Extracting information on the surface monomer unit distribution of PLGA by ToF-SIMS

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The surface chemistry of a range of random poly l-lactide-co-glycolide (PLGA) materials has been investigated using XPS, static secondary ion mass spectrometry (SSIMS) and gentle secondary ion mass spectrometry (G-SIMS). The estimated mole fraction of lactide units provided by SSIMS was in good agreement with bulk composition and appeared not to have been affected by contamination. Conversely, XPS assessment of lactide compositions was unreliable due to hydrocarbon contamination. This was determined by introducing two independent parameters, the ratio of trans-esterified bonds to the total number of ester bonds, P T, and the lactide composition. The model has indicated that, for this set of polymers, P T was approximately 0.25. Furthermore, we have demonstrated that G-SIMS successfully identified the structurally important key fragments leading to direct identification. Analysis by G-SIMS showed that the glycolic acid units from all PLGA compositions are emitted in a lower energy-fragmentation process than lactic acid units. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: XPS; SSIMS; G-SIMS; PLGA; co-polymer; surface analysis

Introduction

In the last two decades, biodegradable polymers have played a crucial part in the field of medicine, particularly in drug delivery systems and biomedical implants. [1–7] The mechanisms and kinetics of polymer degradation are important parameters in controlling drug delivery. The rate of polymer degradation can be altered by either blending biodegradable polymers or using co-polymer systems. [8, 9] The monomers of the most commonly used biodegradable homo-polyesters, poly l-lactide (PLA) and poly glycolide (PGA) can be co-synthesised to form poly l-lactide-co-glycolide (PLGA) via ring opening polymerisation. [10] The chemical structure of PLGA is highlighted in Scheme 1.

It is imperative to understand the surface composition of such co-polymer systems as the interactions take place at the biomaterial/body interface. XPS and static secondary ion mass spectrometry (SSIMS) are two of the most advanced chemical surface analysis techniques in use today, capable of characterising the surface of a material with high sensitivity. Surface chemical characterisation and degradation of PLGA have been previously studied using the above techniques. [11–18] In our study, XPS and SSIMS were employed to quantify the surface composition, determine the short-range order of the monomeric repeat units, and establish the degree of trans-estereification within the various compositions of PLGA. The recently developed technique of gentle secondary ion mass spectrometry (G-SIMS) [19] was also employed to assess its capabilities on the varying compositions of PLGA. G-SIMS has already been successfully used on polymers and organic molecules, [19–21] biodegradable homo-polymers [22] and adhesives [23] SSIMS spectra consist of parent fragment ions which are representative of the original material surface amongst a plethora of high-intensity, structurally degraded fragment ions. Spectral interpretation is complicated by the presence of these high-intensity degradation products. In G-SIMS, the population of fragments emitted by a single ion impact event is described by a partition function relationship with a characteristic surface plasma temperature, T p. For lower primary ion energies or a higher primary ion mass, the surface plasma temperature is reduced and the fragment population moves towards more intact fragments exhibiting less structural degradation. In G-SIMS, two primary ion beam conditions are used, one with high fragmentation and the other with lower fragmentation. It is then possible, using the ratio of two spectra, to extrapolate to a spectrum from a lower surface plasma temperature than is possible experimentally. This is the G-SIMS spectrum, consisting of parent fragment ions and structurally significant ions, making identification of the material surface less complex and more direct.

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Experimental

Polymer synthesis

L-lactide and glycolide were purchased from Purac (Lyon, France) and recrystallised from ethyl acetate. Zinc lactate was supplied by Sigma-Aldrich Chimie (Lyon, France) and dried under vacuum prior to use. Ring opening polymerisation of l-lactide and glycolide was carried out by introducing pre-determined amounts of l-lactide and glycolide into a flask, followed by zinc lactate as a catalyst (0.1 wt%). After degassing, the flask was sealed under vacuum and the polymerisation was allowed to proceed at 140 °C. After 7 days, the product was recovered by dissolution in chloroform, which was followed by precipitation in ethanol, and finally dried. The molar ratios of PLGA synthesised were 80:20, 60:40, 40:60 and 20:80, l-lactide to glycolide respectively. Final compositions of PLGA had a percentage composition error of ±1% measured by NMR.[24]

Thick films (~1 mm) were made for surface analysis by a melt-pressing method at ~230 °C using glass slides sonicated in hexane followed by chloroform.

