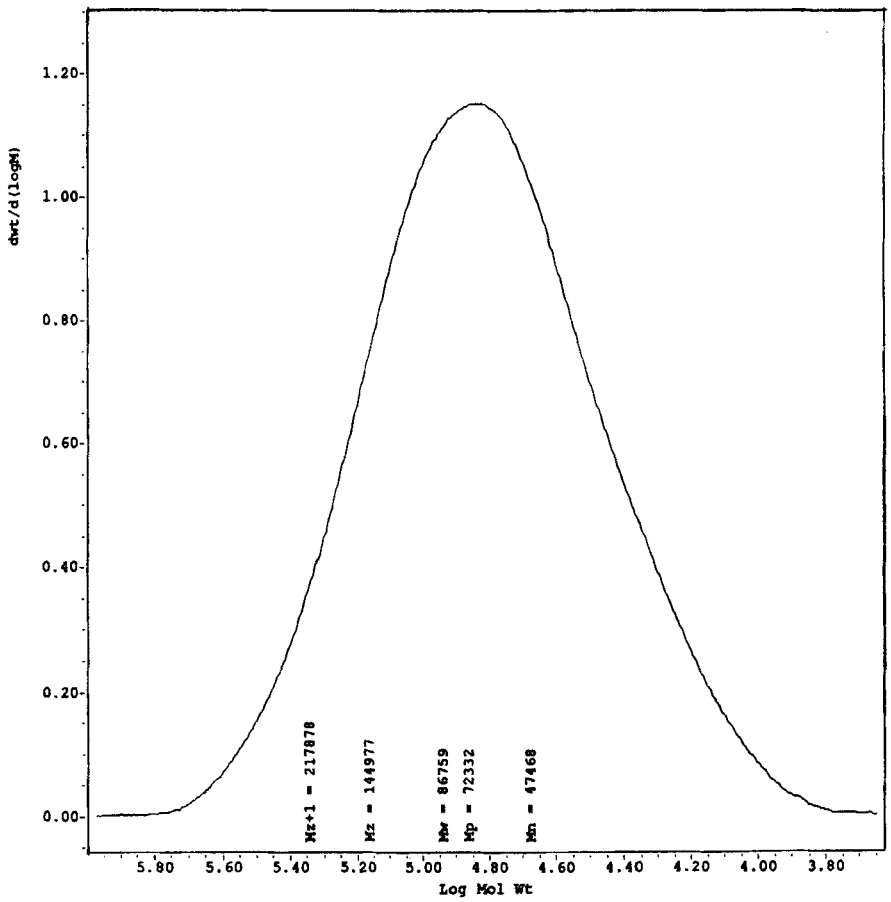

Figure 3. The molecular mass distribution of CAP from SEC-UV chromatography.

Once the molecular mass and concentration of substituent groups, initially and after storage, is known, an estimate of the molecular mass after storage is possible. The following relationship can be used.

$$w_{ac} < M_m >_{CAP} + w_{ph} < M_m >_{CAP} + < M_m >_{cell} = < M_m >_{CAP} \quad (1)$$

where w_{ac} and w_{ph} are weight fractions of acetate and phthalyl groups in the polymer, respectively, and $<M_m>_{CAP}$ and $<M_m>_{cell}$ are the molecular masses of CAP and of the cellulose backbone, respectively. From the initial substituent weight fractions (Table 5) and molecular masses (Table 7), $<M_m>_{cell}$ can be estimated. The same $<M_m>_{cell}$ can then be used together with data from Table 6 to calculate $<M_m>_{CAP}$ after various storage conditions using Eq. 2.

$$< M_m >_{CAP} = \frac{< M_m >_{cell}}{(1 - w_{ac} - w_{ph})} \quad (2)$$

The calculated values of $<M_m>_{CAP}$ are also given in Table 8 for comparison. The calculated values are slightly lower than measured for samples stored at low humidity (i.e., those undergoing little hydrolysis). Low levels of hydrolysis may not cause enough perturbation in the molecular volume of CAP to be detectable by SEC. However, at higher levels of hydrolysis, the calculated values are higher than measured. It is likely that hydrolysis does not occur uniformly over the molecules, that is, some molecules in a sample are more "cellulose-like" than others. The more cellulose-like the molecule is, the more insoluble it should be in THF, and therefore, the molecules in the sample measured by MALLS should be the less-hydrolyzed ones (i.e., the molecular weight will be

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Table 8

Molecular Masses After Storage of CAP Batch 50103 at Different Conditions for 15 Weeks

