A Short-Cut Data Mining Method for the Mass Spectrometric Characterization of Block Copolymers

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Abstract: A new data mining approach as a short cut method is given for the determination of the copolymer composition from mass spectra. Our method simplifies the copolymer mass spectra by reduction of the number of mass peaks. The proposed procedure, namely the selection of the mass peaks, which is based on the most abundant peak of the mass spectrum, can be performed manually or more efficiently using our recently invented Mass-remainder analysis (MARA). The considerable reduction of the MS spectra also simplifies the calculation of the copolymer quantities for instance the number- and weight-average molecular weights (M_n and M_w, respectively), polydispersity index ($Đ = M_w/M_n$), average molar fraction (c_A) and weight fraction (w_A) of the comonomer A and so on. These copolymer properties are in line with those calculated by a reference method taking into account all the mass peaks of the copolymer distribution. We also suggest a highly efficient method and template for the determination of the composition drift by processing the reduced mass spectra.

Keywords: mass spectrometry; copolymers; data mining; Mass-remainder analysis

1. Introduction

For a thorough understanding of the influence of the copolymer structure on the copolymer properties, accurate and detailed characterization of the copolymer chains at molecular level is crucial. The soft ionization mass spectrometry techniques such as matrix-assisted laser desorption/ionization (MALDI) [1,2] or electrospray ionization (ESI) [3] can give detailed information on the composition of the individual copolymer chains. However, the large number of *m/z* peaks makes the evaluation of the mass spectra of copolymers difficult, time and labor-consuming. Although the application of coupled methods, such as HPLC-MS [4], LAC-MS [5], LACCC-MS [6], SEC-MS and IM-MS [7], decrease the complexity of a spectrum, the number of spectra to be evaluated increases significantly. The manual identification of hundreds or thousands of peaks is not feasible; hence, the compositional assignment of the individual copolymer molecules requires the use of computer software tools. Therefore, several data processing approaches and algorithms have been developed and implemented to determine the elemental composition of the numerous *m/z* peaks of the copolymer mass spectra [8–13]. After all, some issues are not yet completely resolved: (i) many of the methods merely assign the chemical composition to the mass spectral peaks; however, they do not or only partly compute the essential copolymer quantities (e.g., the averaged molecular weights of the repeat units, the composition drift [14] and so forth); (ii) the implementation of the mass spectral processing algorithms requires special skills or software development experts; (iii) the general algorithms are not capable of handling the specific copolymer systems.

Recently, we developed the Mass-remainder analysis (MARA), which is capable of handling the mass spectra of copolymers, even those obtained by low-resolution mass

spectrometer. The capability of our method was proved by analyzing copolymers [15], epoxidized vegetable oils [16], crude oil [17], copolymer blends [18] and even for the analysis of flavonoids [19]. The further development of such a filtering method is of paramount importance for the processing of complex mass spectra.

　　　In this work, we report a new data mining approach, which significantly simplifies the copolymer mass spectra and consequently substantially reduces the required computational resources and speeds up the data-interpretation process. Nevertheless, it allows the accurate, reliable and comprehensive characterization of the copolymer mass spectra, for example, the construction of the compositional drift plots.

　　　We demonstrate our new short cut data mining approach for copolymer analysis through the characterization of poly(ethylene oxide)-*block*-poly(propylene oxide)-*block*-poly(ethylene oxide) (PEO−PPO−PEO) copolymers and the reversed PPO−PEO−PPO structures. These block copolymers have extensive industrial applications as surface active agents in detergency, cosmetics, pharmaceuticals and so on [20–22].

2. Experimental

2.1. Chemicals

　　　The RPE2520, RPE1720-1, PE6100-1, PE6100-2, RPE1720-2, PE6200, RPE1740 and RPE3110 copolymers were gifts of BASF (Ludwigshafen, Germany). RPE1720-1 and PE6100-1 copolymers were acquired in 2006, RPE1720-2 and PE6100-2 were received in 2021. Pure water was produced by a Direct-Q system (Millipore, Molsheim, France). Methyl alcohol was obtained from VWR Chemicals (Leuven, Belgium). Table 1 shows the analyzed copolymers and their EO content.

Table 1. List of the analyzed copolymers. EO content is provided by the vendor.