XPS

XPS analysis was performed using a Kratos AXIS spectrometer in constant analyser energy transmission mode. The source employed was monochromated Al Kα radiation (1486.6 eV) with a photoelectron take-off angle of 90° to the surface, operated at 10 mA emission current and 15 kV anode potential. A low-energy electron flood gun was employed for charge neutralisation. Wide-scan spectra covering the binding energy range of 0–1000 eV with a pass energy of 80 eV showed that only carbon and oxygen were present and that the samples were free from any unexpected elements within the top ~10 nm of the polymer surface. High-resolution scans of the C1s and O1s core levels were obtained with a pass energy of 20 eV. Data analysis was performed using Casa XPS version 2.3.12 Dev 1.

SSIMS and G-SIMS

SSIMS spectra were acquired using an ION-time-of-flight (ION-TOF) IV instrument, ION-TOF GmbH (Muenster, Germany). The instrument is equipped with a dual-column beam, with Cs⁺ and Ar⁺, and samples were digitally rastered with a 128 × 128 data point array over the same area of 250 × 250 μm using a beam current of less than 1 pA and 11 keV impact energy. A low-energy electron flood gun was employed for charge neutralisation with a maximum electron dose of 3 × 10¹⁸ electrons/m², which is within the recommended maximum limit established in previous studies.[25]

For practical G-SIMS, the use of a dual-column ion beam is recommended[26] so that the spectra for the two primary ions are always in spatial registration. The use of Cs⁺ and Ar⁺ are also recommended since these primary ions give significantly separated surface plasma temperatures for optimised G-SIMS analysis.[19] In our study, we have employed the recommended configuration. Four sample areas, each separated by 1 mm, were analysed from the central region of each polymer. The samples were analysed with Cs⁺ followed by Ar⁺ with a combined primary ion dose below the static limit (no more than 10¹² ions/cm²). The mass spectra were recorded at high mass resolution (typically m/Δm > 7000) with 200 ps time bins.

Following the mass calibration of the spectra (the method for which is detailed elsewhere[26]), peaks were identified automatically from the Cs⁺ spectra to create a peak list where peaks were determined as having a threshold of 200 counts (peak area) or more for m/z 0–150, and 100 counts or more for m/z 150–350.

Results and Discussion

In the following text, we denote the lactide monomer unit by ‘L’, the glycolide monomer unit by ‘G’, and any general monomer unit by ‘M’. The relative compositions of L and G in the block co-polymer of PLGA are given by the ratio of l-lactide to glycolide (e.g. 80:20 is 80% lactide to 20% glycolide). A term ‘lactide fraction’, used throughout the text, is defined as ‘the molar fraction of lactide units in the polymer’.

Determination of the lactide fraction by XPS and SSIMS

A high-resolution C 1s spectrum of PLGA is shown in Fig. 1. Three different carbon chemical states are apparent within the C 1s core level. These are (in increasing binding energy order) (i) C–C/C–H; (ii) C–O; and (iii) C(=O)–O with a shift (relative to CH binding energy) of 0, 2 and 4 eV (±0.1eV) respectively.[27] The C–O and C(=O)–O environments are from both l-lactide and glycolide, while CH3 results from lactide only. The component intensity is proportional to the number of carbon atoms, and providing that there are no carbon contaminants present, the composition of the PLGA co-polymer within the XPS sampling depth (mole fraction of lactide, X(LPS)) can be determined by Eqn (1) where ICH is the intensity of the CH peak in the XPS spectrum.

\[
X_{(LP)} = \frac{I_{CH}}{I_{C(=O)O} + I_{C-O} + I_{C-C/H}}
\]

Figure 1. The XPS spectrum of PLGA 80:20 with ratio shown in lactide to glycolide. Three functional groups are present and the fraction of lactide on the surface can be found by monitoring C–H (lactide) to C(=O)–O (lactide and glycolide) highlighted in Eqn (1).
The C–C/C=–H component and $I_{C\theta2}$ is the intensity of the C(–O)=O environment.

$$X_{(XPS)} = \frac{I_{CO2}}{I_{CO2}}$$  

(1)

In order to determine the lactide fraction by ToF-SIMS, the [3M–O]$^{+\bullet}$ radical cation series were selected, an approach previously developed by Shard et al.\cite{11–13} The [3M–O]$^{+\bullet}$ radical cation series is a good candidate for quantitative analysis since these ions are formed from the mid-chain environment\cite{28}, and thus, should not be affected by the number of polymer end-groups present on the surface. A representative SSIMS spectrum of PLGA and the [3M–O]$^{+\bullet}$ ion series is presented in Ref. [12].

