

RESEARCH ARTICLE

Solvent-free sample preparation for matrix-assisted laser desorption/ionization time-of-flight mass spectrometry of polymer blends

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Rationale: Solvent-free sample preparation offers some advantages over solvent-based techniques, such as improved accuracy, reproducibility and sensitivity, for matrix-assisted laser desorption/ionization (MALDI) analysis. However, little or no information is available on the application of solvent-free techniques for the MALDI analysis of polymer blends.

Methods: Solvent-free sample preparation by ball milling was applied with varying sample-to-matrix ratios for MALDI time-of-flight mass spectrometry analysis of various polymers, including polystyrenes, poly(methyl methacrylate)s and poly(ethylene glycol)s. The peak intensity ratios were compared with those obtained after using the conventional dried droplet sample preparation method. In addition, solvent-assisted milling was also applied to improve sample homogeneities.

Results: Depending on the sample preparation method used, different peak intensity ratios were found, showing varying degrees of suppression of the signal intensities of higher mass polymers. Ball milling for up to 30 min was required to achieve constant intensity ratios indicating homogeneous mixtures. The use of wet-assisted grinding to improve the homogeneity of the blends was found to be disadvantageous as it caused partial degradation and mass-dependent segregation of the polymers in the vials.

Conclusions: The results clearly show that solvent-free sample preparation must be carefully considered when applied to synthetic polymer blends, as it may cause additional problems with regard to homogeneity and stability of the blends.

1 | INTRODUCTION

Sample preparation in matrix-assisted laser desorption/ionization (MALDI) mass spectrometry (MS) is a crucial step that can significantly affect the quality and reliability of mass spectral data. Typically, sample preparation for MALDI is based on the use of organic solvents, which can cause several problems such as spot inhomogeneity during solvent evaporation,¹ sample–matrix interference² and solvent compatibility issues.³ In recent years, the solvent-free sample preparation method has become a versatile

technique that avoids most of the problems associated with solvent-based sample preparation methods, and has gained considerable attention for its advantages in improving the accuracy, reproducibility and sensitivity of MALDI analysis.⁴ Originally introduced by Skelton et al⁵ and Przybilla et al⁶ in 2000 for the analysis of insoluble polyamides and giant polyaromatic hydrocarbons, this method has shown additional benefits, such as minimization of segregation and suppression effects, milder MALDI conditions, lower laser power, higher analyte signal resolution and the possibility of using new matrix/polymer combinations, since the compatibility of the solvent

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system is no longer an issue.^{4,7} In addition to its use for poorly soluble or insoluble polymers,^{5,8–12} conventional soluble polymers have also become of interest.^{7,10,13–22}

Initially, the solvent-free technique was based on the grinding of components in a mortar using a pestle. This could be done either completely without solvents or with small volumes of organic solvents, known as wet-grinding²³ or evaporation-grinding method.⁸ However, due to the time-consuming nature of these methods and the risk of cross-contamination from extensive tool cleaning, an alternative approach based on ball-milling was developed.¹⁴ In this method, the components are mixed in a glass or plastic vial equipped with small steel balls using a vortex mixer. This approach was later extended to a multi-sample preparation method that enables the simultaneous preparation of 384 samples using a 384-well disposable MALDI plate.²⁴ Other solvent-free preparation techniques, such as sublimation of matrix or surface-layer techniques, will not be discussed here. In a recent review, a comprehensive summary of available data on the advances in solvent-free sample preparation methods for MALDI-MS of polymers and biomolecules is provided.²⁵

However, solvent-free sample preparation also has some disadvantages. These include problems with matrix overloading and less “softer” ionization.²⁶ This leads to increased formation of metastable ions and reduces the upper mass limit, at least for proteins, to 30–55 kDa.²⁷

Currently, there is little or no information available on the application of solvent-free techniques for the MALDI analysis of polymer blends.

MALDI imaging data of sample spots presented by our group in 2014 indicated a ring effect, when using solvent-based dried-droplet preparation.²⁸ This effect describes a chromatography-like mass segregation within the spot even for polymers with low dispersities ($\bar{D} \sim 1.2$). It was demonstrated that segregation is dependent on the time for solvent evaporation. However, even the use of fast-evaporating solvents like tetrahydrofuran (THF) cannot completely prevent segregation. Therefore, this effect is expected to be more pronounced in polymer blends with higher dispersity values and thus different solubilities. In such cases, the application of solvent-free sample preparation methods seems to be particularly promising. For the purpose of the study reported here, ternary polymer mixtures of polystyrene (PS), poly(methyl methacrylate) (PMMA) and poly(ethylene glycol) (PEG) with a mass range from 1000 to 10 000 g mol⁻¹ were prepared and the relative peak intensities were quantitatively investigated after ball-milling for different times. Particular attention was paid to determining the optimum analyte–matrix ratio and the reproducibility of the measurements. The obtained results were compared with data from the solvent-based dried droplet method.