Name	EO Weight Fraction (m/m %)	Blocks
RPE 2520	20	PPO-PEO-PPO
RPE 1720-1	20	PPO-PEO-PPO
PE 6100-1	10	PEO-PPO-PEO
PE 6100-2	10	PEO-PPO-PEO
RPE 1720-2	20	PPO-PEO-PPO
PE 6200	20	PEO-PPO-PEO
RPE 1740	40	PPO-PEO-PPO
RPE3110	10	PPO-PEO-PPO

2.2. Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry

　　　An Autoflex Speed MALDI-TOF mass spectrometer (Bruker Daltonik, Bremen, Germany) was used for the MS analysis. The reflector mode was used with the voltages ionsource-1, ionsource-2, reflector-1 and reflector-2: 19 kV, 16.65 kV, 21 kV and 9.55 kV, respectively. The spectrometer is equipped with a solid state laser (355 nm). Internal calibration was applied using various polyethylene oxides. The matrix was trans-2-[3-(4-tert-Butylphenyl)-2-methyl-2-propenylidene] malononitrile (DCTB) and sodium trifluoroacetate (NaTFA) was used as an ionization agent. The concentrations of the samples, matrix and ionization agent were 10 mg/mL, 15 mg/mL and 5 mg/mL, respectively (the solvent was methanol). The sample, matrix and ionization agent were mixed in the ratio of 2:5:1, individually.

3. Results and Discussion

　　　Ethylene oxide (EO)—propylene oxide (PO)-based amphiphilic block copolymers—is widely used in the chemical industry. Their diverse applications emphasize the importance of the mass spectrometric characterization of these copolymers. Figure 1a depicts the MALDI-TOF mass spectrum of an amphiphilic PPO–PEO–PPO copolymer with 20 wt% ethylene oxide (EO) content and number-average molecular weight (M_n) of approximately 2700 g/mol (RPE2520). Additional MALDI-TOF MS spectra of triblocks with various

number-average molecular weights and EO weight fractions are shown in Figures S1–S7 in the electronic supplementary material.
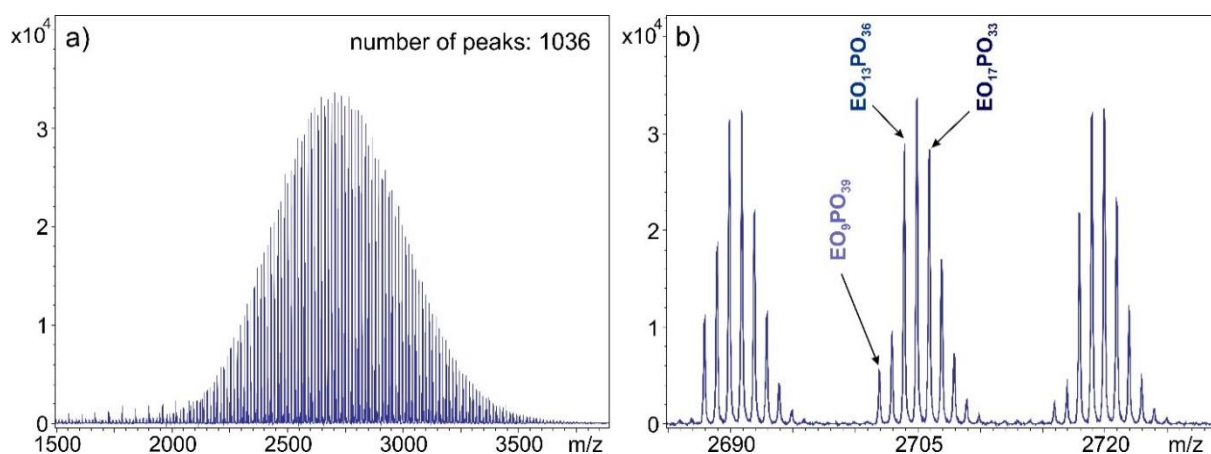
Figure 1. (**a**) MALDI-TOF mass spectrum of PPO–PEO–PPO copolymer with about 20 wt% EO content (RPE2520). (**b**) Zoomed MALDI-TOF mass spectrum showing the peak clusters around the most abundant peak.