Using the intensities of the [3M–O]$^{+\bullet}$ ion series the composition of the co-polymer can be calculated. This is under the assumption that the ion yields for all ions in the [3M–O]$^{+\bullet}$ radical cation series are equal. Shard et al. have demonstrated that there is no strong evidence for non-identical ion yields for these ions.\cite{12} The surface composition can thus be determined using Eqn (2) below:

$$X_{(SIMS)} = \frac{3I_{300} + 2I_{186} + I_{172}}{3I_{200} + I_{186} + I_{172} + I_{158}}$$  

(2)

where $I_x$ is the intensity of an ion at m/z x’ from the [3M–O]$^{+\bullet}$ ion series. The lactide fraction, $X_x$, determined from XPS and SSIMS analyses are shown in Fig. 2 and compared to the bulk co-polymer composition. The XPS result suggests a higher lactide fraction than the bulk, which may be due to adventitious carbon contributing to the analysis depth (1–2 nm). However, it is well known that in SIMS the quantification approach must be carefully tailored as the Matrix effect contributes significantly to variability in ion yields.\cite{29} The general applicability of the SIMS technique for quantification has been discussed previously by Shard et al., and the methodology is applicable to polymeric systems, provided that the secondary ions are carefully chosen and the ratio of ion yields from two components can be determined.\cite{12} Given that the difference in the quantification of co-polymers from two different primary ions is minimal, the methodology and the results presented here signify the superior surface chemical specificity of SIMS over XPS for the quantification of polymeric binary systems.

**Determination of the short-range chain polymer arrangement, and the degree of trans-esterification of PLGA by SSIMS**

The short-range chain polymer arrangement can be further determined by monitoring the individual ion intensities of the [3M–O]$^{+\bullet}$ radical cation series. Shard et al.\cite{11–13} have reported that the short-range chain arrangement of random PLGA can be either randomly distributed monomeric or randomly distributed dimeric units, depending on the initial synthetic methodology employed.\cite{11–13} PLGA co-polymers used in our study were synthesised from homo-dimers, but may possess

<table>
<thead>
<tr>
<th>Ion mass (m/z)</th>
<th>Number of lactide units</th>
<th>Sequences (M1M2M3)</th>
<th>Probability (R.M.)</th>
<th>Probability (R.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>158</td>
<td>0</td>
<td>GGG</td>
<td>($1-X_L$)$^3$</td>
<td>($1-X_L$)$^2$</td>
</tr>
<tr>
<td>172</td>
<td>1</td>
<td>LGG</td>
<td>$3X_L$($1-X_L$)$^2$</td>
<td>$X_L$($1-X_L$)</td>
</tr>
<tr>
<td>186</td>
<td>2</td>
<td>GLG, LGL, LLG</td>
<td>$3X_L^2$($1-X_L$)$^2$</td>
<td>$X_L$($1-X_L$)</td>
</tr>
<tr>
<td>200</td>
<td>3</td>
<td>LLL</td>
<td>$X_L^3$</td>
<td>$X_L^2$</td>
</tr>
</tbody>
</table>

**Table 1.** The expected distribution of ion intensities based on either a random monomeric (RM) or random dimeric (RD) statistical arrangement.

**Figure 2.** Comparison of bulk lactide fraction (solid line) in PLGA compared to lactide fraction determined from XPS (■) and SSIMS (□).
a ‘monomeric’ statistical distribution of repeat units due to trans-esterification reactions during synthesis. Table 1 shows the expected distribution of ion intensities based on either a monomeric or dimeric statistical arrangement. The normalised ion intensities \( N_i \), using Eqn (3) are plotted in Fig. 3.

\[
N_i = \frac{I_i}{I_{200} + I_{186} + I_{172} + I_{158}} \tag{3}
\]

Figure 3 indicates that the observed ion intensities lie close to the dimer model. This is consistent with the co-polymer synthetic methodology, which uses \( l \)-lactide and glycolide dimers. Shard et al.\textsuperscript{[12]} have previously shown that by using \( l \)-lactic acid and glycolic acid monomers in the co-polymer synthesis, there is a close correspondence between the observed and calculated repeat monomeric intensity distributions within the \([3M−O]^{\cdots}\) ion series. Our data, however, lie somewhere between the purely monomeric and purely dimeric model, and this was taken as evidence that trans-esterification occurs during synthesis.\textsuperscript{[11,13]}

