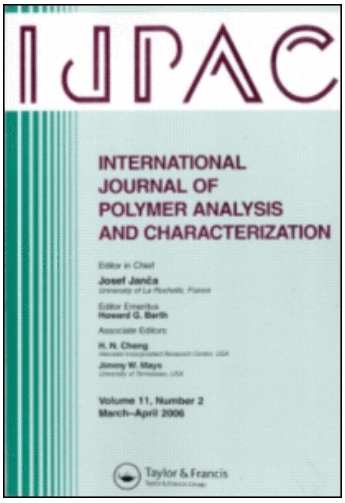

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Development and Validation of a Fast Size Exclusion Chromatographic Method for At-Line Determination of the Conversion of a Polymerization Reaction

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A fast, convenient and accurate method for the determination of conversion of styrene polymerization reactions was developed and validated. Polymer samples were diluted and analyzed with size exclusion chromatography (SEC). Calibration experiments revealed that there is an excellent correlation between the conversion and the observed fractional peak area of the polymer in the chromatogram. Calibration was performed using orthogonal polynomial regression. Validation experiments showed that the predicted conversion is not sensitive to the molar mass distribution of the investigated polystyrene. Furthermore, the stability of the chromatographic system was thoroughly tested. The limit of quantification of the proposed method is approximately 0.008. The precision at higher conversion (∼0.30) is better than 0.003. A comparison of the SEC method with conventional gravimetry showed that this SEC method is faster, less laborious and more accurate. The total analysis time of this SEC method is about 20 min. For the gravimetric method this time is about 32 h.

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Determination of monomer conversion is an important aspect of every polymerization process or experiment. In most kinetic studies either gravimetry or gas chromatography (GC) has been used as a tool to determine monomer conversion. The latter is applied frequently in case of copolymerization, since it has the ability to identify different monomers simultaneously. Gravimetry has been used extensively for studying free-radical (co)polymerization[1]. It was applied to study polymerization in bulk[2], solution[3] and suspension[3]. Gravimetry has been applied in spatially intermittent polymerization (pulsed laser polymerization), which is generally accepted as a reliable method to estimate free-radical propagation rate constants[4].

This work involves the development of a fast and accurate method for the determination of monomer conversion in bulk solutions. Size exclusion chromatography (SEC) is a standard method for the determination of the molar mass distribution (MMD) of polymers. In our case, SEC was applied only for the separation and quantification of monomer and polymer. Conventional methods observe either the polymer or the monomer. Gravimetry is based on estimating the amount of polymer, while with GC the amount of monomer is estimated. Both polymer and monomer are observed in the determination of conversion with SEC. This offers the advantage that the result is not sensitive to the injection volume and, hence, the method is easier to perform and more robust than either gravimetry or GC. This article focuses on the development and validation of the SEC method for conversion measurement. The performance of the proposed SEC method is compared to that of conventional gravimetry.

SEC METHOD

Theory

In general, for a concentration-sensitive detector with a linear response, the peak area A_j[μ Vs] of a component is proportional to the concentration c_j[mg/mL] and the injected volume V_{inj} [mL] according to

$$A_j = c_j S_i V_{inj} \tag{1}$$

where S_j is the sensitivity for component j [μ Vs/mg]. The composition of polymer-monomer mixtures in a bulk system is usually expressed by theconversion (or mass fraction of polymer). This true conversion of the

mixture will be referred to as x ($0 < x < 1$). In order to make the SEC method independent of the density of the investigated polymer-monomer mixture, it is useful to consider the fractional area y of the polymer according to

$$y = \frac{A_p}{A_p + A_m} \tag{2}$$

where A_p is the peak area of the polymer [μ Vs] and A_m is the peak area of the monomer [μ Vs]. Equation (2) is justified in the Appendix. Using equation (1) and the definition of x, the next expression for the fractional area y is derived

$$y = \frac{x}{x + \beta(1 - x)} \tag{3}$$

In this equation β is the relative response factor, which is defined as

$$\beta = \frac{S_m}{S_p} \tag{4}$$

equation (4), S_m and S_p represent the sensitivity of the detector for monomer and polymer. Equation (3) is nonlinear in the parameter β, but this equation may be approximated by a polynomial, using a Taylor series expansion around $x = 0$, when $\beta > 1/2$. This is demonstrated in the appendix.

Basing the calibration model on linear polynomialregression[5] instead of using equation (3) will yield normally distributed calibration parameters. This will allow a straightforward determination of the confidence intervals for the calibration parameters.