	Molecular Mass of CAP (kg/mol)		
Storage p_w	Stored at 20°C	Stored at 40°C	Stored at 60°C
22.1 mbar			
$<M_n>$	31.9	31.9	28.6
$<M_m>$	49.1	48.9	44.8
Calculated $<M_m>$	44.3	46.4	42.4
55.1 mbar			
$<M_n>$		23.9	
$<M_m>$		31.6	
Calculated $<M_m>$		36.9	
65.6 mbar			
$<M_n>$		Not detected	
$<M_m>$		Not detected	
Calculated $<M_m>$		29.7	

The results are from the MALLS(-RI) system. Calculated values are based on Eq. 2.

overestimated). However, the results seem to show the opposite: the measured value is lower than calculated. No explanation can be given for this at the moment; the reason may lie in the difference in behavior of the cellulose-like and CAP-like molecules in the SEC column in a THF solvent.

Even though the calculated values are not in good agreement in all cases with the measured values, this approach can be used to obtain a "ballpark" value for the molecular weight of CAP samples.

CAP polymers are supplied with a nominal viscosity designation, determined on 15% CAP in acetone. The certificate from the manufacturer contains a viscosity value for each batch. This value is to be regarded as a rough indicator of average molecular mass. However, without a relevant correlation or relationship (e.g., Mark-Houwink equation), it is difficult to get a good idea of one parameter from the other. We have compiled the viscosities of a number of batches as measured in in-house batch release tests, values given on the certificates, and the measured $<M_m>$ in Table 9. (The specification limits are between 45 and 90 cP.) Considering the material within each batch to be uniform, the pooled viscosity variation due to method is ± 20 cP, while the mean between batches appears to be approximately 66 ± 8 cP. Essentially, the variability in the method is so large that it cannot be used to distinguish among batches.

Thermal Characterization

CAP samples were analyzed by TGA to obtain separated vaporization and thermal degradation steps, such that absolute values of water content, degree of substituents measured in acetic and phthalic acid, and pyrolysis

Table 9

Viscosity of Different CAP Batches From In-House Batch Release Analysis and as Reported on the Manufacturers' Certificates Plus the Measured $<M_m>$ from MALLS(-RI)

Batch No.	Viscosity (*cP*) (In-House Testing)	Viscosity (*cP*) Mean ± SD (In-House Testing)	Viscosity (*cP*) (Certificate)	$<M_m>$ (kg/mol)
50103	56, 55, 55	55 ± 0.6	63	62.1
50105	85, 86, 78	83 ± 4.4	63	61.0
50106	78, 58, 61	66 ± 10.8	61	61.7
40706	63, 67, 63	64 ± 2.3	68	61.5
50104	62, 59, 61	61 ± 1.5	67	61.2
51197-01	62, 59, 62	61 ± 1.7		
51198-01	74, 71, 64	70 ± 5.1		
51199-01	59, 60, 60	60 ± 0.6		
51248-01	73, 65, 64	67 ± 4.9		
51249-01	67, 66, 71, 81	71 ± 6.8		
61048-01	69, 71, 73, 72	71 ± 1.7		
61049-01	65, 47	56 ± 12.7		

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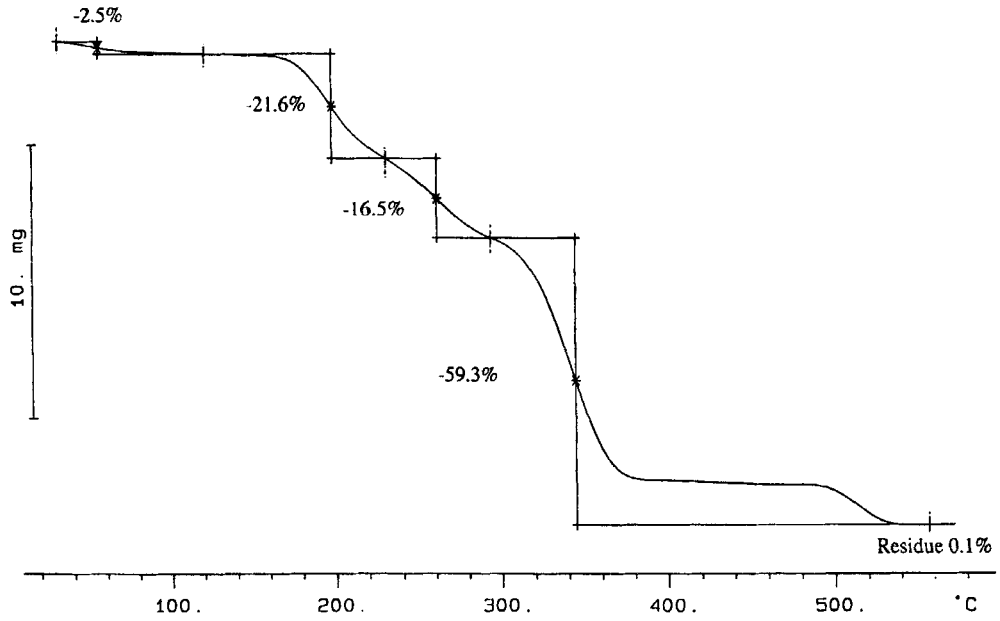