2 | EXPERIMENTAL

2.1 | Materials

PEG, PMMA and PS were obtained from PSS (Polymer Standards Service GmbH – a part of Agilent, Mainz). Their molecular masses according to manufacturer information are listed in Table 1.

TABLE 1 Molecular masses of investigated polymers

Polymer	1k (g mol ⁻¹)	4k (g mol ⁻¹)	10k (g mol ⁻¹)
PEG	1460	4110	11 400
PS	1620	4700	10 400
PMMA	1960	4890	10 900

PEG, poly(ethylene glycol); PMMA, poly(methyl methacrylate); PS, polystyrene.

Matrix *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene] malononitrile was purchased from Tokyo Chemical Industry Co. Ltd (Tokyo, Japan). Silver trifluoroacetate (AgTFA) and potassium trifluoroacetate (KTFA) were obtained from Sigma-Aldrich (Taufkirchen, Germany). THF (Ultra LC/MS grade) and chloroform (HPLC grade) were purchased from Carl Roth (Karlsruhe, Germany). Methanol (UHPLC/MS grade) was obtained from Th. Geyer GmbH & Co. Kg (Renningen, Germany).

Small steel balls with a diameter of 3 mm were used (IHSD-Klarmann, Bamberg, Germany) together with 4 mL glass vials from neoLab GmbH (Heidelberg, Germany).

2.2 | Instrumentation

All experiments were performed using an Autoflex maX mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 355 nm Nd-YAG laser at a 2000 Hz repetition rate working in linear mode. Typically, 2000 shots recorded at four randomly chosen positions of a spot were accumulated for one spectrum. The reproducibility of the results was checked by measuring multiple sample spots.

Data recording, calibration and evaluation were performed using the instrument software (FlexControl, Bruker Daltonics) and Origin 2021 (OriginLab Corporation, USA).

For the determination of the peak intensity ratios, spectra were recorded at a constant laser power and the intensity of the most intense peak of each peak distribution was taken after baseline subtraction. Repetition measurements were always performed on newly prepared spots.

2.3 | Solvent-free (ball-milling) method

The solvent-free sample preparation was done according to the vortex method described by Hanton and Pareas.¹⁴ Thereby, two steel balls each with a diameter of 3 mm were put in a 4 mL glass vial. Ternary molar polymer mixtures and mixtures containing matrices and salt were prepared separately in different glass vials using a balance. Typically, 40 mg of matrix and 1.0 mg of salt were mixed. Polymer blends were prepared by mixing of molar ratios of three polymers with average molecular masses of 1000, 4000 and 10 000 g mol⁻¹. Three mixtures, each containing one of the three polymers in greater excess (20/20/60, 20/60/20 and 60/20/20), were prepared. These individual mixtures

were intensively mixed for 60 s using a vortex mixer (Vortex-Genie 2, Scientific Industries Inc.). Afterwards, materials from the bottom and the inner wall of the glass vial were combined by gently scratching using a small spatula, and vortexed again for another 60 s. Finally, freshly prepared matrix–salt and polymer mixtures were blended in 10/3, 10/2 and 10/1 (mg/mg) ratios and vortexed for 60 s. These ratios exactly correspond to those amounts used in solvent-based sample preparation methods. For example, the 10/1 ratio can be compared with a standard procedure where typically 50 mL of matrix solution (20 mg mL^{-1}), 5 mL of salt solution (5 mg mL^{-1}) and 20 mL of polymer solution (5 mg mL^{-1}) are combined. A small spatula was used to prepare sample spots by putting a few grains of the mixture on the stainless-steel target. To prove the effectivity of mixing, the whole procedure (re-unification, mixing for 60 s) was repeated.

2.4 | Solvent-based (dried-droplet) method

For comparison, a solvent-based sample preparation was also used. For this, the previously prepared solvent-free sample–matrix–salt mixtures were dissolved in 1 mL of an organic solvent and 1 μL of these solutions was dropped on the stainless steel MALDI target. PMMA and PS were dissolved in THF, while a methanol–chloroform mixture (20/80, v/v) was used for PEG. For PEG and PMMA experiments, KTFA was used as dopant, while the ionization of PS required the addition of AgTFA.

2.5 | Solvent-assisted (wet) milling method

In contrast to the method described by Gies and Nonidez,²³ our approach used wet grinding exclusively to prepare the polymer

blends. This was done by weighing molar ratios of polymer samples into a 0.5 mL Eppendorf vial. To this dry mixture (approximately 50 mg), 300 μL of a dispersant (*n*-hexane or isobutane) and two steel balls (3 mm) were added. The suspension was vortexed for different times. After 1, 3, 8, 15 and 30 min, ca 15–20 μL of the slurry was pipetted into another vial. *n*-Hexane or isobutane was removed overnight at room temperature in a vacuum dryer at 5 mBar. Finally, the dried fine powder was vortexed with the matrix–salt mixture in a 10/1 (w/w) ratio for 1 min. Again, a few grains of the mixture were deposited on the stainless-steel target.