Method Development

A three-step method for the determination of monomer conversion with SEC was developed (Figure 1). The first step is to take a representative sample (fixed volume) and to dilute it with tetrahydrofuran. After dilution, the conversion is denoted as x_{dil}. The second step is a triplicate chromatographic analysis of the diluted samples. The observed polystyrene and styrene chromatographic peaks are integrated and the fractional polystyrene area y is calculated using equation (2). The averaged fractional area m_y of the sample is calculated. The final step involves estimation of conversion ($\hat{x}$) using the calibration model.

The calibration procedure is based on prepared samples having known conversions. After triplicate chromatographic analysis of all calibration samples, the mean fractional areas m_y are calculated using equation (2). Finally, the polynomial calibration model $y = p(x)$, which relates the observed fractional area y to the conversion x, is estimated by regression.

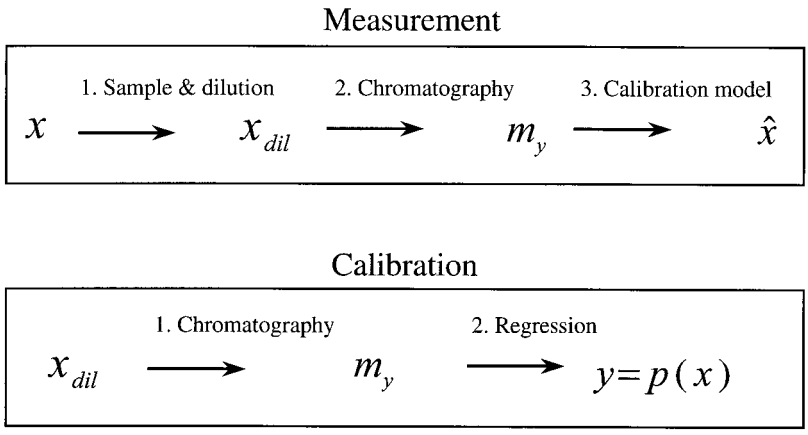

FIGURE 1 Overview of SEC method, where x is the true conversion of sample, x_{dil} is the conversion after dilution, m_y is the averaged fractional peak area, $\hat{x}$ is the estimated conversion and $p(x)$ is the calibration curve.

The prediction error of the obtained calibration curve from M calibration samples is characterized by the root-mean-squared error of calibration *RMSEC*, defined by:

$$\text{RMSEC} = \sqrt{\frac{1}{M-Q}\sum_{i=1}^{M}(\hat{x}_i - x_i)^2} \tag{5}$$

In equation (5), the symbol Q represents the number of parameters of the polynomial calibration model.

Method Validation

The robustness of this SEC method was investigated using internal method validation[6,7]. The most important aspect of this validation is to check for the impact of the molar mass distribution (MMD) on the estimated conversion. If the observed fractional area y depends on the MMD, the applicability of the method is limited severely.

As part of the validation procedure the following basic performance parameters of the SEC method are also determined: precision, bias, accuracy and the limit of quantification. The first three of these parameters may depend on the conversion. Therefore, they are all indexed with x.

The precision of the method, s_x, is related to the estimated standard deviation from N repeated measurements on a sample with known conversion x (type: ISO one-factor intermediate precision condition)

$$s_x = \sqrt{\frac{\sum_{j=1}^{N} \left(\hat{x}_j - m_{\hat{x}}\right)^2}{N-1}} \tag{6}$$

where $\hat{x}_j$ is the estimated conversion of repeated measurement j, and $m_{\hat{x}}$ is the average conversion determined from the N repeated measurements. The bias, D_x, is the difference between the estimated average value $m_{\hat{x}}$ and the true value

$$D_x = m_{\hat{x}} - x \tag{7}$$

This bias D_x is considered not to be relevant if it is much smaller than the precision s_x. The accuracy of the method e_x is related to both the precision s_x and the bias D_x according to

$$e_x^2 = s_x^2 + D_x^2 \tag{8}$$

The limit of quantification x_q of the SEC method follows from the value of the conversion measured for a blank sample x_{bl} and the precision of the method under blank condition s_{bl}:

$$x_q = x_{bl} + k_q * s_{bl} \tag{9}$$

The value of the factor k_q depends on the maximum value that is allowed for the relative standard deviation. Usually a value of $k_q = 10$ is selected (RSD $< 10\%$).

Since the SEC method involves an automated analysis by chromatography, the stability of this device was tested as well. The injection carry-over, the impact of the injection sequence and time-related effects were checked.

Comparison with Gravimetry

The performance of SEC for conversion measurements was also compared to conventional gravimetry by applying both methods to a series of polymer-monomer mixtures with known conversion. The performance was judged by comparing the prediction errors of both methods.