The large number of mass peaks in Figure 1a proves the need for special algorithms or software for the evaluation of these complex mass spectra. Moreover, the zoom of each single line in the mass spectra reveals a peak cluster consisting of partially overlapped isotopic peaks of several EO_nPO_m cooligomers (see Figure 1b), which make the interpretation of the spectra even more challenging. It is specific to the EO/PO copolymers that EO_nPO_m overlaps the second isotope of $EO_{n-4}PO_{m+3}$ (see e.g., $EO_{17}PO_{33}$ and $EO_{13}PO_{36}$ in Figure 1b).

The basic idea of our short cut method is the simplification of the copolymer mass spectrum, i.e., the reduction of the number of mass peaks with a minimal loss or distortion of information on the copolymer structure. The steps of our method are as follows:

(1) Selecting and identifying the most intense peak of the mass spectrum. The number of EO and PO units (n_{EO} and n_{PO}, respectively) of the most intense m/z peak are determined by the Mass-remainder analysis (MARA) [15]. The mass remainder value MR_{PO} is calculated using the exact mass of the propylene oxide comonomer ($C_3H_6O = 58.04187$ Da) as the base unit R of the MARA division (Equation (1)):

$$MR_{PO} = m/z \text{ MOD } R \tag{1}$$

where MOD is the modulo operation.

Then, n_{EO} can easily be obtained by the bijective n_{EO}–MR_{PO} mapping and subsequently n_{PO} can be calculated as detailed in our previous report [15]. For the mass spectrum presented in Figure 1 the composition of the most intense peak is $EO_{13}PO_{36}$.

(2) Reduction of the mass spectrum. The simplified mass spectrum contains only the EO_xPO_y peaks corresponding to the condition $x = 13$ or $y = 36$, that are the n_{EO} and n_{PO} values of the most intense peak. This reduction is done by MARA filtering, as follows: Figure 2 shows the MR_{PO} vs. m/z and MR_{EO} vs. m/z plots of the mass spectrum presented in Figure 1a. MR_{EO} can be obtained by a formula analogous to Equation (1), with the base unit $R = C_2H_4O = 44.02622$ Da. Each dot row represents an EO_nPO_x series with constant n values and an EO_yPO_m series with constant m values in Figure 2a,b, respectively. Accordingly, we reduce the mass spectrum keeping only two series: (a) $EO_{13}PO_x$, the peaks having MR_{PO} values corresponding to $n_{EO} = 13$ (see Figure 2a, $MR_{PO} = 32.92 = (13 \times 44.02622 + x \times 58.04187 + 40.99979)$ MOD 58.04187, where $[H_2O + Na]^+ = 40.99979$ Da is the mass of the end group plus the ionizing agent) and (b) EO_yPO_{36}, the peaks having MR_{EO} values corresponding to $n_{PO} = 36$ (see Figure 2b).