3 | RESULTS AND DISCUSSION

3.1 | Comparison of solvent-based and solvent-free sample preparation

Our study started with a comparison of the two techniques using a 20/20/60 PEG blend. As mentioned in the literature, solvent-based preparation methods may suffer from sample–matrix interferences.² Therefore, the robustness of the solvent-free method was first tested for three different PEG-to-matrix ratios.

Figure 1 shows the MALDI time-of-flight mass spectra of the ternary PEG blend obtained by solvent-free and solvent-based spot preparation. The most obvious feature is that the intensity of the solvent-free MALDI spectra at constant laser power is generally higher (about six times) than that of the solvent-based spectra. Differences in absolute intensities and intensity ratios, as indicated by their relative intensities, of individual PEGs are visible depending on the matrix-to-sample ratio. Higher spectral intensities were observed with increasing amounts of matrix in solvent-free MALDI sample–matrix mixtures. Such effect could not be found in the spectra of

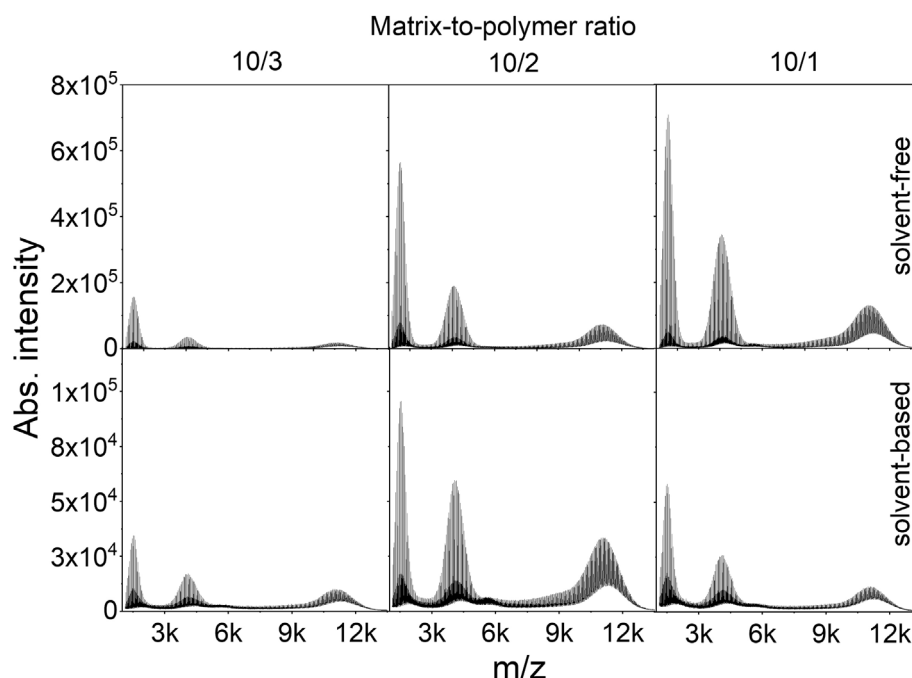


FIGURE 1 Typical MALDI time-of-flight mass spectra of a 20/20/60 PEG (1k/4k/10k) blend with different matrix-to-polymer ratios prepared by solvent-free (top) and solvent-based (bottom) sample preparation.

blends prepared with solvent. In addition, the relative intensity for PEG 1k appeared to be higher in the solvent-free sample mixtures. In contrast, the relative intensities of the higher mass PEGs (4k and 10k) were higher in the solvent-based systems.

For a more systematic study, the experiments were extended to include two additional ternary PEG blends and two other polymer classes.

The intensity ratio of each polymer blend, prepared by either method, was plotted versus the matrix-to-polymer ratio as seen in Figure 2. The following notable aspects were observed from this figure.

Firstly, the peak intensity ratios did never reflect the true molar ratios of the ternary blends, indicating the well-known suppression of higher masses in MALDI-MS. There is always a strong underestimation of higher masses, which is more pronounced in polymer blends prepared without solvent.

Secondly, sample preparation without solvents generally resulted in more reproducible spectra, as indicated by the smaller error bars in Figure 2. The majority of wet blends showed lower reproducibility compared to their dry counterparts. However, when higher amounts

of matrix relative to polymers were used, in many cases solvent-based sample preparation became more reproducible. This phenomenon could indicate segregation of polymers in the sample spot particularly when their amount in the matrix-to-polymer mixture is relatively low. This observation is further supported by the fact that reproducibility improved when the amount of matrix was increased in these polymer systems (10/1 ratio), resulting in lower segregation due to higher viscosity of the solutions. It is also consistent with previous reports that indicate that a higher viscosity of the solution dropped onto the target (in this case, achieved by a higher matrix concentration²⁸ or the use of ionic liquid matrices²⁹) can prevent segregation.

Thirdly, higher matrix concentration often resulted in a decrease of peak intensities (see comments to Figure 1).

