An Analytical Method for Determining Residual Lactide in Polylactide by Gas Chromatography

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An analytical method to determine the residual lactide in polylactide (PLA) was proposed using an internal standard method of gas chromatography (GC). PLA samples and diphenyl ether (DPE) as an internal standard were dissolved in dichloromethane, then PLA was precipitated in anhydrous alcohol. The residual lactide and DPE were extracted to alcohol for GC analysis. At room temperature, lactide could react with alcohol and change into ethyl lactoyl lactate (ELL), but the relative response factor of lactide versus DPE could be obtained through a numerical analysis method. Therefore, the residual lactide content could be quantitatively calculated in PLA. The relative standard deviation (RSD) of the measurements is not more than 7.0%, indicating that the method is suitably precise.

Keywords Polylactide, residual monomer, response factor, unstable product, numerical analysis method

(Received July 18, 2016; Accepted August 30, 2016; Published February 10, 2017)

Introduction

Polylactide (PLA) is one of the biocompatible, bioabsorbable and biodegradable aliphatic polyesters and has been widely applicable in the field of bio-medicine and environmentally friendly materials.1 PLA is of increasing commercial interest in packaging and textiles applications as a result of its interesting properties.2,3 Industrially, PLA is produced by ring-opening polymerization of lactide in bulk, and purified through de-volatilization at high temperature under high vacuum. The performances of PLA are directly affected by the content of residual monomer in polymers, such as having harmful effects during processing and also causing undesired property changes in the end products,4 lowering mechanical strength and thermal stability, and increasing the hydrolytic degradation rate of PLA products.5,6 The quantitative analysis for the residual lactide monomer in PLA is carried out by many methods, such as semi-quantitative thermal gravimetric analysis (TGA),7 high performance liquid chromatography (HPLC),8,9 gel permeation chromatography (GPC),10 gas chromatography (GC),11,12 1H NMR spectra,13,15 and infrared spectroscopy.16

We have developed a method to quantitatively determine the residual lactide monomer in PLA using GC.11 We had found that lactide could react with alcohol and change into ethyl lactoyl lactate (ELL). At room temperature, ELL can be separated from lactide using GC. We had arbitrarily thought that alcohol was not suitable to be used as a precipitant for PLA to extract and quantify the residual lactide monomer in PLA for GC analysis. Subsequently, we also found the relative response factor of lactide versus ELL could be obtained using an internal standard method of GC through a numerical analysis method. Thus the problem that the declination of the GC peak area of lactide with reaction time due to the reaction of lactide and alcohol could be solved for the quantification of residual lactide in PLA using GC. Maybe, this is a roundabout way, but the best way, to obtain the relative response factor of lactide versus ELL, because the pure ELL product cannot be obtained in a laboratory or at the market. Therefore, this method not only could provide a method for the quantification of residual lactide monomer, but also would provide a possible way to obtain the relative response factor of a stable reactant versus an unstable intermediate product.

Experimental

Apparatus and reagents

Measurements were performed using a gas chromatograph (GC2014 Shimadzu, Japan) according to the reference.11 The L-lactide standard reference was from PURAC Biochem, Netherlands. PLA samples were obtained from Zhejiang Hisun Biomaterials Co., Ltd, Taizhou, China. Dichloromethane and anhydrous alcohol were analytical grade reagents made in China, and used directly without further purification. Diphenyl ether (DPE, GC grade) was from Aladdin Industrial Corporation, Shanghai, China.

Procedures

The L-lactide standard reference with weight of 0.01, 0.03, 0.05, 0.07, 0.09 and 0.11 g, and around 0.05 g of DPE were added into each 50 mL volumetric flask. The exact weights of L-lactide standard reference and DPE (mLA and mDPE) were

Notes

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obtain the relative response factor between lactide and DPE (coefficient (k) of the correction term (k_{ELL}) was less than 1.0 and must be in the range of 0 to 1.0. Therefore, the value of k could be obtained when the relative standard deviation (RSD) of \( \frac{1}{f} \) reached the minimum (1.341), and thus indicating the response factor of lactide versus ELL is k = 0.45. The average value of \( \frac{1}{f} = 0.2250 \) could be obtained from the slope of plots of \( \frac{A_{LA} + k_{ELL}}{A_{DPE}} \) versus \( \frac{m_{LA}}{m_{DPE}} \) in Fig. 2. Therefore, the relative response factor of lactide versus DPE was f = 4.444 under the given GC condition. Therefore, the content of residual lactide monomer in PLA can be calculated according to Eq. (3).