Figure 4. TGA thermogram of CAP powder.

products were know. However, the results were not reproducible, and all CAP batches gave different thermograms. Specific steps, except for water loss (see Table 2) and pyrolysis, could not be evaluated due to this lack of consistency. A TGA thermogram is shown in Fig. 4 for a fresh CAP sample (40706). Crystals were detected inside the TGA oven after running CAP; these were identified by FTIR to be phthalic anhydride.

DSC was used to measure the glass transition temperature T_g of the CAP powders. A typical thermogram is shown in Fig. 5, in which both water loss and glass transition phenomena are clearly visible. The T_g's of the fresh

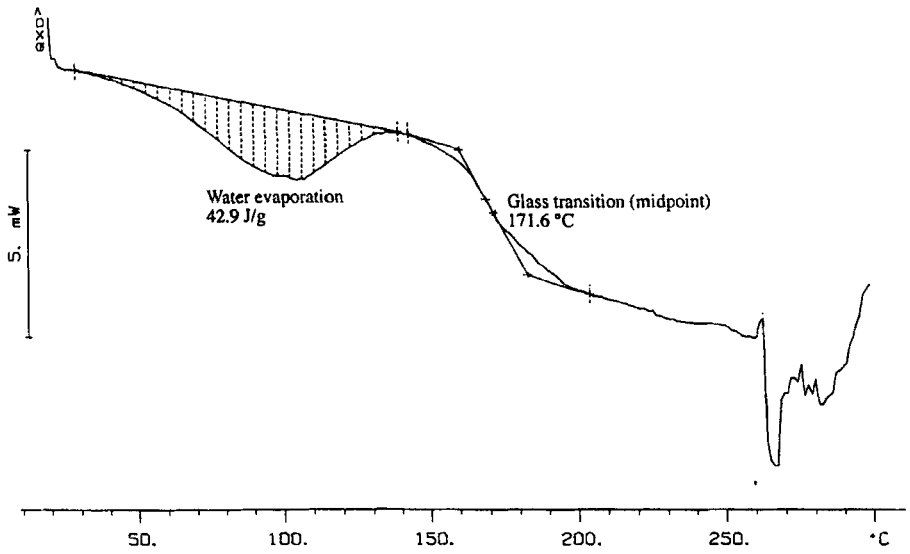

Figure 5. DSC thermogram of CAP powder showing water loss and glass transition temperature.

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Table 10

Glass Transition Temperature of Fresh CAP Powder from DSC

Batch No.	T_g (°C)
50103	174
50105	173
50106	172
40706	172
50104	172

CAP powders are summarized in Table 10, and those after storage are shown in Table 11. The values in Table 10 compare well with that quoted by the manufacturer (= 175°C) and by Sakellariou et al. (13) (= 171°C), but differ greatly from the value (18.5°C) obtained by Porter and Ridgeway (14). Sakellariou et al. (13) emphasized the importance of eliminating residual solvents when measuring T_g on films of polymers since solvents can serve as plasticizers, drastically lowering the measured value. (In a separate set of experiments with free-cast films of CAP from acetone, analyzed by thermal mechanical analysis, we obtained T_g's in the range 151°C–167°C for the same batches; the difference is likely due to residual solvent content in the films; see Ref. 15).

On examining the storage data in Table 11, it is seen that only the storage at the most severe conditions (40°C, 65.6 mbar ≡ 89% RH) seems to have any measurable effect on this parameter. From the analysis of total acetic and phthalic content above, we know that, under this storage condition, CAP loses a large fraction of substituents in 15 weeks, so we are essentially measuring a different polymeric material along with free acetic and phthalic acids serving as plasticizers. Thus, glass transition is not a very sensitive parameter for examining the functional suitability of CAP powder.