We now extend the previous model to show that it is possible, using SIMS, to determine the degree of trans-esterification. Assuming that the probability of encountering an ester link that has undergone a trans-esterification reaction is independent of the nature of the adjacent repeat units, we can assign a global probability, \( P_T \), which represents the ratio of trans-esterified bonds to the total number of ester bonds. The following relationships can therefore be determined:

\[
\begin{align*}
N_{200} &= X_L^3 P_T + X_G^3 (1 - P_T) \\
N_{186} &= 3X_L^2 X_G P_T + X_L X_G (1 - P_T) \\
N_{172} &= 3X_G^2 X_L P_T + X_L X_G (1 - P_T) \\
N_{158} &= X_G^3 P_T + X_G^2 (1 - P_T)
\end{align*} \tag{4}
\]

The data may now be fitted with two independent parameters, lactide composition, \( X_L = 1 - X_G \), which can also be determined from Eqn (2), and the probability of finding a trans-esterified bond, \( P_T \). The values of \( P_T \) determined using Eqn (4) with \( X_L \) values from SIMS (shown in Fig. 2) are given in Table 2. Figure 4 shows that the lactide composition determined experimentally (\( X_L \)) correspond directly to those established using the trans-esterification model (\( P_T \)). This suggests that for these polymers, \( P_T \) is \( \sim 0.25 \). Since trans-esterification can occur more than once at the same bond, the number of trans-esterification events per repeat unit, \( E \), can be calculated using Eqn (5):

\[
E = -\ln(1 - P_T) \tag{5}
\]

Table 2. \( P_T \) values calculated from Equation (4). Standard deviations are shown in brackets

<table>
<thead>
<tr>
<th>PLGA Composition</th>
<th>( P_T )(S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80:20</td>
<td>0.22 (0.1)</td>
</tr>
<tr>
<td>60:40</td>
<td>0.22 (0.03)</td>
</tr>
<tr>
<td>40:60</td>
<td>0.32 (0.03)</td>
</tr>
<tr>
<td>20:80</td>
<td>0.19 (0.22)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Figure 3. The normalised SSIMS intensity distribution of the \([3M−O]^{\cdots}\) radical cation series from Cs\(^+\) \( \square \). Lactide fraction (\( X_L \)) calculated from Eqn (2) are given in the top left hand corner. The dimeric (dashed line) and monomeric (solid line) models calculated from Table 1 are plotted with normalised SSIMS ion intensities calculated from Eqn (3). Observed ion intensities lie close to the dimer model for all PLGA compositions.

Figure 4. The number of trans-esterification events per repeat unit, \( E \), can be calculated using Eqn (5):
possibly applicable to other co-polymers. As mentioned in the Introduction, this is provided that the ion series are well characterised and the relative ion yields of all ions in the series are known. Shard et al. have shown that if the ions have non-identical yields, it is possible to incorporate ion yields into Eqn (2). Furthermore, selected ions must not be affected via chain-end effects, since the ion yields or surface composition given by the chain-end ions may be different from the main-chain ions. The additional model presented here has provided information on trans-esterification events during the synthesis. In this study, a large proportion of co-polymers are expected to be randomly distributed dimeric units, since co-polymers were synthesised via ring opening polymerisation from lactide and glycolide dimers. Shard et al. have previously synthesised PLGA co-polymers from lactide acid and glycolide acid monomers and the co-polymers found to be randomly distributed monomeric structures.

SSIMS and G-SIMS analysis of PLGA

Positive ion spectra are employed in this study, since SSIMS positive ion spectra are found to be informative with regards to PLGA and the ToF-SIMS spectrum of PLGA is given in Ref. [13]. The G-SIMS positive ion spectra from various compositions of PLGA are shown in Fig. 5 for m/z ≤ 350. G-SIMS spectra are shown with a g-index of 13, as recommended by Gilmore and Seah. In Fig. 5, the repeat unit of lactide-only fragments are denoted ‘□’, glycolide-only fragments are denoted ‘♦’, and mixed fragments are denoted ‘♦’. Throughout the spectra there are some fragments with the same unit mass (highlighted with underlined numbers in Table 3).