EXPERIMENTAL

Materials and Methods

Styrene 99 + % (Acros Organics) was used to prepare SEC calibration samples. Three grades of polystyrene with different average molar masses were used. Polystyrene A (Acros Organics, $M_w = 1.4 \times 10^5$ g/mol, PDI = 2.6) was used to prepare polymer-monomer mixtures for calibration and validation of the SEC method. Polystyrene B (International broad MMD standard: Shell SRM 706 1, $M_w = 2.6 \times 10^5$ g/mol, PDI = 2.4) was used to prepare samples, which were used to investigate MMD dependence of the SEC method. Polystyrene C (obtained from a free-radical polymerization, $M_w = 33 \times 10^3$ g/mol, PDI = 1.9) was used to prepare polystyrene-styrene mixtures, which were used for comparing SEC with gravimetry. Tetrahydrofuran p.a. (Acros Organics) was filtered over a membrane disc (Sartorius, type 82121-005-04) under vacuum to remove particles and dissolved gases. This filtered tetrahydrofuran was used both as solvent and eluent.

The SEC device consisted of a liquid chromatographic pump (Perkin-Elmer, series 10 liquid chromatograph) with an auto injector (Spark Holland, type SpH 125 fix, 20 μL). The separation column (Polymer Laboratories, 5-μm gel particles), was placed in a column oven (Spark Holland, type SpH 99, 308 K). A differential refractive index detector (Erma-inc., type ERC-7510, 308 K) was connected to the integrator (Hewlett-Packard, type HP 3396 A) for determination of the peak area (total run time: 6 min). Unknown samples (1 mL) were diluted (1:50 v/v) with tetrahydrofuran and analyzed with SEC (triplicate injection). Detector signals below the baseline, which were observed close to the monomer peak, were ignored during peak integration. The total analysis time of the SEC method is about 20 minutes.

Determination of conversion with gravimetry was done by injection of the sample (1 mL), under vigorous magnetic stirring, into 100 g of methanol p.a. (Acros Organics). The obtained polymeric slurry was filtered, washed and dried (32 h at 353 K, ambient pressure) in order to remove monomer and solvent traces. The total analysis time thus is about 32 h.

Method Development

In order to maximize accuracy, the calibration was carried out using 12 calibration mixtures of polystyrene A and styrene ($x = 0.01$, 0.02, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50). Every calibration sample was prepared by mixing x g of polystyrene and $(1 - x)$ g of styrene and subsequently adding tetrahydrofuran, until the total volume was equal to 50.0 mL. The accuracy of the conversion of the prepared samples was

0.0001. Fifteen min of magnetic stirring (500 rpm) yielded clear, homogeneous solutions. For all calibration samples the mean fractional area m_y was determined from triplicate chromatographic analysis.

In order to determine the sensitivity ratio β, a nonlinear regression was performed, using equation (3). The calibration curve, which relates the observed mean fractional area m_y and the conversion x, was created using an orthogonal polynomial fit.

Internal Method Validation

The effect of the MMD on the SEC method was investigated using polystyrene B. The sample and dilution steps were not part of this test. Twelve samples were prepared in the same way as described above and analyzed. In order to determine the basic performance parameters of the SEC method three different stocks were prepared having conversion $x = 0.01$, 0.10 and 0.30. Ten samples from each stock were analyzed. The performance parameters were calculated using these 30 (3×10) observations. Stability of the chromatographic system was checked by testing for the presence of bias from injection carry-over, time and injection disturbance.

Injection carry-over may result in a bias that depends on the conversion of the previously injected sample. In order to investigate (short-term) time-related effects, the stability experiment covered a period of four days. Disturbance of the chromatographic device by repeated injections was investigated by comparing the predicted conversion as a function of the order in a sequence (first injected, second, etc.). In order to reveal the chromatographic bias, based on a limited number of experiments, the following experimental design was chosen. Four different samples having conversion of $x = 0.016$, 0.073, 0.131 and 0.403, were analyzed once a day in a changing order. A Latin Square design was applied to maximize the variation of the injection order[8]. This design is shown in Table I. On the first day the samples were injected in the order A-B-C-D, while on the second day the order was B-D-A-C, etc.

TABLE I Latin Square design in order to test for chromatographic bias. The capital letters represent polystyrene B samples having different conversion—A: $x = 0.016$, B: $x = 0.073$, C: $x = 0.131$, D: $x = 0.403$.

Injection order	Day 1	Day 2	Day 3	Day 4
1	A	B	C	D
2	B	D	A	C
3	C	A	D	B
4	D	C	B	A

The chromatographic bias was tested by making plots of the prediction error versus time, versus the injection order and versus the composition of the previously injected sample. Long-term stability of the method was investigated by comparing calibration data that were separated in time by several months. Several hundreds of samples were analyzed with the SEC method during this time period. The prediction error of new calibration data was determined with a calibration curve that was generated four months earlier.

