Determination of copolymer ratios of poly(lactide-co-glycolide) using near-infrared spectroscopy

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Abstract

The near infrared (NIR) spectroscopic technique was used to determine copolymer ratios of polylactide-co-glycolide samples. Appropriate quantities of DL-polylactic acid and lactic-co-glycolic acid polymers with 86:14, 75:25, 64:36 and 52:48 lactide to glycolide ratios were dissolved in methylene chloride to obtain 5% (w/w) solutions. NIR spectra of the samples were obtained from the solutions using a Polyol Analyzer™ operated in the transmittance mode. Linear regression calibration models were generated at 2130 and 2288 nm from the second derivative spectral data obtained from the NIR technique. The lowest and highest standard errors of calibration (SEC) at 2130 nm were 1.29 and 1.63%, whereas those obtained from the calibration models generated at 2288 nm were 2.00 and 2.03%, respectively. Partial least squares (PLS) calibration models were also generated from the second derivative spectral data from 1100 to 2500 nm. The lowest and the highest SEC for the models were 1.46 and 1.53%, respectively. The calibration models were then used to predict the lactide contents of the unknown (test) samples. The highest percent error of prediction was 2.56% for samples with 86% lactide content when the linear regression calibration at 2130 nm was used, whereas the highest percent error of prediction was 1.56% for samples with 64% lactide content when the linear regression calibration at 2288 nm was used. The highest percent error of prediction was 1.73% for samples with 75% lactide content when the two-factor PLS calibration model was used. © 1999 Elsevier Science B.V. All rights reserved.

1. Introduction

The use of polymers as excipients for pharmaceutical products has grown tremendously over the last three decades. Lately, one particular class of polymers, namely, biodegradable polyesters, such as polylactic acid, and copolymers of lactic and glycolic acid, has gained considerable importance in the development of biodegradable drug delivery systems. This is because these polymers are non-toxic, biocompatible and biodegradable. In vivo, they completely degrade into non-toxic degradation products. Moreover, their degradation kinetics can be modified by copolymerization.

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The characterization of these polymers can often be time consuming and/or expensive. For example, one widely used technique for characterization of copolymer ratios is proton nuclear magnetic resonance (pNMR). This technique requires expensive equipment, special testing areas and can be time consuming. Therefore, there is clearly a need for an analytical technique that can make polymer characterization both rapid and inexpensive.

One possible alternative to the traditional testing of polymers may be the use of near-infrared spectroscopy (NIRS). The technique has been used to study both films and fibrous forms of polymers [1–3]. It has also been used for the end-point determination of poly(oxyethylene) esterification [4], determination of antioxidants in polyolefins [5], and determination of cloud point of waxes [6]. There have also been quantitative studies done for starch in polyethylene [7] and acrylic copolymers [8]. A review of the literature indicated that studies involving the use of NIRS for determining the copolymer ratios of biodegradable polymers have not been reported. Hence, this study was conducted to evaluate the utility of the NIRS technique to determine the copolymer ratios of lactide/glycolide copolymers in solutions.