The positive ion ToF-SIMS spectra throughout the range of PLGA compositions all contained repeat monomeric fragments of typical lactide and glycolide fragments as well as high intensities of structurally degraded fragment ions and metastable ions as observed from previous studies. These include the [nM − OH]⁺, [nM − O]⁺, [nMH − O]⁺, [nM − H]⁺ and [m + H]⁺ ions. As with the previous study, the [nG − OH]⁺ ions are not observed. All existing characteristic PLGA fragments, including glycolide, lactide and mixed fragments in SSIMS spectra are summarised in Table 3 for m/z ≤ 350. It is interesting to note that the [nM − CO₂]⁺ and [nM − CO₂ ± H]⁺ ions are also present for glycolide, lactide and mixed fragments, with lactide only showing n ≤ 2, whereas glycolide and mixed fragments only show n ≥ 1. The [2M − CO₂]⁺ and [2M − CO₂ + H]⁺ ions are previously assigned to form cyclic structures and the possible postulated structures are discussed in Ref. [13]. Fragments with the same unit mass (numbers underlined in Table 3) can be usually resolved by the accurate mass assignment (e.g. the [G + L − H]⁺ ion at m/z 129.0188 to the [2L + H − O]⁺ ion at m/z 129.05516) except for a small number of fragments which exhibit the same chemical formula (e.g. the [2G − CO₂ + H]⁺ ion (C₃H₅O₂⁺, at m/z 71) and which has the same chemical composition as the [L − H]⁺ ion. After normalising the spectra throughout the composition by total ion counts, general increase in the intensity of lactide and mixed characteristic fragments were observed with decrease in the intensity of glycolide-only fragments, with increase in the bulk lactide composition. The SSIMS spectra are heavily populated with fragmented peaks, which make direct identification difficult.

In contrast, G-SIMS spectra have removed fragments, which are produced from high energy-fragmentation processes (high surface plasma temperature) that lead to post-emission rearrangement ions, significantly simplifying the spectrum. The G-SIMS peaks are simple fragments of the PLGA that retain the structural information. This demonstrates that G-SIMS may be successfully applied to the PLGA co-polymer. As the PLGA bulk composition changes from lactide-rich to glycolide-rich (i.e. from 80 : 20 to 20 : 80), lactide-only fragments decrease in intensity, and the glycolide-only fragments increase in intensity as expected. The decrease in lactide-only fragments appears to be greater than would be expected purely on the basis of composition; i.e. the [nG + H]⁺ ions begin to dominate the spectra for the 60 : 40 co-polymer, even though there are fewer glycolide than lactide units. The sudden decrease in the number and intensity of the [nM − OH]⁺ ion species from 80 : 20 to 60 : 40 suggests that the lactide monomer plays a vital part in the formation of [nM − OH]⁺ ions and also mixed fragments. This may be due to an inability of glycolide to form [nG − OH]⁺ ion series as a result of a methyl-pendant group being absent. Lactide, on the other hand, contains a methyl-pendant group which allow the McLafferty rearrangement, producing the [M − OH]⁺ ion (shown in Fig. 4). Normalised intensities of the [3M − O]⁺ ion series for each co-polymer from lactide compositions (calculated from Eqn (2)) shown as points with fits from the trans-esterification model (calculated from Eqn (5)) as lines.
It is possible to form \([nM - OH]^+\) ions of various chain length \((n \geq 1)\), as the co-polymer chain can cleave wherever a lactide unit is present.

It should also be noted that the decrease in the number of \([nM \pm X]^+\) (where \(X\) can be a combination of O, C or H) fragments and their intensities are also observed as the composition is changed from 80 : 20 to 60 : 40. This can be due to a number of reasons. First, as for the formation of \([nM - OH]^+\) ions discussed above, lactides may play a major part in the emission and formation of \([nM \pm X]^+\) fragments. Second, \([nM \pm X]^+\) ions are predominantly formed from random sequence than block sequence, and the proportion of block sequence which may be present on the surface as glycolide composition is increased. Third, glycolide may have much higher secondary ion yields than lactide, and thus, less proportion of \([nL \pm X]^+\) and \([nM \pm X]^+\) ions are formed compared to glycolide-only fragments.

In Fig. 6 is presented the intensity ratio of the four secondary ions GGG, GGL, GLL and LLL of the \([3M - O]^+\) radical cation series for \(Cs^+\) primary ions to \(Ar^+\) primary ions (only 60 : 40 shown as an example). This intensity ratio is known as \(F_x\). In G-SIMS, fragments that result from low-energy emission processes have higher \(F_x\) values than those that result from high-energy processes. The \(F_x\) value falls linearly as the number of \(L\) units in the fragment increases. A similar trend is observed for all compositions studied. This indicates that the emission of glycolide fragments results from a lower energy-fragmentation process than lactide fragments. Fragments with a high \(F_x\) value (low energy-fragmentation pathway), and which have a significant secondary ion intensity will have a strong G-SIMS intensity. Consequently, the G-SIMS spectra exhibit higher intensities of glycolide fragments than expected from the glycolide composition. The lactide fragments, however, were present in the G-SIMS spectra leading to their correct identification.