Comparison with Gravimetry

In order to compare the performance of the proposed SEC method with conventional gravimetry, eight mixtures of polystyrene C and styrene were prepared. Polystyrene C was chosen to have a completely independent set of test results. The investigated polystyrene conversion covered the range $x = 0.016$, 0.026, 0.044, 0.072, 0.130, 0.196, 0.231 and 0.403. The conversion of these eight samples was determined with both gravimetry and the SEC method.

RESULTS AND DISCUSSION

Method Development

A clear baseline separation between the polystyrene and the styrene peak with SEC was observed during all experiments. Two typical recorded chromatograms of calibration samples ($x = 0.027$, 0.401, polystyrene A) are shown in Figure 2.

Nonlinear regression using equation (3) yields the relative response factor (β) of 0.817. The *RMSEC* value for this calibration model was 0.00122. The low value of *RMSEC* indicates that equation (3), which was derived with the assumption of a linear detector response, is valid. The value of β shows that a polynomial approximation (see Appendix) is allowed ($\beta > 1/2$). Orthogonal polynomials were generated up to order four. To determine the optimal order of the calibration polynomial the *t*-values (Table II) of the orthogonal polynomial coefficients were calculated. In Table II the *t*-values for the coefficients c_3 and c_4 are lower than the critical *t*-value, showing that the order of the optimal calibration polynomial is two. The final calibration model is $y(x) = -0.271x^2 + 1.23x - 0.0002$. A randomization test[9] showed that the *RMSEC* value for this calibration model is not different from the *RMSEC* value for the nonlinear calibration model. Figure 3 shows the residuals of both calibration models.

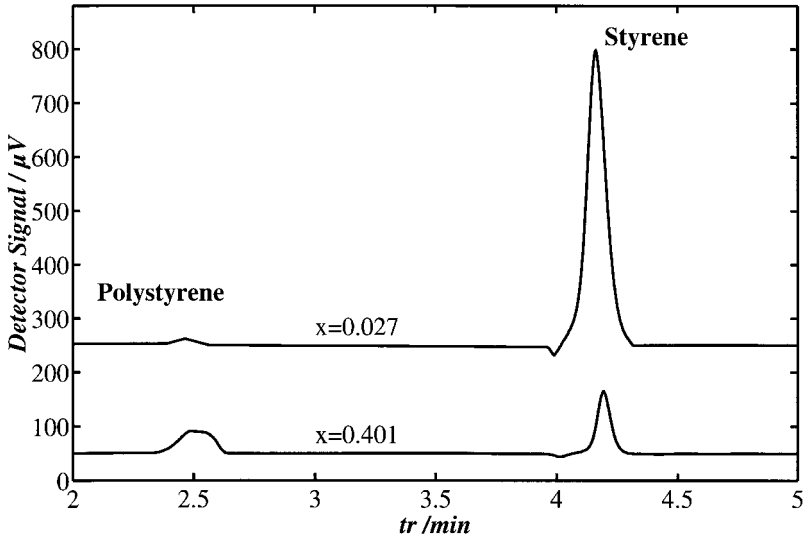

FIGURE 2 Chromatograms of two polystyrene A calibration samples ($x = 0.027$ and $x = 0.401$).

Internal Method Validation

For the series of samples of polystyrene B the prediction errors were calculated. The prediction errors for the conversion estimate are shown in Figure 4. Taking into account the 95% confidence limits, hardly any deviation from zero can be observed. This fact and the expectation that biased results are most likely to occur only for higher M_w values (e.g., due to viscosity effects in the column) indicate that the proposed method

TABLE II t-values of the orthogonal polynomial coefficients ($t_{c0}, t_{c1}, t_{c2}, t_{c3}, t_{c4}$) and the critical t-values (t_{crit}) as a function of the polynomial order (m).

m	t_{c0}	t_{c1}	t_{c2}	t_{c3}	t_{c4}	t_{crit}
0	5					2.20
1	131	90				2.23
2	1089	744	25			2.26
3	1122	766	25	1.80		2.31
4	1041	710	23	1.68	0.373	2.36