Fourthly, the relative intensities obtained after solvent-free preparation *always* differed from those of the corresponding blend prepared under solvent-based conditions. In general, the matrix-to-sample ratio has a much greater effect on the intensity ratio in solvent-prepared blends.

Finally, these results were largely identical regardless of the polymer class (and the associated choice of the cation).

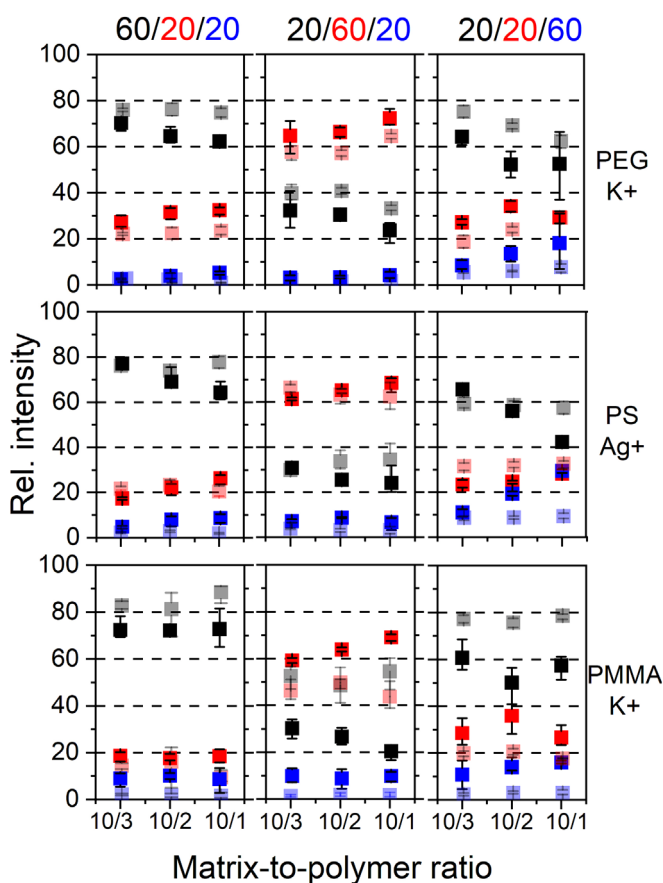


FIGURE 2 Relative peak intensity (at the maximum of the MALDI peak distribution) of three ternary (1k/4k/10k) polymer blends at different matrix-to-polymer ratios prepared using solvent-based (filled squares) and solvent-free (transparent squares) sample preparation: PEG (top), PS (middle) and PMMA (bottom). See also Tables S1–S3. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

3.2 | Influence of milling time

The influence of the time required to obtain reproducible MALDI mass spectra was tested by measuring the 60/20/20 (1k/4k/10k) PMMA blend at different spots after vortexing for 1 to 15 min. Characteristic MALDI mass spectra are shown in Figure 3 (left). Depending on the morphology of these spots, probably determined by different grain size and layer thickness, spectra with different (absolute) spectral intensities were recorded, as shown in the x-axis of Figure 3 (middle). This is probably due to the general procedure, which is based on scraping powder off a spatula onto the steel target, which is often not very reproducible. Nevertheless, the relative intensities of the three polymers in the blend remained constant regardless of the varying absolute spectral intensities. However, the intensity ratio obtained after 15 min of mixing differed from that obtained after 1 min of mixing, indicating a time-dependent vortexing effect. As presented in Figure 3 (right) this effect occurred continuously over the entire timespan. For this experiment, two different handling methods were investigated. In *method 1*, after a certain mixing interval, the blend powder adhering to the inner wall of the glass vial was consequently removed and re-unified with the powder on the bottom of the glass vial before starting the next vortexing interval, whereas in *method 2* no re-mixing occurred. Interestingly, no significant differences were observed. In conclusion, the observed data clearly indicate that even after 15 min the chosen vortex method may not be sufficient to produce homogeneous polymer blends.

Since the maxima of all peak distributions of the blend did not shift over the entire mixing time (see spectra in the left-hand panel of Figure 3) a degradation of the polymers after 15 min of intensive (dry) vortexing can be excluded.

3.3 | Solvent-assisted (wet) grinding

To support homogenization in the glass vials, the solvent-assisted (wet) ball milling method was investigated in a subsequent series of

experiments. In contrast to the solvent-based methods, solvents were used that did not dissolve either the chosen ternary polymer mixture or the matrix-salt mixture. For the PMMA blends, *n*-hexane was used as dispersant. In analogy to the solvent-free method, the suspensions

FIGURE 3 MALDI time-of-flight mass spectra of a 60/20/20 (mol%) blend of (1k/4k/10k) PMMA (left); relative peak intensities at different target (spot) positions showing various absolute intensities (middle); time-dependent change of relative peak intensities for the blend applying two methods of grinding (method 1, no treatment indicated by filled squares; method 2, after removing the powder adhering to the inner glass wall and re-unification with bottom powder indicated by transparent squares) (right). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