2. Methodology

2.1. Preparation of polymer solutions with varying copolymer ratios

Appropriate quantities of DL-polylactic acid and lactic-co-glycolic acid polymers (Birmingham Polymers, Birmingham, AL, USA) with 86:14, 75:25, 64:36, and 52:48 lactide to glycolide ratios were dissolved in methylene chloride to obtain 5% (w/w) solutions. These solutions were prepared in triplicate for each polymer ratio. The ratios of lactic and glycolic acid in the copolymer samples used in this study were determined by the supplier
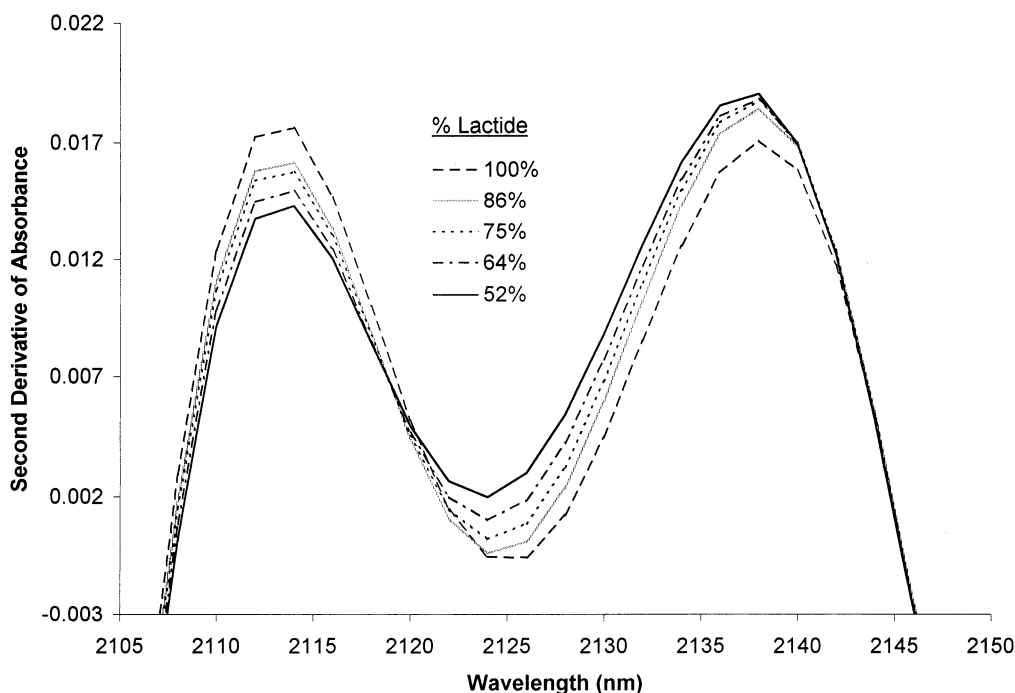

Fig. 1. Second derivative NIR spectra of solutions of lactide/glycolide polymers containing varying lactide contents between 2105 and 2150 nm.
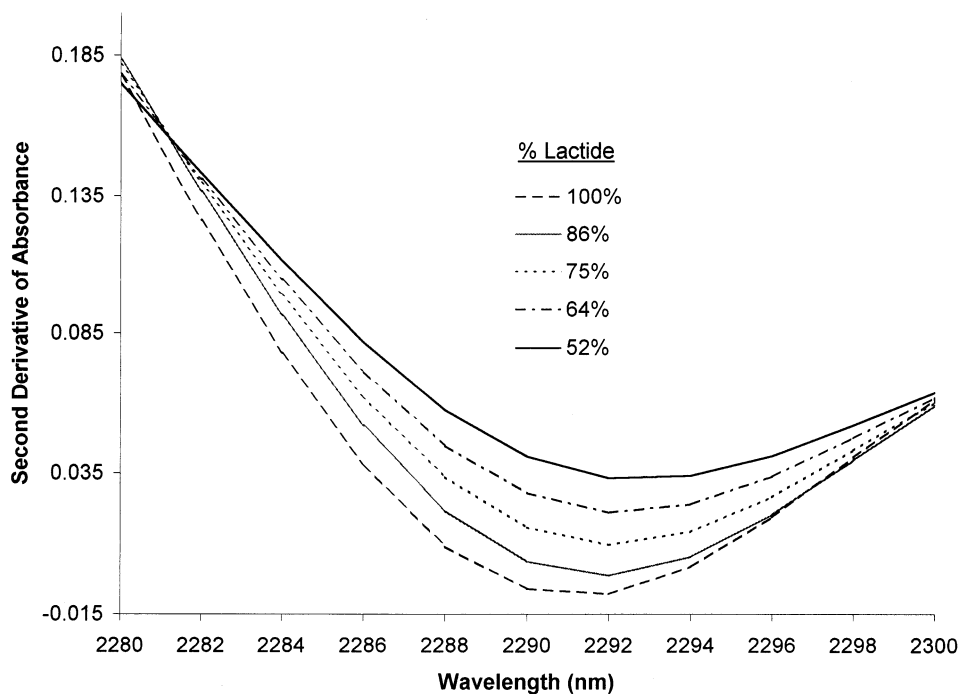
Fig. 2. Second derivative NIR spectra of solutions of lactide/glycolide polymers containing varying lactide contents between 2280 and 2300 nm.

using the proton nuclear magnetic resonance technique.