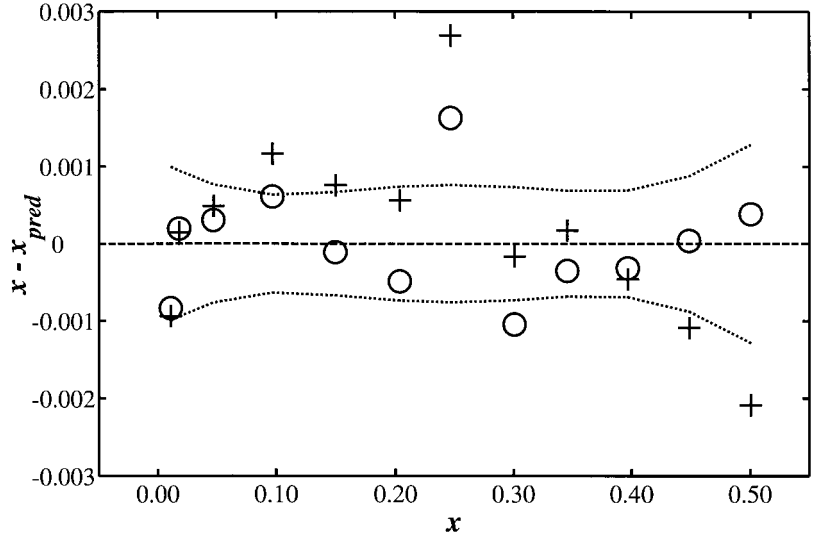

FIGURE 3 Residuals for the linear calibration model (second-order polynomial, circles) and the nonlinear calibration model (equation (3), crosses). The 95% confidence limits are determined using the linear calibration model (dotted lines).

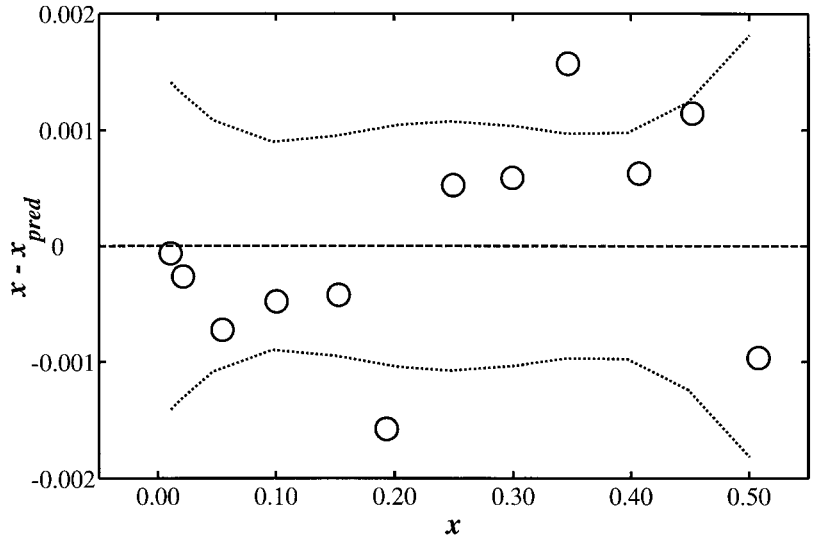

FIGURE 4 The prediction errors for the polystyrene B samples (circles) and the 95% prediction limits (dotted lines).

TABLE III Results of method validation: performance parameters.

	Conversion x		
	0.01	0.10	0.30
Precision s_x	0.00005	0.0007	0.0027
Bias D_x	−0.00004	0.0007	−0.0007
Accuracy e_x	0.0001	0.0010	0.0027

yields a conversion estimate that is insensitive to changes in the MMD of the polymer.

In Table III the values of the basic performance parameters are listed. The data in this table indicate that the precision s_x of the SEC method depends on the conversion level. For low conversion (< 0.10) the best absolute precision obtained is 0.00005. For high conversion (> 0.10) the precision is still acceptable (0.0027). Applying an F-test proved that this difference in precision is significant. Thus the error in the predicted conversion is heteroscedastic.

Some bias seems to be present as well. However, the bias observed at a conversion of 0.01 is smaller than the accuracy at which the calibration samples have been prepared. At the 0.30 conversion level the observed bias is not relevant because the accuracy e_x is dominated by the precision s_x of the SEC method.

The conversion at blank level x_{bl} was determined from the intersection of the second-order calibration curve with the conversion axis ($x_{bl} = 0.0002$). Because the observed accuracy e_x at conversion $x = 0.01$ yields a lower value than the prediction error of the calibrated polynomial ($RMSEC = 0.0008$), it is concluded that the calibration curve is the main source of error at low conversion values. For this reason the accuracy under blank conditions was supposed to be equal to the $RMSEC$ of the calibration curve. Using this value, the limit of quantification was calculated using equation (9) for $k_q = 10$ and the x_q proved to be 0.0082.

The results from the stability tests of the chromatographic system are shown in Figures 5 to 8. In Figure 5 the prediction error is plotted versus time (day). Figure 6 shows the prediction error versus the conversion of the previously injected sample, and Figure 7 shows the prediction error as a function of the order in the injection sequence. Considering the precision of the method, it is concluded that no significant chromatographic bias is present.