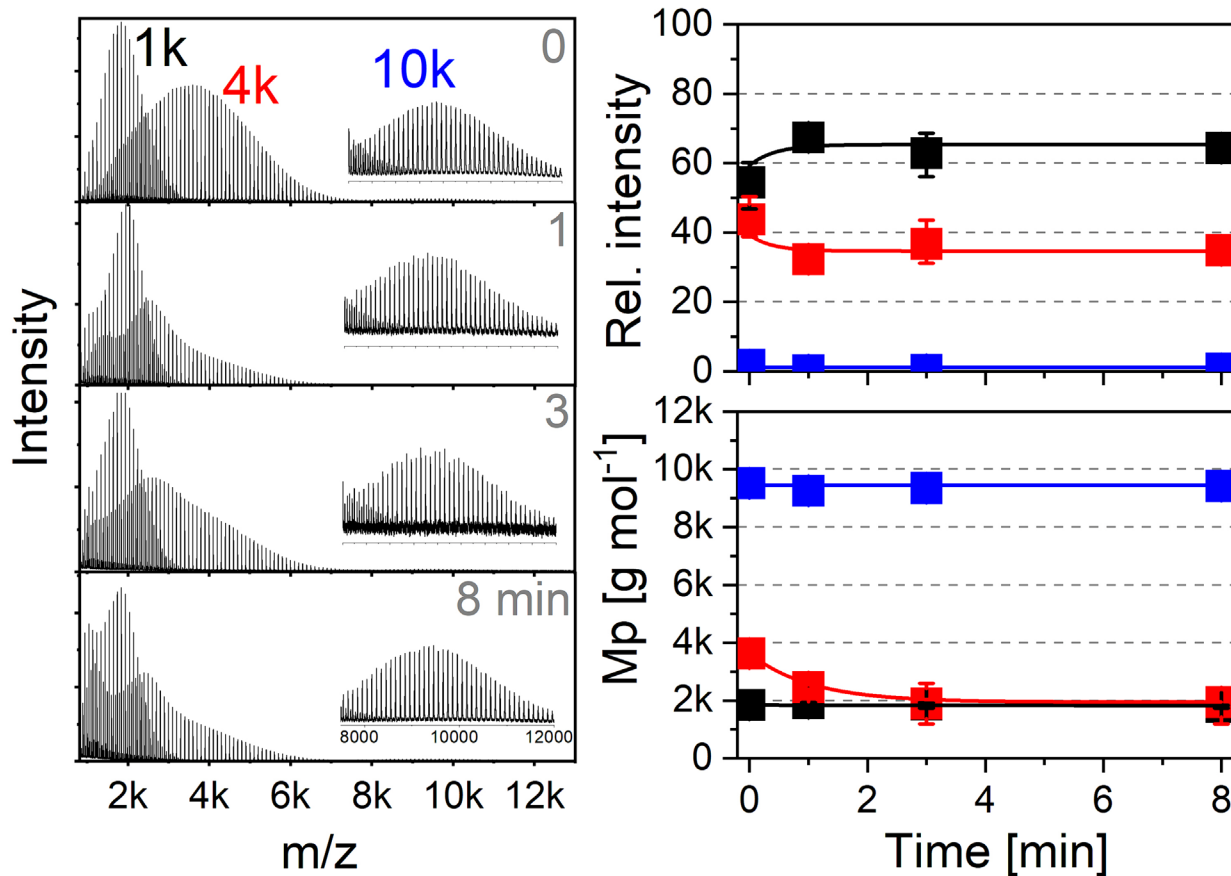
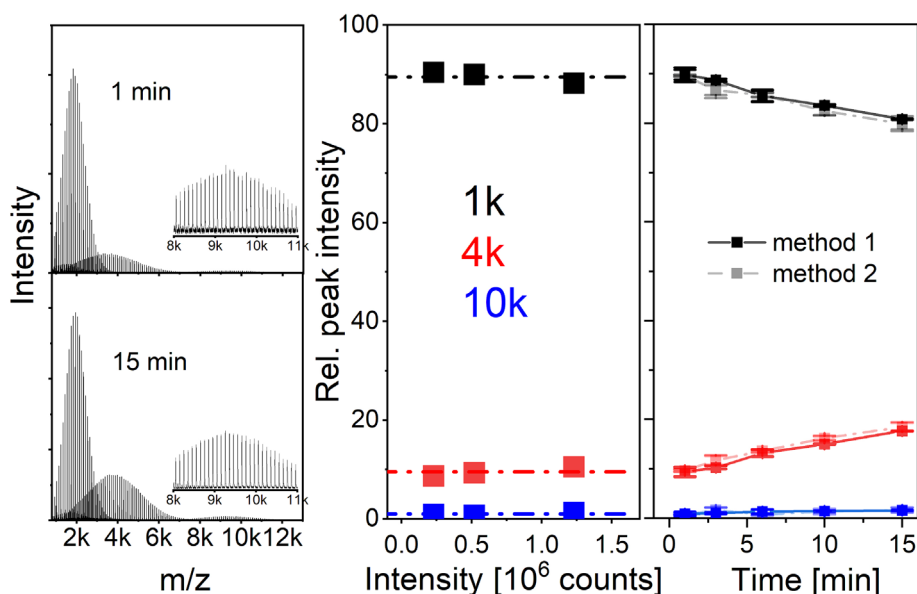