2.2. Near-infrared spectroscopic instrumentation

Samples of polymer solutions were placed into a 2 mm quartz cuvette for analysis. The samples were scanned from 1100 to 2500 nm using a Polyol Analyzer™ (Foss NIRSystems, Silver Spring, MD, USA) operated in the transmittance mode. The resulting spectral data of these solutions were used to generate appropriate calibration models using Vision® software (Foss NIRSystems).

2.3. Spectral analysis

A total of six linear regression calibration models (three at 2130 nm and three at 2288 nm) were generated from the second derivative spectral data. This was because of the maximum separation in the second derivative spectral absorbance

at these wavelengths. Three partial least-squares (PLS) calibration model were also generated from the second derivative spectral data obtained from the NIR technique. The wavelength range for the PLS calibration models was 1100–2500 nm. The criteria for selecting the calibration model was based on the mean squared error of cross-validation procedure in the Vision® software. The two factors used for the PLS calibration model was less than the number suggested by the cross validation procedure in the software.

Each calibration model (either linear regression or PLS) was generated from the spectral data obtained from four different copolymer ratios ranging from 52 to 100% lactide content. For each model, one lactide concentration was left out and used as the prediction set for the calibration model. This was done in order to make the calibration models rugged and eliminate the bias that may arise during the prediction of lactide content of the polymer solutions if the spectral data for the prediction set were also included in the cali-
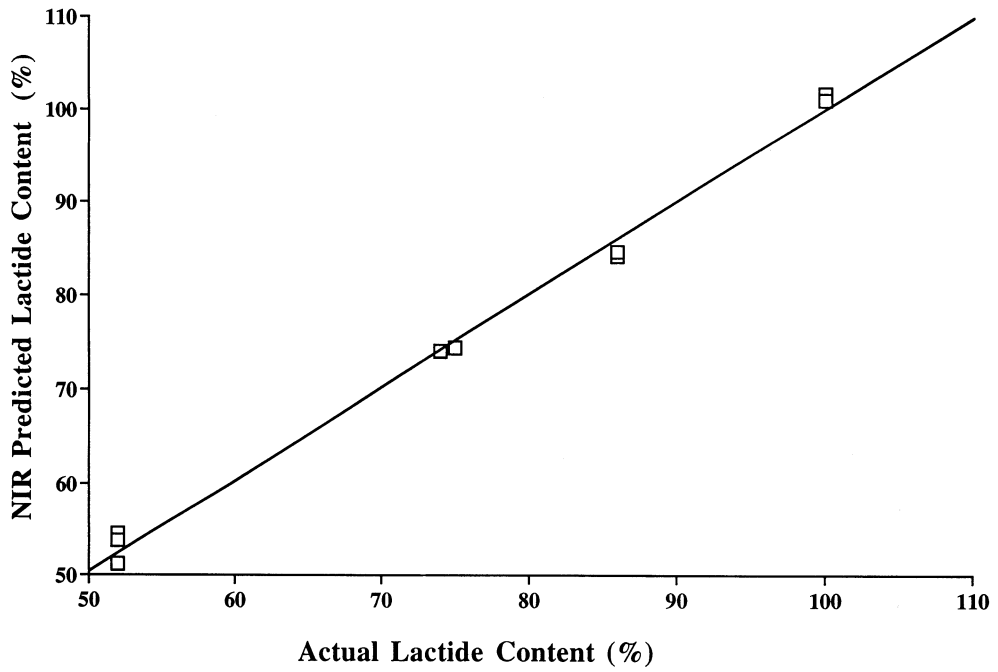
Fig. 3. Linear regression calibration model plot of solutions of lactide/glycolide polymers without 64% (w/w) lactide content at 2130 nm.
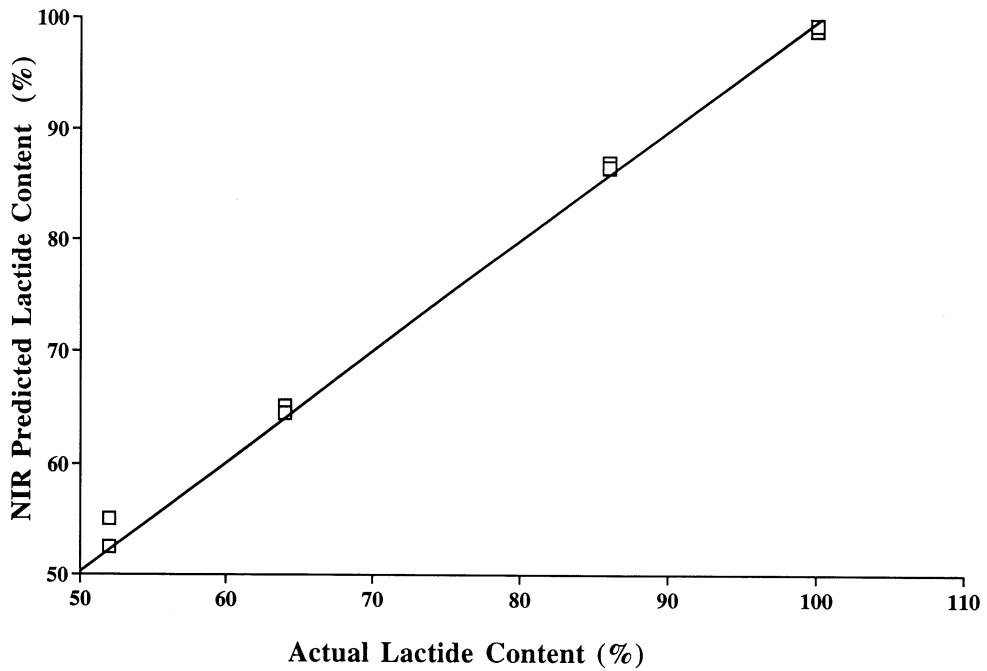

