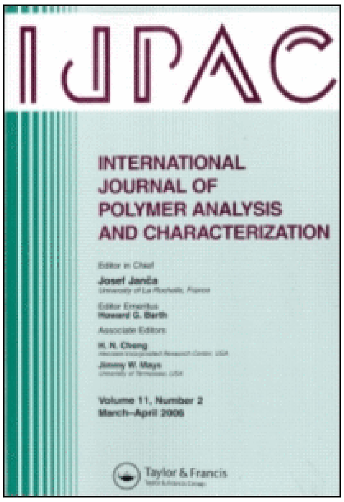

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A Practical Method to Determine Polymer Concentration in Solution by Density

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A Practical Method to Determine Polymer Concentration in Solution by Density

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Abstract: This work describes a method for analyzing polymer concentration in solution using density. The method can be applied to any polymer/solvent combination given certain experimental conditions; however, this study is specific to commercial samples of poly (n-butyl methacrylate) (PBMA) or poly (ethylene-co-vinyl acetate) (PEVA), two polymers of interest to Cordis Corporation. The test method was validated with respect to ICH requirements of linearity, accuracy, precision, range, etc.[1,2] The kinetic dissolution of PBMA or PEVA in tetrahydrofuran (THF) was evaluated as a practical analysis of Cordis process parameters. The results are provided as examples of the test method application.

Keywords: Concentration; Density; PBMA; PEVA; Polymer dissolution; Polymer solubility

INTRODUCTION

It is important to understand physicochemical properties of polymers when developing formulations for pharmaceutical and medical device applications. One of these properties is their behavior in solution, more specifically, the polymer-solvent interactions. Polymer dissolution is not a one-step process as with small molecules; rather, it first requires solvent

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diffusion into the polymer, which causes swelling, followed by chain disentanglement.[3] Gaining a better understanding of the dissolution profile leads to a more comprehensive characterization.

Various experimental techniques have been utilized to characterize polymer behavior in solution, including optical microscopy, interferometry, gravimetry, and steady-state fluorescence. Disadvantages of these techniques include time and resource requirements, specific instrumentation requirements, or an applicability limited to polymer films.[3] Two commonly used techniques to measure polymer concentrations are differential refractometry and UV/visible spectrophotometry.[4] However, refractive index is very sensitive to molecular weight, and spectrophotometry is limited to polymers containing a chromophore that absorbs light in the UV or visible region.[4]

Density is a function of concentration and the relationship can be described with linear functions, as long as the concentrations are within the range of Newtonian behavior. Therefore, the concentration of a polymer in any solvent can be determined by density. There are several advantages of density over the methods mentioned above. For example, a density meter is inexpensive to purchase and quick and easy to use; only small amounts of polymer are necessary; development of an entire method is relatively fast with the preparation of standard curves being the rate-limiting step; and, most importantly, the method is independent of molecular weight. High molecular weight polymers experience chain entanglements, thus exhibiting non-Newtonian behavior under certain conditions in solution.[5] However, if the concentration range allows the polymers to behave in a Newtonian manner, molecular weight variability will not affect the linear relationship.[5] Thus, considerations at the outset include: (1) the concentration range chosen must exhibit Newtonian behavior (i.e., linearity); (2) density should not be a function of the molecular weight of the polymer; and (3) the solubility of polymer in the solvent must be great enough to observe a measurable difference in density as compared to the solvent blank.

Details of the test method including test method validation will be presented. Understanding the kinetic dissolution of polymer into solution is necessary, and therefore it is included as a practical application of the method.