Long-term stability was tested by calculating prediction errors of the calibration samples with a calibration model that was created four months earlier. Figure 8 shows no significant deviation. Based on this

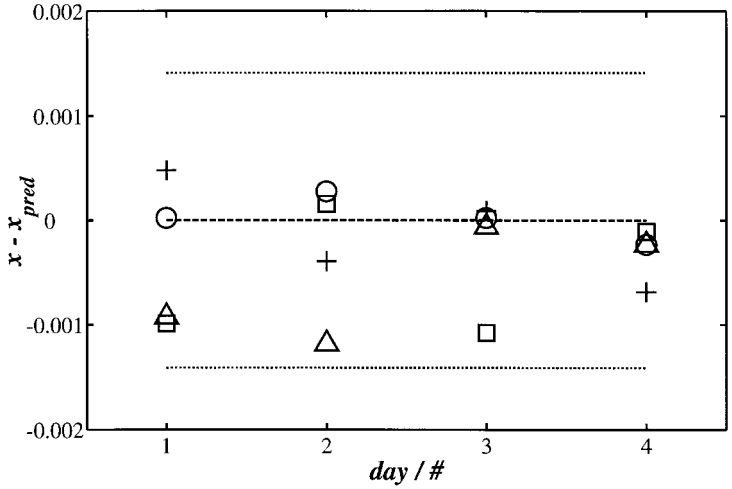

FIGURE 5 Prediction error as a function of time for conversion $x = 0.020$ (circles), $x = 0.070$ (triangles), $x = 0.130$ (squares) and $x = 0.400$ (crosses). The 95% prediction limits (dotted lines) are based on the largest prediction error for the conversion interval in which the conversion of the four samples lies.

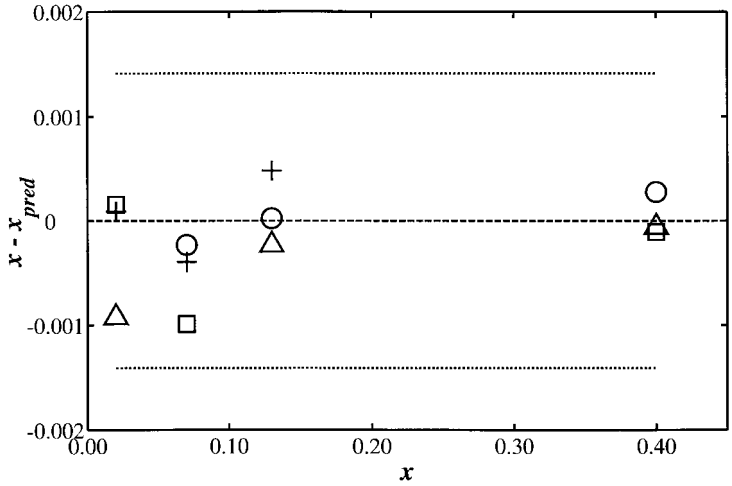

FIGURE 6 Prediction error as a function of the conversion for conversion $x = 0.020$ (circles), $x = 0.070$ (triangles), $x = 0.130$ (squares) and $x = 0.400$ (crosses). See legend of figure 5 for the way the 95% prediction limits (dotted lines) are determined.

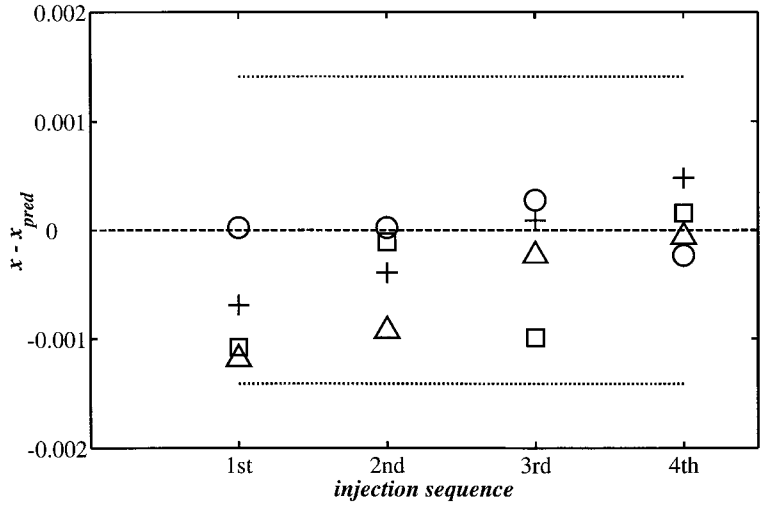

FIGURE 7 Prediction error as a function of the injection order for conversion $x = 0.020$ (circles), $x = 0.070$ (triangles), $x = 0.130$ (squares) and $x = 0.400$ (crosses). See legend of figure 5 for the way the 95% prediction limits (dotted lines) are determined.