FIGURE 4 Time-dependent wet-grinding of a 20/60/20 PMMA blend: MALDI time-of-flight mass spectra recorded after different grinding times (left), and corresponding course of relative intensities and average mass at maximum of peak distributions (right). Note that PMMA 4k has a different end group combination to enable signal detection in overlapping mass regions. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

were vortexed for various time periods and, after removal of the solvent (see Section 2), mixed with matrix and salt. The results of the time-dependent vortexing of a (20/60/20) PMMA blend using the wet-assisted sample preparation method are shown in Figure 4. The most remarkable result is that PMMA 4k apparently shows typical signs of degradation after just 1 min of vortexing. In addition to a significant decrease in the signal intensity, a shift of the intensity maximum and the formation of a low-molar-mass peak distribution at approximately m/z 1200 were observed.

Surprisingly, both the intensity and the intensity maximum of PMMA 1k and 10k appeared to be completely unaffected by vortexing, although at first glance the signals of PMMA 1k showed increasing intensities in the lower mass region. However, this effect is often observed in MALDI analysis of overlapping polymer peak distributions and can be attributed to various effects, such as the formation of lower mass PMMA 4k degradation products that act as additional matrix and promote energy transfer from the matrix to the PMMA 1k molecules.³⁰ This is also supported by the fact that the intensity course of the peaks of PMMA 1k in the lower mass region corresponds exactly to that of the 4k degradation products.

The only reasonable explanation for the notable degradation of PMMA 4k seems to be in the nature of the end groups of all three polymers. A PMMA 4k with narrower dispersity like the other two PMMAs was not available at the time of the experiment. Therefore, a PMMA 4k with a larger dispersity and a different combination of end groups had to be chosen, which allowed clear differentiation of peaks in overlapping mass regions. In this case, one of the hydrogen end groups was replaced by a *tert*-butyl (C_4H_9 -) end group. Surprisingly, the mechanical stability of this PMMA was significantly lower during the wet grinding process, as shown by the spectra. To investigate further, all three PMMAs were separately ground in *n*-hexane (as used for grinding the blend). The MALDI mass spectra (see Figures S1 and S2 and Figure 5) support the assumption of end-group-specific

degradation. The figures demonstrate that degradation of PMMA 4k can be observed immediately after the beginning of wet-assisted grinding. Both the maximum peak intensities and the molecular mass dispersities decrease, whereas PMMA 1k and PMMA 10k show no signs of degradation in their mass spectra (Figure S2), demonstrating the higher mechanical stability of these PMMA types with hydrogen end groups. A similar degradation effect of PMMA 4k was also observed when using methanol as a more polar solvent, indicating a degradation that is independent of the solvent. Mechanochemical degradation of polymers has long been known. Recent progress in mechanochemical degradation is summarized in a review focusing on its use for polymer recycling.³¹ A possible explanation for the observed degradation effect could be the formation of mechano-radicals by milling.³² The loss of the *tert*-butyl end group of PMMA 4k, which shows a remarkable stability due to a +I effect, could lead to the simultaneous formation of a radical at the end of the polymer chain. This could lead to an accelerated oxidation of the polymer chain.³³ However, this degradation effect was observed only when the wet-assisted mixing method was used. PMMA 4k in solvent-based and solvent-free prepared blends did not show any degradation. Thus, it must be concluded that the dispersant used contributes to polymer degradation.

As reported recently by Belenguer et al, surprising solvent effects in inducing chemical reactions during grinding were observed. Those authors investigated the effects of particle size and solvent environment on the thermodynamic stability of two pairs of polymorphs subjected to ball mill neat grinding and so-called liquid-assisted grinding. Using state-of-the-art computational techniques, they found that the presence of a solvent had a dual effect: stabilizing certain surfaces in the crystallites and providing a medium for dissolution, nucleation and further growth. Similar to the results of those authors for polymorphs, the thermodynamics of polymer degradation may also depend on the crystal size due to the effect of