EXPERIMENTAL SECTION

Materials

Tables I–IV describe the PBMA and PEVA materials for method development, validation and application. The materials in Tables II and III

Table I. Materials: Method development and validation

Polymer	Supplier	Mw (Da)*	Mn (Da)*	PDI*
PBMA	Aldrich	281,000	146,000	1.92
PBMA	Poly sciences	230,000	125,000	1.84
PBMA	Lucite	260,000	140,000	1.86
PEVA	Aldrich	76,600	32,800	2.34
PEVA	Arkema	53,300	24,200	2.20
PEVA	Dupont	81,400	20,800	3.91

*Viscotek GPC Triple Detection TDA 302. THF @ 1.00 mL/min. Columns: (Plgel mixed B-LS: 500 to 10,000,000 Da) @ 30°C. Detectors @ 35°C. Concentration: ca. 10.0 mg/mL. Injection volume: 80.0 µL. Polystyrene monodisperse standard calibration.

were used only for robustness and ruggedness validation. Molecular weight information is included in these tables for reference. One aspect of method accuracy was demonstrated with a commercial resin, styrene maleimide (SMA® 4000I, Sartomer Company, Inc., 13,000 Da). The solvents used for this study were tetrahydrofuran, Burdick & Jackson, >99.9% GC/GPC grade, and toluene, EMD, > 99.9% HPLC grade.

Methods

We present a method that measures the densities of polymer solutions with an Anton Paar DMA 5000 digital density meter. The density of the liquid sample is calculated from the resonant frequency of the instrument's oscillating U-shaped glass tube. The instrument maintains accurate temperature control through a high-precision platinum thermometer providing density values that are reported to 10^{-4}.[6] The density values are an average of triplicate measurements. The density value is used to calculate the concentration of a solution from the corresponding density versus concentration (based on initial weight) standard curve.

A series of density-to-concentration standard curves were obtained for each polymer in THF or toluene. For this study, the measurements

Table II. Materials: PBMA for robustness and ruggedness validation

Polymer	Supplier	Lot #	Mw (Da)	Mn (Da)	PDI
PBMA	Polysciences	1	156,000	115,000	1.36
PBMA	Polysciences	2	230,000	125,000	1.84
PBMA	Polysciences	3	319,000	318,000	1.00

Table III. Materials: PEVA for ruggedness validation

Polymer	Supplier	Lot #	Mw (Da)	Mn (Da)	PDI
PEVA	Aldrich	1	76,600	32,800	2.34
PEVA	Arkema	2	53,300	24,200	2.20
PEVA	Dupont	3	81,400	20,800	3.91

were performed at 30°C; however, concentrations can be calculated using the curves generated at any temperature. Each curve was created by pooling density measurements performed on each polymer from several suppliers with variable molecular weight and polydispersity indices. In order to behave in a Newtonian manner, the PEVA or PBMA in THF or toluene solutions were maintained below 60 mg/mL.

The solution densities after 24 h dissolution of at least five concentrations per group were measured and plotted to create a single regression line for all lots evaluated. The linear regression equation and regression coefficient (R^2) were calculated.

Sample solutions were allowed to dissolve in capped vials while being stirred at 30°C for 24 h. After 24 h, dissolution for all materials evaluated was considered complete. The solution was then filtered through a 2.7 μm pore size PTFE filter (and diluted if necessary), and the density was measured at the temperature at which the standard curves were created. The average density value of triplicate measurements was used in the linear equations to determine the solution concentration.

RESULTS AND DISCUSSION

The method was validated according to International Conference on Harmonisation (ICH) guidelines for analytical validation procedures. PBMA or PEVA in THF or toluene was used in this study to demonstrate the method's adherence to the validation requirements.

Table IV. Materials: Method application

Polymer	Supplier	Lot #	Avg. Particle	Mw (Da)	Wh (Da)	PDI
PBMA	Polysciences	2	404 μm	230,000	125,000	1.84
PBMA	Polysciences	3	1241 μm	319,000	318,000	1.00
PEVA	Aldrich	1	322 μm	76,600	32,800	2.34
PEVA	Dupont	3	3 × 4 mm	81,400	20,800	3.91

Method Validation

Linearity

Because the method must demonstrate linearity in order to perform with reasonable accuracy, the first method validation requirement is fulfilled. If deviations from linearity are observed, experimental conditions, such as concentration range, should be adjusted. A series of density-to-concentration (based on initial weight) standard curves were obtained for PBMA or PEVA in THF or toluene at 30°C. As mentioned previously, 30°C was evaluated as an example for the purposes of this study, but the method can be applied to any temperature. The concentrations and average of triplicate density measurements from the materials listed in Table I in THF or toluene were combined to generate each curve. As displayed in each of Figure 1, linearity between concentration and density were observed. The linear equations were used to calculate the concentration of polymer in solution.

