Polymer Testing 50 (2016) 79–82

Contents lists available at ScienceDirect

Polymer Testing

journal homepage: www.elsevier.com/locate/polytest

Analysis method

Quantification of residual monomer in polylactide by gas chromatographic internal standard method

Xinchao Bian [a, b], Lidong Feng [a, b, *], Gao Li [a], Zhiming Chen [b], Xuesi Chen [a]

[a] Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, Jilin, China
[b] Zhejiang Hisun Biomaterials Co., Ltd, Taizhou, 31800, Zhejiang, China

ARTICLE INFO

Article history:
Received 23 October 2015
Accepted 30 November 2015
Available online 18 December 2015

Keywords:
Polylactide
Residual monomer
Lactide
Gas chromatography

ABSTRACT

An analytical method has been developed to quantitatively determine the residual lactide monomer in polylactide (PLA) using an internal standard method of gas chromatography (GC). The experimental results showed that diphenyl ether (DPE) was an appropriate internal standard for quantitative analysis of residual lactide in PLA. PLA and DPE were dissolved in dichloromethane and precipitated in hexane. At the same time, the residual lactide in PLA and DPE as an internal standard were extracted to hexane from the polymer solution. The resulting solution could be directly injected into a GC system. Therefore, the residual lactide was determined quantitatively using an internal standard method of GC. This method is practical for measuring the residual lactide content in PLA. When the lactide content is 5.0%, the relative standard deviation (*RSD*) of the measurements is 1.7%, while *RSD* is 6.9% at the low level of 0.4%, which indicates that the method is sufficiently precise.

1. Introduction

Poly (lactic acid) or polylactide (PLA) is a market-leading biopolymer in a variety of bio-chemical products. PLA is produced by ring-opening polymerization of lactides, which is a reversible reaction. The concentration of residual lactide in PLA is 3–6wt% at equilibrium. Devolatilization of PLA is capable of lowering residual lactide monomer concentration to below 0.3 wt%. The residual lactide content has a great effect on performance of the final PLA products [1]. The presence of residual monomer in the polymer can lower mechanical strength and thermal stability. In drug delivery systems consisting of PLA and a protein, even very small amounts (<1% w/w) of residual lactide can react with the drug during processing, and thus forming a conjugate considered an impurity in the implant material [2]. The residual lactide can also increase the hydrolytic degradation rate of PLA products [3,4]. The residual lactide interferes with the quantification of D-lactate content in PLA using polarimetry [5].

Many methods can be used to quantitatively determine the residual lactide in PLA. The residual monomer in PLA, lactide, can be determined semi-quantitatively and rapidly by thermal gravimetric analysis (TGA). The major advantage of TGA is a short analysis time, but its shortcoming is insufficient accuracy [6] because other compositions can also vaporize or decompose during testing using TGA, thus leading to incorrect higher test results .The characteristic peaks of lactide in ^{1}H NMR spectra can be used for estimating the amount of residual lactide in PLA [7–9], and infrared spectroscopy has also been studied for the determination of lactide content in PLA [10]. The residual monomer content can be measured using an isocratic reverse phase HPLC assay with UV detection at 210 nm [2] or by quantitative HPLC using hydrolysis kinetics [11]. Gel permeation chromatography (GPC) has been used to quantify residual lactide concentration in PLA [12]. Extraction of the residual monomer followed by gas chromatography is also documented in the literature [13].

In the present paper, the residual monomer in polylactide is quantitatively determined by a gas chromatographic internal standard method. PLA samples and an internal standard were dissolved in a suitable solvent, the PLA component was precipitated in another anti-solvent for PLA, and the residual lactide and the internal standard were extracted into the anti-solvent. The resulting solution could be directly injected into a GC system for obtaining the residual lactide content in PLA. The solvent and anti-solvent for PLA, as well as internal standard for lactide quantification, were studied and selected in detail. This method is suited to quantitatively determine the residual lactide content in PLA.

* Corresponding author. Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, Jilin, China.
E-mail address: fengld@ciac.ac.cn (L. Feng).

http://dx.doi.org/10.1016/j.polymertesting.2015.11.022
0142-9418/

2. Experimental section

2.1. Apparatus and reagents

The gas chromatography (GC2014) equipped with FID detector was made in SHIMADZU, Japan, and the capillary chromatographic column was SPB-5 (30 m × 0.53 mm × 0.5 μm) from SUPELCO, USA. The GC operating conditions were as follows. The temperatures of Injector, FID and Column were set at 250 °C, 250 °C and 140 °C, respectively, with carrier gas N_2 at 2.0 mL/min, split ratio 20/1, injection volume 0.5 μL. The L-lactide standard reference was from PURAC biochem, Netherlands. PLA samples were obtained from Zhejiang Hisun Biomaterials Co., Ltd, Taizhou, China. Chloroform, dichloromethane (DCM), anhydrous alcohol and hexane were analytical grade reagents made in china, and used directly without further purification. Diphenyl ether (DPE) was GC grade from Aladdin Industrial Corporation, Shanghai, China.

2.2. Experimental procedures

Chloroform, DCM, anhydrous alcohol and hexane were used for GC blank analysis. 0.05 g of L-lactide was dissolved in 10.0 mL of chloroform, DCM, anhydrous alcohol, as well as a mixture solvent of DCM/hexane (3.0 mL of DCM was dissolved in hexane and made into a 25 mL solution), respectively. Each solution was used for GC analysis.