Table 11

Glass Transition Temperatures from DSC of CAP Powder 50106 Stored for 15 Weeks

	Glass Transition Temperatures (°C)		
Storage p_w	Stored at 20°C	Stored at 40°C	Stored at 60°C
22.1 mbar	171	173	171
55.1 mbar		175	
65.6 mbar		155	

Other Methods

No crystallinity was detected in the CAP powders by XRD, both before and after storage. The headspace above CAP samples placed in sealed vials under nitrogen or oxygen atmospheres at 105°C for 24 hr was analyzed by HS-GCMS. The results from storage and heating under oxygen atmosphere showed the expected acetic acid and phthalic acid products and an unexpected product, formic acid, in the gas phase (Fig. 6). This has not been reported earlier (see, e.g., Ref. 8); this species may have been missed in earlier reports since the volatile formic acid will not be present when the film or powder is extracted for a normal free-acid analysis. A feasible mechanism for the formation of this product is not available presently. A summary of products formed and conditions required is given below.

Acetic acid	Formed in O_2 and N_2 atmospheres at 105°C; also some at room temperature (RT)
Phthalic acid	Formed in O_2 atmosphere at 105°C; detectable only by the SMPE technique
Phthalic anhydride	Formed in N_2 atmosphere at both RT and 105°C
Formic acid	Formed in O_2 and N_2 atmospheres at both RT and 105 °C
Other polar components	Formed in O_2 and N_2 atmospheres at both RT and 105°C

CONCLUSIONS

Cellulose acetate phthalate powder has been studied by various methods. New methods have been developed to examine free-acid content, substituent composition, and molecular mass distribution; FTIR, NMR, and thermal analysis have also been performed on fresh samples, as well as samples stored under various temperature and humidity conditions.

It is clear that humidity is a more critical storage parameter than temperature, although the two act in conjunction. Higher humidity is more deleterious to the functionality of the polymer than high temperature. Functionality in this case is taken to be determined by the substituents and by the molecular mass distribution.

SEC is a good method to obtain the initial molecular mass of the CAP polymer, but polymer subject to hydrolysis will not elute true compared to CAP due to its conversion from CAP-like to cellulose-like polymer. This may lead to erroneous results, depending on the degree of

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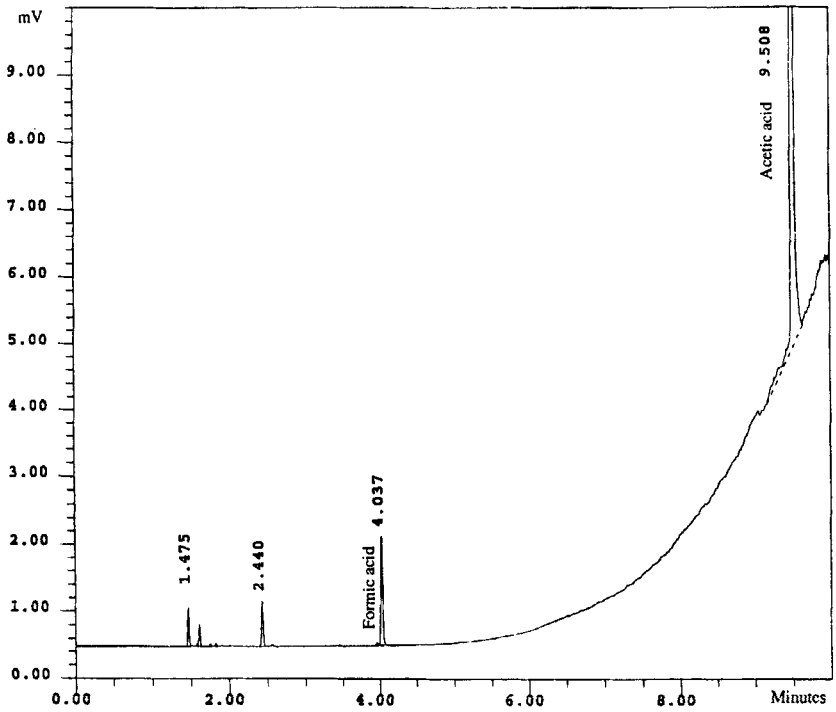

Figure 6. An HS-GC chromatogram of CAP powder stored in oxygen at 105°C for 24 hr. The peaks at 4.04 min and 9.51 min were identified as formic acid and acetic acid, respectively.

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substituent loss. UV and RI detection give similar results, while the absolute MALLS detection gave lower values of $<M_n>$ and $<M_w>$. A method to perform a rough estimation of the molecular mass of CAP has also been suggested. It may be possible to use the values of $<M_n>$ and $<M_w>$ obtained here for any other batch of the same viscosity grade of CAP.

NMR can be used to obtain a good estimate of the fraction substituents in the polymer. However, an attempt to obtain the pattern of substitution of the CAP molecule by NMR was unsuccessful.

Glass transition temperatures of CAP samples were measured. However, this characteristic of the polymer is judged not to be as sensitive to the loss of substituents as the molecular weight.

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