Accuracy

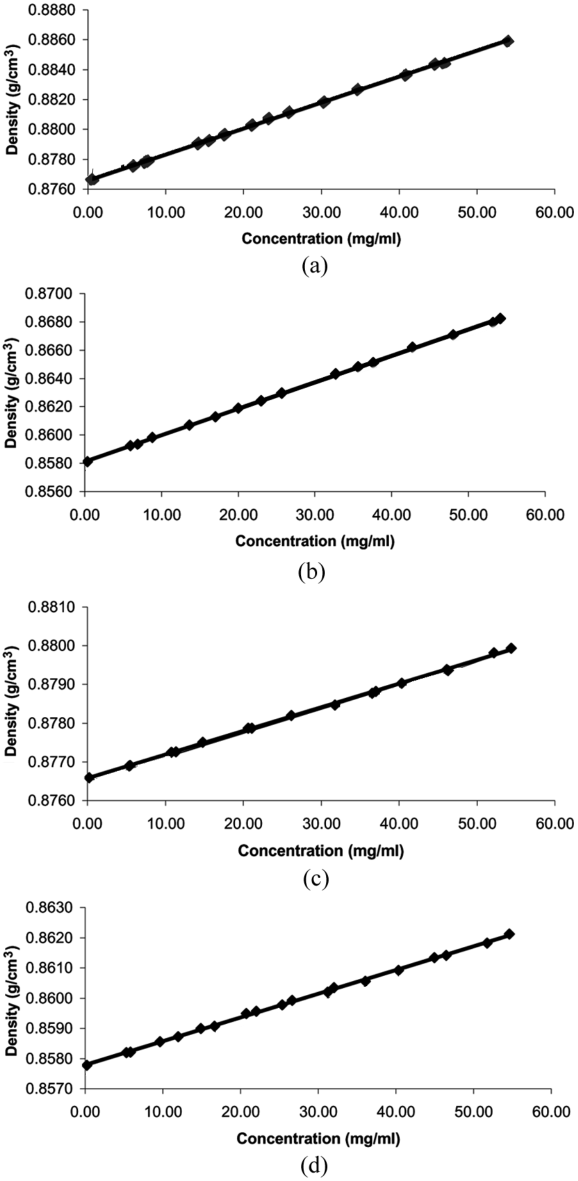
Method accuracy was confirmed in two ways. First, the accuracy of the standard curves was determined by comparing the measured concentration values to the concentrations based on initial weight. The standard curve accuracy considers the size of error included in method results. Second, the accuracy was demonstrated by comparing the measured concentration to a commercial polymer's accepted reported value.

Standard Curve Accuracy Error

The percent accuracy error for each standard curve (Figure 1) was determined by comparing the initial concentration based on weight to the measured concentration calculated from the corresponding linear equation for density. Solution densities of the materials in Table I in THF or toluene were measured, and the accuracy errors for each curve were averaged across the lots for each polymer. The average standard curve accuracy errors are shown in Table V.

Comparison to Accepted Value

An application of the method is the ability to determine the solubility of polymer in a particular solvent. The accuracy of the method as it applies to polymer solubility can be confirmed by demonstrating the agreement between the measured concentrations and an accepted reported value for solubility of a polymer in THF or toluene. The polymer evaluated is a low molecular weight resin, styrene maleimide. According to the product bulletin from the manufacturer, its solubility in THF at 23°C is



(a)

(b)

(c)

(d)

Figure 1. Linear regression curves at 30°C for PBMA in THF (a). The linear fit can be expressed as density $= 2 \times 10^{-04} *$ concentration $+ 0.8765$. The linear fit for PBMA in toluene; (b) can be expressed as density $= 2 \times 10^{-04} *$ concentration $+ 0.8576$; PEVA in THF; (c) is density $= 6 \times 10^{-05} *$ concentration $+ 0.8765$ and the linear fit for PEVA in toluene; (d) can be expressed as density $= 8 \times 10^{-05} *$ concentration $+ 0.8575$. The regression coefficient for each linear regression curve ranged from 0.9992 to 0.9997.