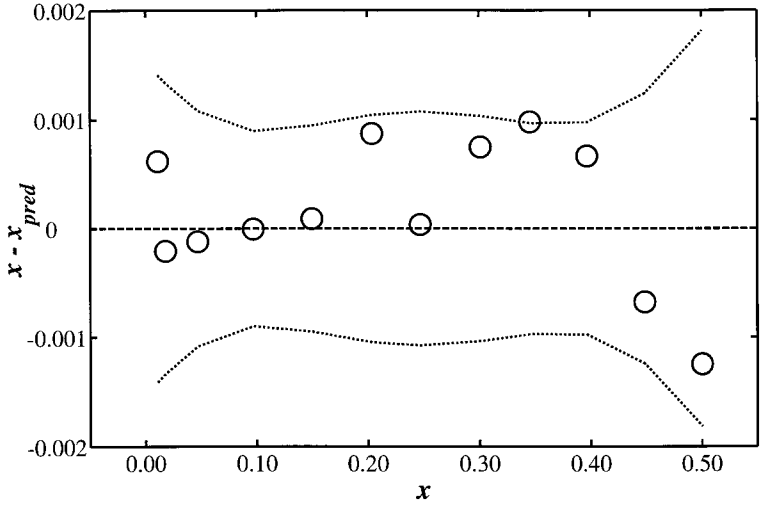

FIGURE 8 Prediction errors of calibration samples (polystyrene A) on a calibration model that was created four months earlier with the 95% prediction limits (dotted lines).

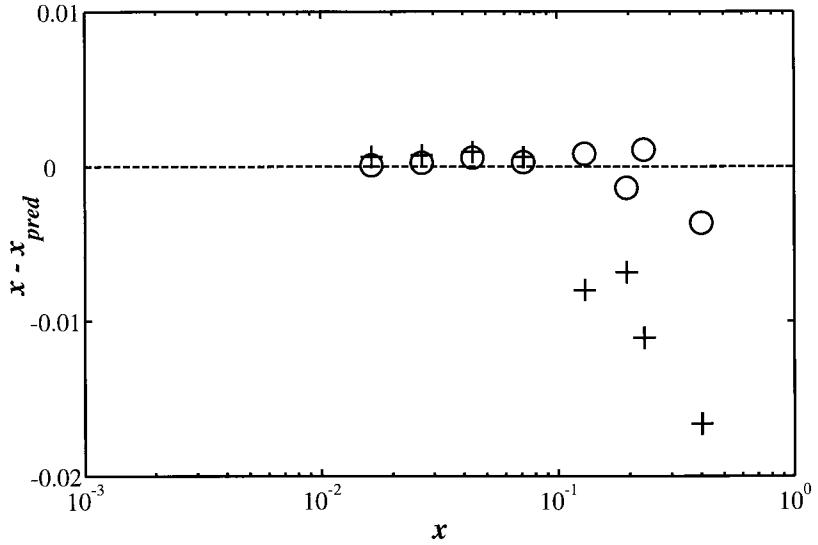

FIGURE 9 Prediction errors for the SEC method (circles) and for gravimetry (crosses).

observation, the chromatographic system was considered to be stable during a long period.

Comparison with Gravimetry

In Figure 9 the prediction errors of polystyrene C samples with SEC and gravimetry are shown. It is clear that in the conversion range from 0.01 to 0.1 the performance of both SEC and gravimetry is acceptable. For conversion above 0.10 a systematic difference between the two methods is visible. While the performance of SEC is still in accordance with the determined basic performance parameters, gravimetry shows a bias that increases with increasing conversion. This bias is probably due to residual monomer that still is present after drying. From these results it is concluded that SEC is a more reliable method than gravimetry.

CONCLUSIONS

A fast SEC method has been developed for the determination of monomer conversion. Based on the assumption of a linear detector response, an expression was derived that relates the fractional peak area y to the conversion x. It is shown that it is sensible to replace the nonlinear

expression relating peak area y to the conversion x by a low-order polynomial. An orthogonal polynomial regression yielded a second-order calibration model.

Internal method validation was performed in order to demonstrate that SEC conversion measurement is independent of the MMD of the sample. The error of the SEC method proved to be heteroscedastic. The best precision is reached in the low conversion range. A low limit of quantification was calculated, i.e., $x_q = 0.0082$. The stability of the chromatographic setup was tested and proved to be stable for the time interval considered (several months).