Fig. 4. Linear regression calibration model plot of solutions of lactide/glycolide polymers without 75% (w/w) lactide content at 2288 nm.
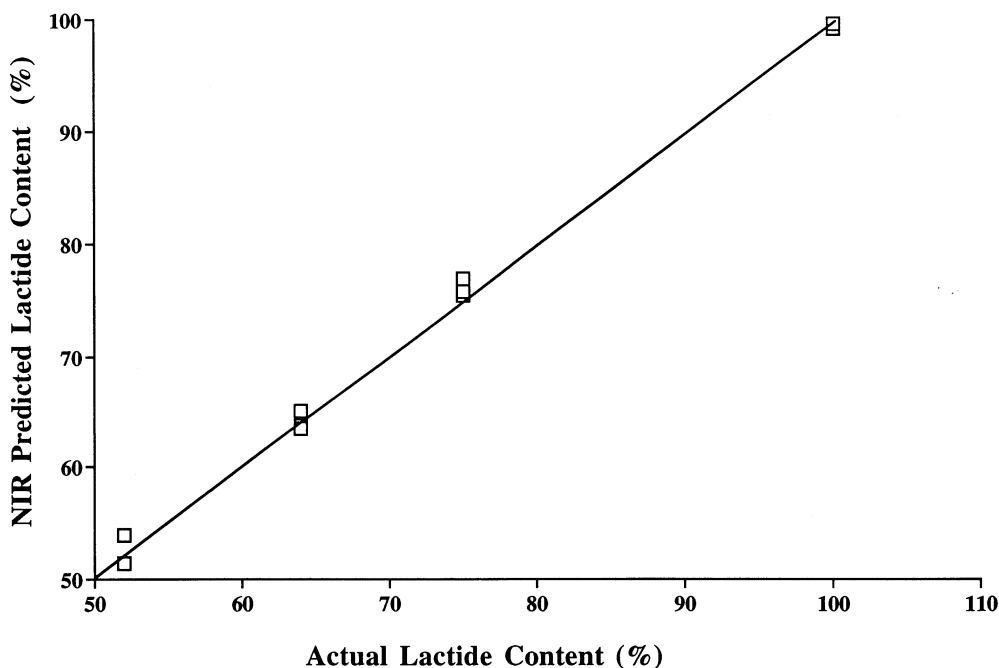
Fig. 5. Partial least-squares calibration model plot of solutions of lactide/glycolide polymers without 86% (w/w) lactide content.

the actual lactide contents of the polymer solutions used in the prediction set, the correlation coefficients, standard errors of calibration (SEC) and standard errors of prediction (SEP) for each model.