The reduced mass spectrum contains only two series, $EO_{13}PO_x$ and EO_yPO_{36}, represented by blue and red colors, respectively, (see Figure 3a.) As the peak numbers indicate (1036 of the original and 42 of the reduced), a remarkable reduction ratio (0.04) can be achieved.
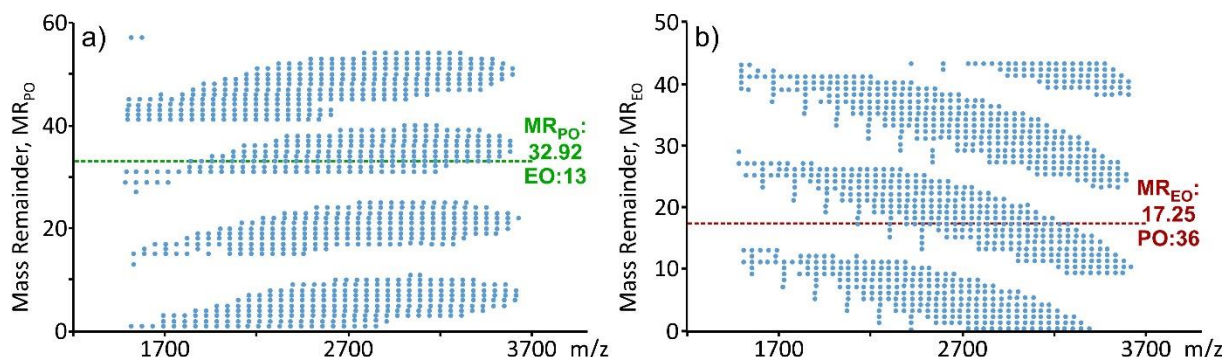
Figure 2. (**a**) The MR_{PO} vs. *m/z* and (**b**) MR_{EO} vs. *m/z* plots of the MALDI-TOF mass spectra of PPO–PEO–PPO copolymer with about 20 wt% EO content (RPE2520). The green and red horizontal lines illustrate the MARA filtering process.
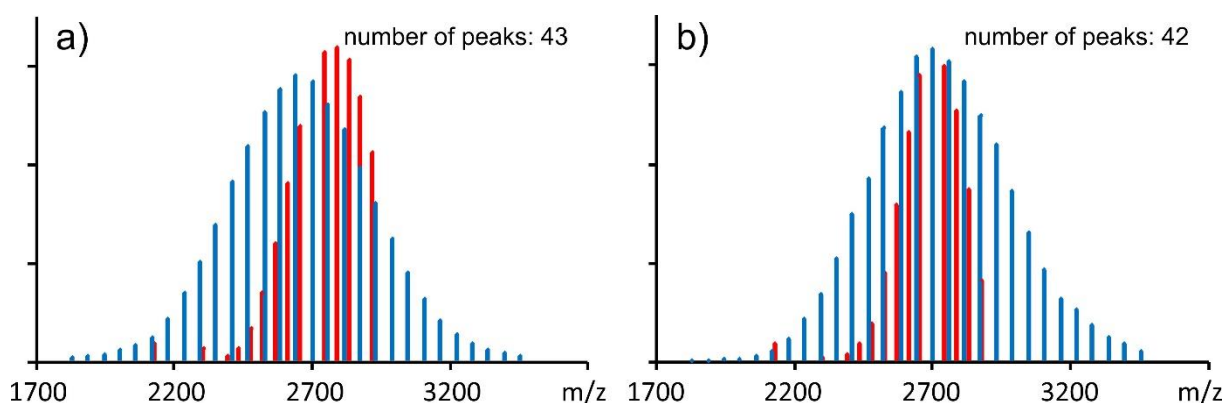
Figure 3. Simplified mass spectrum as the result of our data reduction method of the MALDI-TOF mass spectrum of PPO–PEO–PPO copolymer with about 20 wt% EO content (RPE2520) (**a**) before and (**b**) after intensity correction. $EO_{13}PO_x$ and EO_yPO_{36} represented by blue and red colors, respectively.

(3) Intensity correction. Each peak of the reduced mass spectrum (Figure 3a) is a member of a peak cluster in the raw spectrum, each containing partially overlapped isotopic peaks, as seen in Figure 1b. Therefore, in order to compute valid copolymer quantities, the peak intensities of the reduced mass spectrum must be corrected to reflect the abundance of the polymer chains of various chemical compositions. This correction is an essential part of the MARA algorithm, as detailed in our previous paper [15]. The intensity corrections were made applying polynomial functions calculated from the natural abundance of ^{13}C and ^{18}O isotopes. The parameters of the polynomials are shown in the electronic supplementary material in Tables S1 and S2. Figure 3b shows the reduced mass spectrum after the intensity correction step.

(4) Statistical description of the copolymer composition. The significant reduction of the number of peaks also simplifies the calculation of the usual copolymer quantities such as the number-average and weight-average molecular weights (M_n and M_w), polydispersity index ($Đ = M_w/M_n$), average molar fraction (c_A) and weight fraction (w_A) of repeat unit *A*, number-average number of comonomers *A* and *B* (n_n^A, n_n^B), weight-average number of comonomers *A* and *B* (n_w^A, n_w^B) and the polydispersity index for the repeat units ($Đ_A = n_w^A/n_n^A$, $Đ_B = n_w^B/n_n^B$) [23], as it is exemplified in the electronic supporting material *Short-Cut.xlsx*.