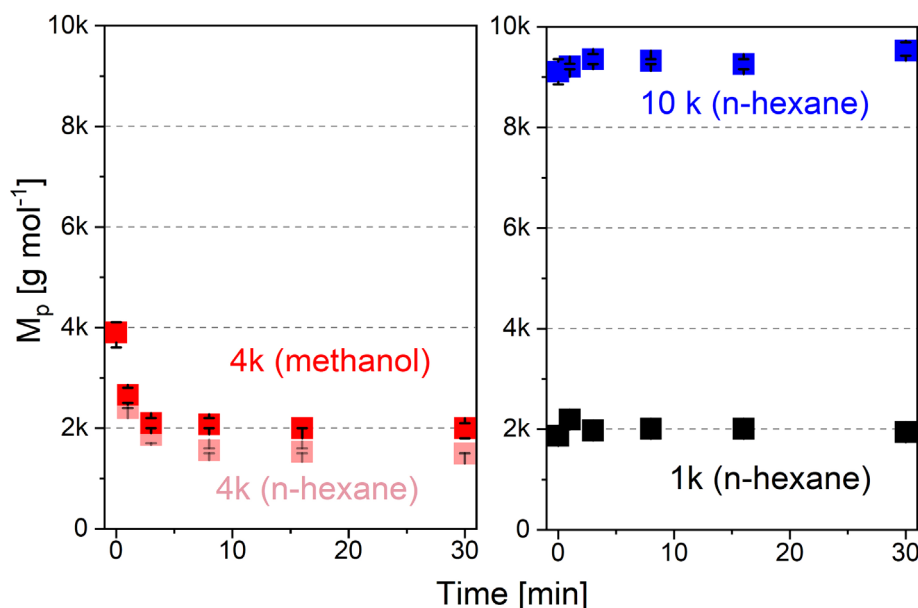


FIGURE 5 Course of maximum peak intensities after time-dependent wet-grinding of PMMA 4k (left) and PMMA 1k and 10k (right). [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 6 Time-dependent wet-grinding of a 20/60/20 PS blend: MALDI time-of-flight mass spectra recorded after different grinding times (left); corresponding course of relative intensities and average masses at maximum of peak distributions (middle); comparison of relative intensities after 30 min from two different positions in the vial (right). [Color figure can be viewed at wileyonlinelibrary.com]

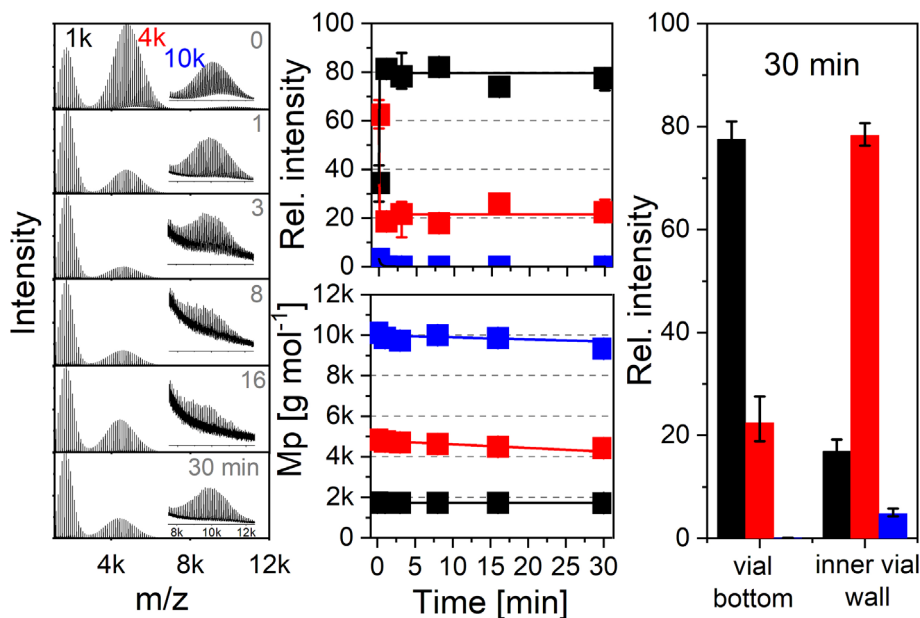
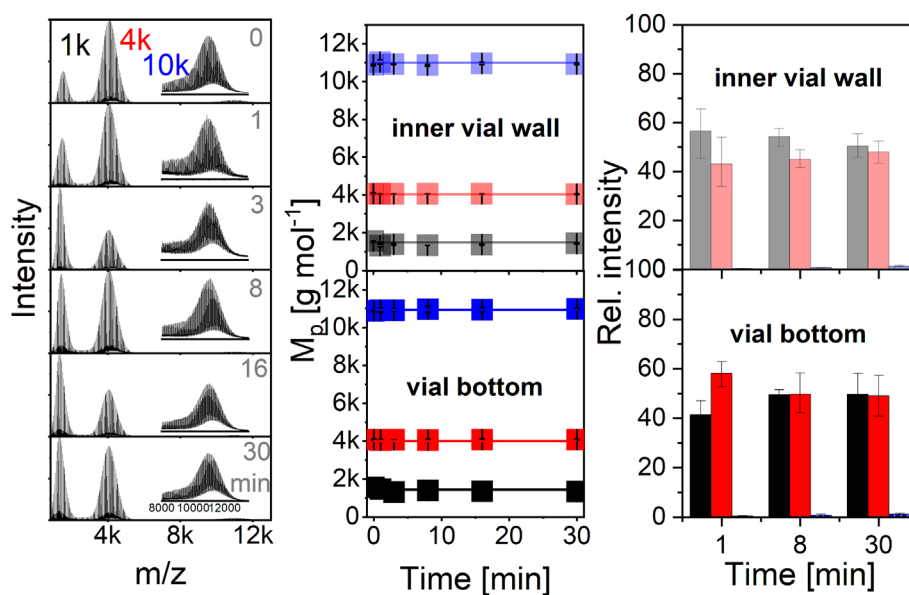