Finally, the performance of SEC was compared with conventional gravimetry. Although gravimetry performed reasonably in the low conversion range ($x < 0.10$), a severe estimation bias is observed in the high conversion range ($0.10 < x < 0.40$). This bias is probably caused by the presence of residual monomer, indicating that the drying process is not finished after 32 h. Conversion measurement with the SEC method showed no relevant bias over the entire investigated conversion range ($0.0225 < x < 0.40$). Conversion measurement with SEC is less laborious, faster and far more accurate than conventional gravimetry.

APPENDIX

Justification of Equation (2)

The determination of the conversion with the SEC method starts by taking a sample of volume V_{sample} from a polystyrene-styrene mixture. The amount of polystyrene m_P [mg] that is present in the sample follows from

$$m_P = x \cdot \rho(x) \cdot V_{sample} \tag{A.1}$$

where x is the conversion [-], $\rho(x)$ is the bulk density at x [mg/mL] and V_{sample} is the volume of sample [mL]. After dilution with solvent (THF) the concentration of polystyrene in the diluted sample c_P (mg/mL) follows from

$$c_P = x \cdot \rho(x) \cdot \frac{V_{sample}}{V_{dil}} \tag{A.2}$$

where V_{dil} is volume after dilution [mL]. Because of the large difference in density of styrene ($\rho = 0.909$) and polystyrene ($\rho = 1.05$), the conversion dependency of the density $\rho(x)$ cannot be neglected here. Equation (A.2) shows that, since $\rho(x)$ varies nonlinearly with the conversion (x), the polystyrene concentration is a nonlinear function of the conversion. After chromatographic analysis, the area of the chromatographic

peak from polystyrene A_P[μ Vs] is proportional to the concentration of polystyrene in the injected solution (assuming a linear detector response) according to

$$A_P = c_P S_P V_{inj} \tag{A.3}$$

where V_{inj} is the injection volume of chromatography device [mL] and S_P is the sensitivity of detector for polystyrene [μ Vs/mg]. Substitution of the concentration c_P in the previous expression, using equation (A.2), yields

$$A_P = x \cdot \rho(x) \cdot S_P \cdot \frac{V_{inj} \cdot V_{sample}}{V_{dil}} \tag{A.4}$$

Derivation of an expression for the area of the styrene peak A_S [μ Vs] was performed in the same way, and yielded

$$A_S = (1 - x) \cdot \rho(x) \cdot S_s \cdot \frac{V_{inj} \cdot V_{sample}}{V_{dil}} \tag{A.5}$$

where S_S is the sensitivity of detector for styrene [μ Vs/mg]. In order to perform a normal calibration, the density $\rho(x)$ as a function of the conversion x has to be known. However, the variables that are present in both equations (A.4) and (A.5) are identical for the same sample. Therefore, it is useful to define the fractional polystyrene area y as is done in equation (2).

Replacing the Nonlinear Calibration Model by a Linear Calibration Model

The calibration model equation (3), which is nonlinear in the parameter β, links the conversion of the polymer sample to the measured fractional peak area of the polymer. This equation may be approximated by a polynomial by applying Taylor series expansion around $x = 0$. In this way a linear calibration model is constructed. The application of the Taylor series on equation (3) yields the following expression:

$$y = \frac{1}{\beta}x + \frac{(1-\beta)}{\beta^2}x^2 + \frac{(1-\beta)^2}{\beta^3}x^3 + \frac{(1-\beta)^3}{\beta^4}x^4 + \frac{(1-\beta)^4}{\beta^5}x^5 + \cdots \tag{A.6}$$

which may also be expressed as the summation

$$y = \sum_{p=1}^{p=\infty} c_p \cdot x^p \tag{A.7}$$

In this expression the values of the coefficients c_p are defined by

$$\begin{aligned} c_1 &= \frac{1}{\beta} \\ c_{p+1} &= \frac{1-\beta}{\beta} \cdot c_p \quad p > 1 \end{aligned} \tag{A.8}$$

The values of all polynomial coefficients c_p are identical under the following condition:

$$\frac{1-\beta}{\beta} = 1 \tag{A.9}$$

This yields a critical value for the parameter β:

$$\beta_{\text{crit}} = \frac{1}{2} \tag{A.10}$$

If the value of $\beta < \beta_{\text{crit}}$, the absolute value of the polynomial coefficient c_p in equation (A.7) increases with the order p. For $\beta > \beta_{\text{crit}}$ the polynomial coefficients c_p will converge to zero. Therefore, the nonlinear regression using equation (3) in the main text can be avoided by using a polynomial calibration model, if the relative sensitivity β exceeds the critical value β_{crit}.

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