3. Results and discussion

Figs. 1 and 2 show the second derivative of NIR spectra from 2105 to 2150 nm and 2280 to 2300 nm, respectively. These spectra were obtained from polymer solutions with varying lactide contents ranging from 52 to 100%. A clear separation of second derivative spectra from polymer solutions of varying lactide contents can be seen in the regions between 2120 and 2135 nm (Fig. 1), and between 2284 and 2294 (Fig. 2). Two characteristic bands with maxima at approximately 2126 and 2292 nm were seen in the spectra, most likely due to the alkane and alkene groups that can be found in the backbone of the polymers. Linear regression calibration models were generated at 2130 and 2288 nm because the

maximum separation in the second derivative spectral absorbance was observed at these wavelengths. These calibration models were used to predict the lactide contents of the test samples. Linear regression calibration plots generated at 2130 and 2288 nm and used for predicting 64 and 75% lactide in the test samples are shown in Figs. 3 and 4, respectively. Each data point in the calibration plots represents an individual sample.

Besides using the spectral data for generating the linear regression calibration models, the data were also used to generate two-factor PLS calibration models. The PLS calibration plot used to predict 86% lactide in the test samples is shown in Fig. 5. SEC, SEP and the correlation coefficient values were obtained for all the calibration models generated from the spectral data. These values are depicted in Table 1.

Table 2 shows a comparison of actual versus the predicted lactide contents of polymers. The predicted values for the test samples were determined using the linear regression and the PLS calibration models. It is apparent from the table that the highest percent error of prediction was

Table 1
Standard errors of calibration and prediction for the linear regression and PLS calibration models generated from the spectral data

Types of calibration model	Lactide content for generating calibration models (%)	Lactide content of the prediction set (%)	Standard error of calibration (%)	Correlation coefficient (r)	Standard error of prediction (%)
Linear regression at 2130 nm	52, 75, 86, 100	64	1.631	0.996	1.267
	52, 64, 86, 100	75	1.563	0.997	1.196
	52, 64, 75, 100	86	1.286	0.998	0.811
Linear regression at 2288 nm	52, 75, 86, 100	64	1.995	0.995	1.288
	52, 64, 86, 100	75	2.026	0.995	1.493
	52, 64, 75, 100	86	2.020	0.995	1.428
PLS (two-factor)	52, 75, 86, 100	64	1.527	0.997	1.166
	52, 64, 86, 100	75	1.463	0.998	1.147
	52, 64, 75, 100	86	1.488	0.997	1.340

Table 2
Comparison of actual versus predicted lactide contents of polymers

Actual lactide content (%)	Predicted lactide content using linear regression at 2130 nm, Mean ± SD[a] (%)	Percent error of prediction (%)	Predicted lactide content using linear regression at 2288 nm, Mean ± SD[a] (%)	Percent error of prediction (%)	Predicted lactide content using PLS, Mean ± SD[a] (%)	Percent error of prediction (%)
64	63.6 ± 0.21	0.55	65.0 ± 0.32	1.56	64.0 ± 0.95	0
75	74.0 ± 0.20	1.33	75.3 ± 0.76	0.4	76.3 ± 0.74	1.73
86	83.8 ± 0.26	2.56	86.8 ± 0.29	0.92	86.9 ± 0.78	1.05

[a] Mean and standard deviation of three samples used in the prediction set.

2.56% for samples with 86% lactide content when the linear regression calibration model at 2130 nm was used, whereas the highest percent error of prediction was 1.56% for samples with 64% lactide content when the linear regression calibration model at 2288 nm was used. The highest percent error of prediction was 1.73% for samples with 75% lactide content when the two-factor PLS calibration model was used.

4. Conclusions

When predicting the lactide content of the polymer solution samples, all three models (linear regression at 2130 and 2288 nm, and two-factor PLS) used were able to predict the lactide content within an acceptable range of accuracy. This study shows that it is possible to use NIR for the nondestructive analysis of polymers in solution. Although the study was limited to the copolymer ratio in solution, it may also be possible to use NIR for other determinations outside the scope of this study. Thus, this study shows that NIR potentially provides a rapid, reproducible and relatively inexpensive means of characterizing polymer systems.

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