A sample solution was prepared, containing 0.02-0.03 g of the L-lactide standard reference and 0.03-0.04 g of DPE. First, L-lactide and DPE were dissolved in 3.0 mL of DCM in a 25 mL volumetric flask, and the exact weights of L-lactide and DPE were recorded. Three different operators performed GC analysis, and five parallel determinations were carried out by each person.

0.01-0.06 g of the L-lactide standard reference and 0.01-0.04g of DPE were dissolved in 3.0 mL of DCM in a 25 mL volumetric flask, and the exact weights of L-lactide and DPE were recorded. The ratios of DPE to lactide were between 0.4 and 3.0. Then, hexane was added up to the 25 mL mark. The flask was shaken for a moment by hand. The solutions were used for GC analysis.

0.25 g of PLA and 0.01-0.03 of DPE were dissolved in 3.0 mL of DCM in a 25 mL volumetric flask, and then hexane was added up to the 25 mL mark. The flask was shaken upside down for a moment, and then the supernatant was filtered. The obtained filtrate would be used for GC analysis. The two PLA specimens were performed by six parallel determinations.

3. Results and discussion

3.1. Selecting solvent and precipitant for PLA

The residual lactide monomer in PLA was extracted from PLA solution using precipitant or so-called anti-solvent. The optimal solvent and precipitant for PLA should meet the following four conditions. Firstly, PLA and lactide can fully be dissolved in the solvent. Secondly, PLA in this solvent can be precipitated in the precipitant as completely as possible, while lactide cannot be precipitated at the same conditions. For this, the lactide must reach to a certain solubility in the precipitant for PLA so that the residual lactide in PLA can be quantitatively transferred into the precipitant from PLA. Thirdly, ideally, the solvent and precipitant for PLA should not react with the target analyze, lactide, in samples. Last but not least, all of the impurities in the solvent and precipitant must not include any interference components for lactide.

Chloroform and DCM are good solvents for PLA, and anhydrous alcohol and hexane can mostly precipitate PLA from its chloroform and DCM solutions. The suitability of these reagents for the determination of the residual lactide in PLA is discussed as follows. GC blank analysis for chloroform, DCM, anhydrous alcohol and hexane showed that interfering impurities do not exist in any of the solvents. GC analysis data for L-lactide dissolved in chloroform, DCM, anhydrous alcohol and DCM/hexane (3.0 mL of DCM was dissolved in hexane to make into a 25 mL solution) for 60 min are shown in Table 1. Chromatogram of L-lactide dissolved in DCM and anhydrous alcohol is shown in Fig. 1. The test results showed that L-lactide soluble in DCM, chloroform and DCM/hexane was stable, and thus the lactide content was identical to each other in these solvents. However, L-lactide dissolved in anhydrous alcohol was not stable and thus the lactide content dropped to 97.13%, because a new impurity 'Ethyl lactoyl lactate' was produced due to the reaction between alcohol and lactide. Therefore, DCM and chloroform are suitable as solvents for PLA, but anhydrous alcohol is not suitable as a precipitant for PLA.

Hexane is an excellent precipitant for PLA, and thus can almost completely precipitate PLA from its solutions. However, the solubility of lactide is very low in hexane, and so the solubility was tested according to the ratio of solvent to precipitant for PLA, which 3.0 mL of DCM was dissolved in hexane to make into a 25 mL solution. In this DCM/hexane blend reagent, the solubility of lactide is about 0.27 g/100 mL, and then lactide of 0.068 g can dissolved in 25 mL of DCM/Hexane blend reagent. According to this solubility, if the sample of PLA is 0.25 g, then the maximum content of lactide that can be detected is 27.2%. The residual monomer content is generally not more than 10% in PLA through ring-opening polymerization without purification, and less than 1.0% after purification. Therefore, the solubility of lactide is high enough for the measurement in the mixture reagent of DCM and hexane.

3.2. Selecting an internal standard

The primary principle of internal standard selection under a given chromatographic condition is that the internal standard must be sufficiently separated from all the components of the samples and that the internal standard peak is free of interference from all components of the samples. Furthermore, due to the instrument and operators the disproportional effect between the internal standard and the target analytes should be as far as possible the same for different operators. A better estimate of the ratio of internal standard to the analyte for peak height or peak area should be obtained, through repeating analysis, that is, better injection repeatability.

DPE is suitable as an internal standard for DPE can be completely separated from lactide and its impurities and thus is free of interference from all components of samples, as shown in Fig. 2. Another advantage of DPE is its low volatility, and thus the operation is easy. The single-point relative calibration factors are obtained from different operators for DPE and L-lactide, as shown in Table 2. The single-point relative calibration factors (f) do not have significant

Table 1
GC data for L-lactide dissolved in different solvents for 60 min.

Solvent	LA[a],%	Unknown impurity,%	Ethyl lactoyl lactate,%
Anhydrous alcohol	97.13	0.27	2.59
DCM	99.77	0.23	–
Chloroform	99.73	0.27	–
DCM/hexane[b]	99.75	0.25	–

[a] LA is the total content of lactides, including L-, D- and meso-lactides.
[b] 3.0 mL of DCM was dissolved in hexane to make into a 25 mL solution.