Furthermore, it is obvious that our short cut method is very effective in data reduction, but the essential question remains open as to whether the information on the copolymer structure is valid or distorted. To answer this question, various copolymer mass spectra were evaluated by two different ways: by this novel short cut method and by our recently invented and reported robust algorithm, as a reference method that is implemented into a homemade software [8]. The latter technique was validated by nuclear magnetic resonance (NMR) spectroscopy [8]. Table 2 contains the detailed chemical compositions of 8 industrially important EO/PO copolymers determined by both the short cut and the reference method used for processing their MALDI-TOF spectra.

Table 2. Chemical composition of various triblock copolymers determined by the short cut and the reference method [8].

Name	Process Method	M_n	M_w	$Đ$	c_{EO}	w_{EO}	n_n^{EO}	n_w^{EO}	$Đ_{EO}$	n_n^{PO}	n_w^{PO}	$Đ_{PO}$
RPE2520	reference	2727	2758	1.011	0.256	0.207	12.6	13.2	1.05	36.7	37.2	1.01
	short cut	2678	2694	1.006	0.259	0.210	12.7	13.3	1.04	36.6	37.1	1.01
RPE1720	reference	2102	2142	1.019	0.299	0.241	11.4	12.2	1.06	26.8	27.5	1.03
	short cut	2082	2102	1.010	0.299	0.245	11.7	12.4	1.06	26.7	27.4	1.03
PE6100	reference	1801	1863	1.034	0.072	0.055	2.2	4.7	2.14	28.6	29.5	1.03
	short cut	1623	1675	1.032	0.071	0.056	2.4	4.6	1.93	27.3	28.3	1.04
PE6100	reference	1930	1975	1.023	0.091	0.071	3.0	5.4	1.78	30.2	30.9	1.02
	short cut	1763	1799	1.020	0.091	0.071	3.2	5.4	1.70	29.6	30.6	1.03
RPE1720	reference	2291	2324	1.015	0.300	0.245	12.5	13.3	1.06	29.2	29.7	1.02
	short cut	2259	2274	1.007	0.302	0.248	12.8	13.4	1.05	29.2	29.9	1.02
PE6200	reference	2528	2577	1.019	0.369	0.307	17.4	19.8	1.14	29.7	30.2	1.02
	short cut	2431	2458	1.011	0.369	0.309	17.2	19.3	1.12	29.6	30.0	1.02
RPE1740	reference	2445	2468	1.009	0.510	0.441	24.1	24.5	1.02	23.1	23.6	1.02
	short cut	2389	2401	1.005	0.509	0.441	24.1	24.6	1.02	22.8	23.3	1.02
RPE3110	reference	3440	3471	1.009	0.210	0.168	12.9	13.7	1.06	48.7	49.3	1.01
	short cut	3402	3422	1.006	0.209	0.167	12.8	13.4	1.05	48.5	49.0	1.01

Comparing the corresponding reference and short cut quantities in Table 2, it can be concluded that our short cut method correctly determines the composition of the Pluronic-type triblock copolymers. For example, one of the most important parameters, the average molar fraction of the EO units (c_{EO}, that fundamentally determines the micelle formation of the Pluronics necessary, e.g., for drug delivery systems) shows only 0.49% average relative difference between the Short cut (S) and the reference (R) values (calculated as the average of abs$(S - R)/R \times 100$ for all the eight triblock copolymers). Moreover, the paired two-sample t-test has determined that the mean difference between the corresponding c_{EO} values is zero ($p = 0.65$).

For the comprehensive characterization of the copolymers, it is often necessary to determine—in addition to the distribution parameters summarized in Table 2—the variation of the composition with the polymer chain length, called the composition drift [14]. The number of peaks of the reduced mass spectrum (e.g., 42, see Figure 3) is not enough to construct the composition drift plot, but the original mass spectrum can be modelled ("restored") by constructing the outer product of the intensities of the two series of the reduced spectrum as two vectors. In our example, the $EO_{13}PO_x$ series has 29; the EO_yPO_{36} series has 14 elements, resulting in a 29×14 outer product matrix. The construction of this model mass spectrum and the subsequent composition drift plot calculation can be easily implemented by a common spreadsheet application, as demonstrated in the electronic supporting material *Short-Cut.xlsx*. Figure 4 shows the composition drift plot of