Table V. Accuracy errors of measured standard curves compared to initial concentrations based on weight

Standard curve	Avg. absolute % error
PBMA in THF, 30°C	+/−13.48
PBMA in toluene, 30°C	+/−7.016
PEVA in THF, 30°C	+/−2.084
PEVA in toluene, 30°C	+/−2.798

>40 g/100 mL (400 mg/mL). For this purpose, one standard curve of resin solution concentration to density was created at 23°C. As shown in Figure 2, the linearity and correlation parallel those in the method for PEVA and PBMA.

Solutions of SMA® 4000I in THF of 360, 400, and 450 mg/mL were prepared, representing the concentrations bracketing the reported value. The solutions were stirred at 23°C for 24 h. After filtration and dilution, average density values were obtained. The calculated concentrations for the three solutions in THF were within an average of 11% of the initial concentrations by weight. Because the resin was visually dissolved in all three solutions, the maximum solubility is greater than 400 mg/mL, as the manufacturer reports. This confirms that the density method performs with reasonable accuracy as compared to a reported value.

Repeatability

Method validation in relation to repeatability is the precision of measurements obtained under the same operating conditions. Five individual

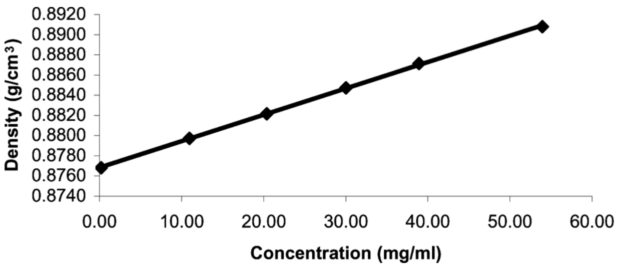


Figure 2. Linear regression curve for commercial resin in THF at 23°C to demonstrate method accuracy. The solubility concentration was calculated from linear equation density $= 3 \times 10^{-04} * \text{concentration} + 0.8766$. The regression coefficient was 0.9996.

solutions of the same lot of PEVA or PBMA in THF or toluene at low and high concentration range were measured, and the concentrations were calculated from the corresponding linear equations. The relative standard deviation for each polymer in each solvent at low and high concentrations was determined. The results in Table VI show an average %RSD (relative standard deviation) less than 0.3%.

Table VI. Multiple sampling of a single solution to demonstrate method precision

Sample description	Density (g/cm^3)	Measured conc. (mg/mL)	Sample RSD (%)
PEVA in THF	0.8797	52.93	
PEVA in THF	0.8797	52.77	
PEVA in THF	0.8797	52.99	
PEVA in THF	0.8797	52.76	
PEVA in THF	0.8797	52.76	0.2079
PEVA in THF	0.8771	10.38	
PEVA in THF	0.8771	10.37	
PEVA in THF	0.8771	10.39	
PEVA in THF	0.8771	10.39	
PEVA in THF	0.8771	10.37	0.0963
PBMA in THF	0.8854	44.38	
PBMA in THF	0.8854	44.35	
PBMA in THF	0.8854	44.44	
PBMA in THF	0.8854	44.37	
PBMA in THF	0.8854	44.35	0.0834
PBMA in THF	0.8783	9.220	
PBMA in THF	0.8784	9.260	
PBMA in THF	0.8783	9.200	
PBMA in THF	0.8783	9.230	
PBMA in THF	0.8783	9.230	0.2349
PEVA in toluene	0.8617	52.17	
PEVA in toluene	0.8617	52.04	
PEVA in toluene	0.8617	52.08	
PEVA in toluene	0.8617	52.18	
PEVA in toluene	0.8617	52.05	0.1277
PEVA in toluene	0.8583	9.758	
PEVA in toluene	0.8583	9.771	
PEVA in toluene	0.8583	9.792	
PEVA in toluene	0.8583	9.783	
PEVA in toluene	0.8583	9.796	0.1596
PBMA in toluene	0.8669	46.49	
PBMA in toluene	0.8669	46.46	

(*Continued*)