\[
RM\% = f \times \frac{(A_{LA} + k_{ELL})/A_{DPE}}{m_{LA}/m_{DPE}} \times 100% 
\]

RM\% is the content of residual lactide monomer (%); f is the relative response factor of lactide versus DPE; A_{LA} is the total peak area of lactide, including meso-, d-, and l-lactide (mV s\(^{-1}\)); A_{DPE} is the peak area of ELL (mV s\(^{-1}\)); k is the relative response factor of lactide versus ELL; A_{DPE} is the peak area of DPE (mV s\(^{-1}\)); m_{LA} is the weight of DPE (g); and m_{PLA} is the weight of PLA (g).

The test results for quantitatively determining residual lactide monomer using GC are shown in Table 1. The relative standard deviation (RSD) denoting the repeatability of this method was 4.8 - 7.0% for different reaction times (0 - 48 h), thus indicating that the method was sufficiently precise. The residual lactide monomer content for the sample was 6.45% according to the reference,\(^1\) and so the obtained results of the two methods were not significantly different, verifying the present method was accurate.

### Conclusions

The residual lactide monomer in PLA could be quantitatively determined using GC under the condition of anhydrous alcohol as a precipitant for PLA to extract residual lactide in PLA. When anhydrous alcohol was used as a precipitant for PLA, lactide reacted with alcohol and changed into ELL, leading to

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**Results and Discussion**

At room temperature, when lactide was dissolved in anhydrous alcohol, lactide could react with alcohol and change into ethyl lactoyl lactate (ELL), as shown in Fig. S1 (Supporting Information), and the ELL content as a function of time is shown in Fig. S2 (Supporting Information), thus leading to the decline of the GC peak area of lactide with reaction time. Therefore, when the lactide content was determined using an internal standard method of GC, the calculation of the relative response factor of lactide versus ELL, where k is the relative response factor of lactide versus ELL, as seen in Eq. (1).

\[
f = \frac{A_{DPE}/(A_{LA} + k_{ELL})}{m_{DPE}/m_{LA}} 
\]

For the convenience of plotting, Eq. (1) was changed to Eq. (2).

\[
\frac{A_{LA} + k_{ELL}}{A_{DPE}} = \frac{1}{f} \times \frac{m_{LA}}{m_{DPE}} 
\]

The solutions of lactide/DPE mixture were analyzed by GC to obtain the relative response factor between lactide and DPE (k). When lactide was dissolved in anhydrous alcohol, the ELL content increased and the lactide content decreased with increasing reaction time, but k and \( \frac{A_{LA} + k_{ELL}}{A_{DPE}} \) are fixed values independent of reaction time. If k was equal to 1.0, the relationship between \( \frac{A_{LA} + A_{ELL}}{A_{DPE}} \) and \( \frac{m_{LA}}{m_{DPE}} \) for different reaction times are shown in Fig. S3 (Supporting Information).

\[
\frac{A_{LA} + A_{ELL}}{A_{DPE}} \text{ was in direct proportion to } \frac{m_{LA}}{m_{DPE}}, \text{ and the curve of } \frac{A_{LA} + A_{ELL}}{A_{DPE}} \text{ versus } \frac{m_{LA}}{m_{DPE}} \text{ went through the zero point. By linear regression, a linear equation for } \frac{A_{LA} + A_{ELL}}{A_{DPE}} \text{ versus } \frac{m_{LA}}{m_{DPE}} \text{ could be obtained for different reaction times. The slope } \frac{1}{f} \text{ of the linear equation increased with reaction time, indicating the coefficient (k) of the correction term (k_{ELL}) was less than 1.0 and must be in the range of 0 to 1.0. Therefore, the value of k could be obtained when the relative standard deviation (RSD) of } \frac{1}{f} \text{ obtained for different reaction times reached the minimum using a numerical analysis method, as shown in Fig. 1. When } k \text{ was equal to 0.45, RSD of } \frac{1}{f} \text{ reached the minimum (1.341), and thus indicating the response factor of lactide versus ELL is } k = 0.45. \]