the PPO–PEO–PPO copolymer with about 20 wt% EO content (RPE2520) created by the reference and the short cut method.
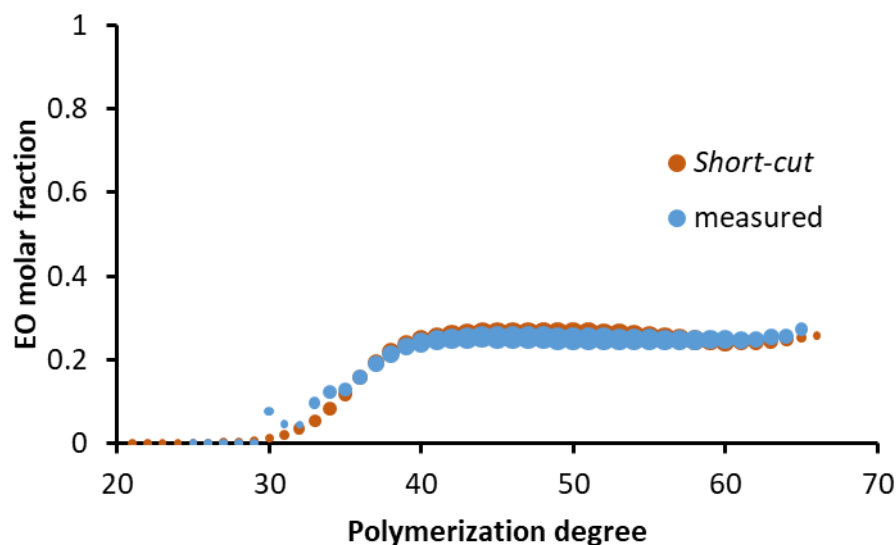
Figure 4. Composition drift plots of the PPO–PEO–PPO copolymer with about 20 wt% EO content (RPE2520) calculated by the short cut (red) and measured by the reference (blue) method. The size of the dots represents the sum of intensity correspond to each polymerization degree in logarithmic scale.

As seen in Figure 4, the curves constructed by the reference and short cut method coincides with each other, especially in the middle polymerization degree (PD) domain. The zero EO molar fraction in the low PD region, revealed by both methods, indicates the presence of PPO homopolymers in the copolymer sample. A small deviance in the range of 30–35 polymerization degrees is the result of higher intensity deviation of small intensity peaks as it turns out from the size of the dots in Figure 4. In this region the intensity of the peaks is close to the detection limit; thus, the acceptance or the decline of even one peak during the peak-picking has a high effect on the resulting EO molar fraction. The good agreement between the composition drift determined by the two methods justifies the capability of our short-cut method for copolymer analysis.

4. Conclusions

A novel, short cut method was proposed for processing of the copolymer mass spectra. The key was to considerably reduce the number of mass peaks in order to facilitate peak assignment and calculation of the characteristic copolymer parameters. Our method was tested by evaluating of the MALDI-TOF MS spectra of various EO/PO copolymers. It was concluded that the short cut method determines very well the compositional properties of the Pluronic-type triblock copolymers. The simplification of the mass spectra keeps only two series (42 peaks in the example of this paper) that can be identified and assigned manually or by our previously reported MARA method. A large benefit of our method is that all the subsequent calculations can be implemented in a common spreadsheet application in a very plain and straightforward way. The construction of the composition drift plot merely requires a sophisticated spreadsheet implementation, but we propose a "easy to follow and apply" template for it in the electronic supplementary material. The proposed short cut method can also be applied for the analysis of other copolymers.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pr10010042/s1, Figure S1. MALDI-TOF mass spectrum of sample RPE-1720-1, Figure S2. MALDI-TOF mass spectrum of sample PE-6100-1, Figure S3. MALDI-TOF mass spectrum of sample PE-6100-2, Figure S4. MALDI-TOF mass spectrum of sample RPE-1720-2, Figure S5. MALDI-TOF mass spectrum of sample PE-6200, Figure S6. MALDI-TOF mass spectrum

of sample RPE-1740, Figure S7. MALDI-TOF mass spectrum of sample RPE-3110, Table S1. The constants of the polynomials originated from the intensities of isotopic peaks as a function of C atom number., Table S2. The constants of polynomials originated from the intensities of isotopic peaks as a function of O atom number.

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