Similar analysis were carried out for the \([3M + H]^+\) ion series \(([3G + H]^+, [2G + L + H]^+, [G + 2L + H]^+\) and \([3L + H]^+\) ions at \(m/z\) 175, 189, 203 and 217 respectively) to investigate whether the end-group contribution may affect the formation of the \([nM + H]^+\) ions (not shown). The results obtained were comparable to the \([3M - O]^+\) ion series, confirming that the glycolide-containing fragments result from a lower energy-fragmentation process than lactide-containing secondary ions.
Table 3. PLGA characteristic positive ions for m/z ≤ 350. Numbers show the mass positions (m/z), letter n refers to peak mass position above m/z 350 or not detected in SSIMS spectra. Underlined numbers highlight having same unit mass, which can be resolved by accurate mass assignment for successful identification of each fragment

PLGA characteristic positive ions (m/z below 350)

<table>
<thead>
<tr>
<th>Unit</th>
<th>G</th>
<th>L</th>
<th>4G</th>
<th>3G + L</th>
<th>2G + 2L</th>
<th>G + 3L</th>
<th>4L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Unit</td>
<td>[M + H]⁺</td>
<td>59</td>
<td>73</td>
<td>[4M + H]⁺</td>
<td>233</td>
<td>247</td>
<td>261</td>
</tr>
<tr>
<td>2 Units</td>
<td>2G</td>
<td>G + L</td>
<td>2L</td>
<td>5G</td>
<td>4G + L</td>
<td>3G + 2L</td>
<td>2G + 3L</td>
</tr>
<tr>
<td>3 Units</td>
<td>3G</td>
<td>2G + L</td>
<td>G + 2L</td>
<td>3L</td>
<td>6G</td>
<td>5G + L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[3M + H]⁺</td>
<td>175</td>
<td>189</td>
<td>203</td>
<td>217</td>
<td>[6M + H]⁺</td>
<td>349</td>
</tr>
</tbody>
</table>


Conclusions

In this article, we have successfully shown that for co-polymer mixtures SSIMS can be used as a quantitative technique for determining surface-to-bulk compositions. It has been demonstrated that SIMS can be used to analyse secondary ion fragments only associated with non-adventitious surface species. As opposed to XPS, there are no issues related to surface contamination, thus giving the technique apparent advantages over the more traditionally used XPS. The results have indicated that the relative intensity of glycolide fragments to lactide fragments was higher for spectra acquired using Cs⁺ primary ions than with Ar⁺ primary ions. However, this leads to only a small difference (±2.67%) in the quantification of lactide composition which difference was found to be small. It is important to note that by using SIMS for the quantitative analysis of co-polymers, several possible phenomena within the co-polymers must be taken into account. When selecting an appropriate ion series for the analysis, the effect of co-polymer orientation and surface segregation may affect the quantification. Furthermore, the effect of non-identical ion yields in the selected ion series must also be considered, as highlighted in the previous study by Shard et al.[12]

The SSIMS analysis of the [3M – O]⁺ radical cation series has indicated that it was possible to resolve the short-term arrangement
of repeat monomer units in various PLGA compositions. The PLGA co-polyesters investigated here have shown that the short-range repeat monomer arrangement lies close to the random dimeric model as a result of the co-polymer synthesis being carried out from lactide and glycolide. Furthermore, the [3M−O]+ radical cation series distribution suggests that a proportion of polymer bonds, \( P_t \), was determined and these were in good agreement with the lactide fractions determined from the experimental data suggesting that the number of repeat-esterification events were 29% of the number of repeat units of these polymers.

G-SIMS analysis has also successfully been demonstrated for various PLGA co-polymer compositions. The G-SIMS method\(^{[19]}\) has suggested that the glycolide fragments resulted from a lower energy-fragmentation process than lactide fragments. The G-SIMS method\(^{[19]}\) applied throughout the PLGA compositions has suggested that the glycolide fragments resulted from a lower energy-fragmentation process than lactide-containing fragments.

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