![Fig. 1 RSD of \( \frac{1}{f} \) for different reaction times versus k.](image-url)
the decline of the GC peak area of lactide with reaction time. The calculation of the relative response factor ($f$) of lactide versus DPE requires a correction term ($k_{ELL}$), and the value of $k$ (relative response factor of lactide versus ELL) could then be obtained using a numerical analysis method. Under the given GC condition, $k = 0.45$ and $f = 4.444$ were obtained. Therefore, the residual lactide content could be quantitatively calculated in PLA. The relative standard deviation (RSD) of the measurements is not more than 7.0%, indicating that the method is suitably precise. This method is not only practical for the quantification of residual monomer unstable in the precipitant for a polymer, but also provides a possible way to obtain the relative response factor of a stable reactant versus an intermediate product. When the product is an unstable intermediate or an ingredient that is difficult to separate and purify, this method provides a possibility for accurately quantifying the product content.

Acknowledgements

The authors gratefully acknowledge the financial support from the National High Technology Research and Development Program ("863" Program) of China (Grant No. 2015AA034004) and National Natural Science Foundation of China (Grants Nos. 51573178, 51403199 and 51303176).

**Supporting Information**

The chromatogram of L-lactide dissolved in anhydrous alcohol, the ELL content as a function of time and plots of $\frac{A_{LA} + k_{ELL}}{A_{DPE}}$ versus $\frac{m_{LA}}{m_{DPE}}$ for different reaction times ($k = 0.45$) are available free of charge on the Web at http://www.jsac.or.jp/analsci/.

**References**

1. R. Miyoshi, N. Hashimoto, K. Koyanagi, Y. Sumihiro, and T. Sakai, *Int. Polym. Proc.*, 1996, 11, 320.
2. S. Jacobsen, P. Degee, and H. G. Fritz, *Polym. Eng. Sci.*, 1999, 39, 1311.
3. H. R. Kricheldorf, *Chemosphere*, 2001, 43, 49.
4. S. Jacobsen, H. G. Fritz, P. Degee, P. Dubois, and R. Jerome, *Polymers*, 2000, 41, 3395.
5. S. H. Hyon, K. Jamshidi, and Y. Ikada, *Polym. Int.*, 1998, 46, 196.
6. A. Gleadall, J. Z. Pan, M. A. Kruft, and M. Kellomaki, *Acta Biomater.*, 2014, 10, 2233.
7. L. D. Feng, G. Li, X. C. Bian, Z. M. Chen, Y. L. Liu, Y. Cui, and X. S. Chen, *Polym. Test.*, 2012, 31, 660.
8. A. Rothen-Weinhold, N. Oudry, K. Schwach-Abdellaoui, S. Frutiger-Hughes, G. J. Hughes, D. Jeannerat, U. Burger, K. Besseghir, and R. Gurny, *Eur. J. Pharm. Biopharm.*, 2000,
9. L. D. Feng, Z. T. Gao, X. C. Bian, Z. M. Chen, X. S. Chen, and W. Q. Chen, Polym. Test., 2009, 28, 592.
10. A. Kowalski, A. Duda, and S. Penczek, Macromolecules, 2000, 33, 7359.
11. X. C. Bian, L. D. Feng, G. Li, Z. M. Chen, and X. S. Chen, Polym. Test., 2016, 50, 79.
12. D. R. Witzke, R. Narayan, and J. J. Kolstad, Macromolecules, 1997, 30, 7075.
13. K. A. M. Thakur, R. T. Kean, and E. S. Hall, Anal. Chem., 1997, 69, 4303.
14. I. C. McNeill and H. A. Leiper, Polym. Degrad. Stab., 1985, 11, 267.
15. M. Stolt, M. Viljanmaa, A. Södergård, and P. J. Törmälä, Appl. Polym. Sci., 2004, 91, 196.
16. B. Braun, J. R. Dorgan, and F. Steven, Macromolecules, 2006, 39, 9302.