FIGURE 7 Time-dependent wet-grinding of a 20/60/20 PEG blend: MALDI time-of-flight mass spectra recorded after different grinding times (left); corresponding course of mass at maximum of peak distributions taken from two different vial positions (middle); course of the intensity ratio depending on the grinding time (right). [Color figure can be viewed at wileyonlinelibrary.com]



the surface energies, which are affected by the nature and concentration of the solvent.^{34–36} However, a clear interpretation is not possible at this point, and our results can only serve to show that there are obviously end-group-specific differences in the stability of polymers with otherwise identical chain structure that have to be considered when using wet-assisted grinding of polymers and polymer blends.

Finally, the (wet) ball milling method was also tested for the sample preparation using ternary PS and PEG (20/60/20) blends composed of polymers with same end groups. Figure 6 shows the results of the time-dependent wet grinding of a PS blend using isobutane. *n*-Hexane could not be utilized due to the complete blend adhering to the inner glass wall shortly after the beginning of the experiment, thus preventing intensive grinding of the sample. After

only 1 min of wet grinding was a significant decrease in spectral intensity observed for both PS 4k and 10k polymers. As demonstrated in Figure 6 (middle), these initial changes remained constant, and no significant differences were found even after a longer grinding time of 30 min.

Therefore, the most plausible explanation is a preferential adhesion of polymers with larger masses to the inner surface of the glass vial. After 30 min, samples were taken from the inner surface of the vial and from the vial bottom. Figure 6 (right) shows a comparison of the MALDI intensity data obtained from both locations. The data clearly indicate a much higher intensity of both PS 4k and PS 10k located on the inner surface of the vial, while the intensity of PS 1k is significantly reduced. This supports the assumption that higher mass polymers segregate in the glass vial during the wet grinding process.

As shown in Figure 6 (middle), the M_p values of PS 4k and PS 10k showed a slight but constant decrease, whereas the value of PS 1k remained constant throughout the entire grinding process, indicating lower mechanochemical stability of the higher mass PS polymers during wet grinding.

The last experiment on wet grinding focused on the ternary PEG 20/60/20 blend. These results are shown in Figure 7. To detect possible segregation effects in the vial (as seen before for PS), samples were taken from both the bottom and the inner wall of the vial throughout the period of grinding. Similar to the PMMA grinding experiment, *n*-hexane was used as dispersant. The mass spectra, shown in Figure 7 (left), do not indicate any visible signs of degradation, which is proved by the constant position of the intensity maxima of all three polymer distributions (see Figure 7, middle).

However, similar to the previous PS experiment, different relative peak intensities were found between the inner wall and the bottom of the vial after 1 min of grinding. After 8 min, and even more after 30 min, the intensity ratios became constant, demonstrating that PEG blends can be wet-assisted ground for 30 min without segregation and degradation.

4 | CONCLUSIONS

The following conclusions can be stated based on the results of this work:

First, the frequently reported higher intensity of polymer peaks in MALDI mass spectra observed with solvent-free sample preparation can be confirmed.

Second, the MALDI spectra of polymer blends prepared with either solvent-free or solvent-based sample preparation method show different intensity ratios of the individual polymers and are therefore not comparable. The mass spectra of samples prepared with the solvent-free method are generally more reproducible and less dependent on the amount of matrix.

Additionally, the MALDI spectra of blends prepared with the solvent-free method show stronger peak suppression of higher masses, or, conversely, an overestimation of lower mass peak intensities.

Third, mixing over a period of 15 min may not be sufficient, as the results of a time-dependent grinding experiment showed insufficient reproducibility of peak intensities.

Fourth, the addition of liquid dispersants to the blends while grinding (wet-assisted grinding) caused several additional problems including polymer degradation, as demonstrated with a PMMA blend, and segregation of higher mass polymers from the blends, and thus provided less benefit. In contrast, blends prepared by dry grinding showed no evidence of polymer degradation even after 30 min of vortexing.

In conclusion, despite the advantages of solvent-free sample preparation for the analysis of some classes of polymers, its use for the MALDI analysis of polymer blends has provided some unexpected results that must be considered and carefully evaluated.

AUTHOR CONTRIBUTIONS

Steffen M. Weidner: Conceptualization; investigation; validation; visualization; funding acquisition; data curation; supervision; writing - original draft. **Mete Sungur Dalgic:** Investigation; methodology; visualization; data curation.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/rcm.9756>.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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