Table VI. Continued

Sample description	Density (g/cm^3)	Measured conc. (mg/mL)	Sample RSD (%)
PBMA in toluene	0.8669	46.54	
PBMA in toluene	0.8669	46.59	
PBMA in toluene	0.8669	46.34	0.2033
PBMA in toluene	0.8595	9.638	
PBMA in toluene	0.8595	9.683	
PBMA in toluene	0.8595	9.662	
PBMA in toluene	0.8595	9.668	
PBMA in toluene	0.8595	9.663	0.1677

Range

The method requires certain experimental conditions that allow non-Newtonian polymers to assume Newtonian behavior. Therefore, for this work, the concentration range is between 0.5000 and 60.00 mg/mL. Solutions above 60.00 mg/mL gave RSDs greater than 1% and deviated from linearity. This concentration range represents the experimental conditions at which non-Newtonian polymers, such as PEVA and PBMA, will not be affected by molecular weight. Polymer solutions outside the range must be diluted in order to maintain the range of the method.

Limits of Quantitation

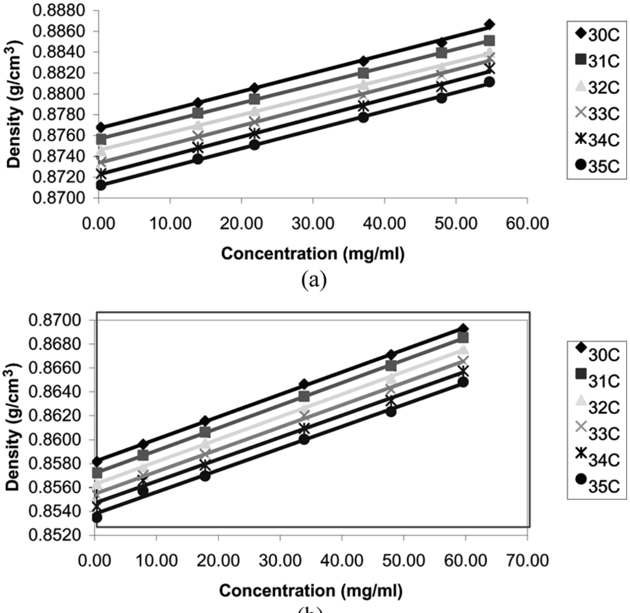
The minimum quantitation limit for PEVA is 1.667 mg/mL and for PBMA 0.5000 mg/mL. These values were obtained from the corresponding linear equations in which the density is 0.0001 (the minimum reportable density value[3]) greater than the solvent blank. The polymer must be soluble enough in a particular solvent so as to obtain a minimum of five concentrations in order for a density standard curve to be constructed. The maximum limit for this method is high concentration in which viscosity causes a polymer-solvent gel. This prevents accurate dilution and density measurements.

Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small variation in method parameters. The data presented in Table VII shows robustness of the method in its ability to obtain the same concentration after 24 h at any temperature in spite of

Table VII. Method robustness demonstrated across temperatures and materials

Sample	Temp (℃)	Density, (g/cm^3)	Measured conc. (mg/mL)
PBMA in THF			
1	30	0.8813	23.94
	31	0.8801	23.06
	32	0.8790	23.14
	33	0.8780	24.20
	34	0.8769	24.22
	35	0.8758	24.18
2	30	0.8813	23.88
	31	0.8802	23.41
	32	0.8791	23.45
	33	0.8780	23.97
	34	0.8769	23.99
	35	0.8758	24.00
3	30	0.8813	23.77
	31	0.8802	23.31
	32	0.8791	23.32
	33	0.8781	24.34
	34	0.8769	23.83
	35	0.8759	24.28
PBMA in toluene			
1	30	0.8628	25.76
	31	0.8620	27.07
	32	0.8610	27.02
	33	0.8600	26.06
	34	0.8590	26.13
	35	0.8582	26.47
2	30	0.8628	25.96
	31	0.8619	26.32
	32	0.8609	26.67
	33	0.8600	26.01
	34	0.8591	26.36
	35	0.8581	26.23
3	30	0.8628	25.97
	31	0.8619	26.34
	32	0.8610	27.03
	33	0.8600	26.05
	34	0.8591	26.05
	35	0.8581	26.24



(a)

(b)

Figure 3. Linear regression curve for PBMA in THF (a) or toulene; (b) at 30–35°C. The ability to determine concentration at any temperature demonstrates method robustness. The linear curves can be expressed as follows: THF: 30°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8765$; 31°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8755$; 32°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8744$; 33°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8732$; 34°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8721$; 35°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8710$. toluene: 30°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8576$; 31°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8566$; 32°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8557$; 33°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8548$; 34°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8541$; 35°C density $= 2 \times 10^{-04} *$ concentration $+ 0.8532$.

variable molecular weight and polydispersity indices. However, as shown in Figure 3, because temperature is critical to density, the linear equations change at each temperature. Therefore, method robustness for temperature is considered limited because individual standard curves must be created in order to calculate accurate concentrations.

Ruggedness

The ruggedness (reproducibility) of an analytical method is the degree of reproducibility of test results obtained under normal test conditions. The data in Table VIII demonstrate reproducible concentrations

Table VIII. Ruggedness (reproducibility) demonstrated across lots from different suppliers

Sample	Average density, 30°C (g/cm^3)	Measured conc. (mg/mL)
PEVA in THF		
Aldrich	0.8781	27.31
Dupont	0.8781	27.48
Arkema	0.8781	27.37
	% RSD	0.3210
PEVA in toluene		
Aldrich	0.8597	27.04
Dupont	0.8597	26.90
Arkema	0.8596	26.77
	% RSD	0.5035
PBMA in THF		
Polysciences #1	0.8813	23.94
Polysciences #2	0.8813	23.88
Polysciences #3	0.8813	23.77
	% RSD	0.3696
PBMA in toluene		
Polysciences #1	0.8628	25.75
Polysciences #2	0.8628	25.96
Polysciences #3	0.8628	25.97
	% RSD	0.4763

Table IX. Method application: PBMA in THF at 30°C kinetic dissolution

Time	Measured conc. (mg/mL)	Measured conc. (mg/mL)
Polysciences Lot #2		
5 min	3.170	26.55
15 min	3.157	37.05
30 min	3.160	42.03
1 hr	3.168	41.74
2 hr	3.155	42.32
24 hr	3.200	47.57
48 hr	3.182	46.64
Polysciences Lot #3		
5 min	2.943	41.01
15 min	2.942	41.53
30 min	2.960	42.18
1 hr	2.977	43.61
2 hr	2.935	44.55
24 hr	2.990	47.24
48 hr	3.018	47.52

Table X. Method application: PEVA in THF at 30°C kinetic dissolution

Time	Measured conc. (mg/mL)	Measured conc. (mg/mL)
Dupont Lot #3		
5 min	0.4222	4.394
15 min	0.6222	6.722
30 min	1.783	7.600
1 hr	2.667	19.49
2 hr	3.100	34.48
24 hr	3.250	47.96
48 hr	3.456	47.94
Aldrich Lot #1		
5 min	2.406	18.47
15 min	3.550	26.10
30 min	3.544	29.67
1 hr	3.550	35.83
2 hr	3.528	43.06
24 hr	3.600	49.23
48 hr	3.550	49.77

measured with different lots of PEVA or PBMA at 30°C after 24 h dissolution.

Method Application: Kinetic Dissolution

A practical application of the method is the ability to monitor the dissolution of polymer into solution. PBMA and PEVA in THF (high and low concentrations in the method range) were allowed to dissolve at 30°C, and the densities were measured at several time points up to 48 h. (See Tables IX and X.) The concentrations were calculated from the appropriate 30°C linear equation (Figure 1). The polymer was considered in solution when the concentration remained constant. The materials used for method application are shown in Table IV. The particle size of each sample is shown because of its influence on kinetic dissolution.

CONCLUSIONS

In contrast to small molecules in solution, there is limited information for measuring polymers in solution and, more specifically, kinetic dissolution. Importantly, the method described herein is robust for molecular weight variability under conditions noted. As described, the method meets analytical test method specifications when evaluating PEVA and PBMA in THF and toluene. The method's simplicity and reliability allow it to be a widely accepted practical way to analyze polymer concentration in solution.

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