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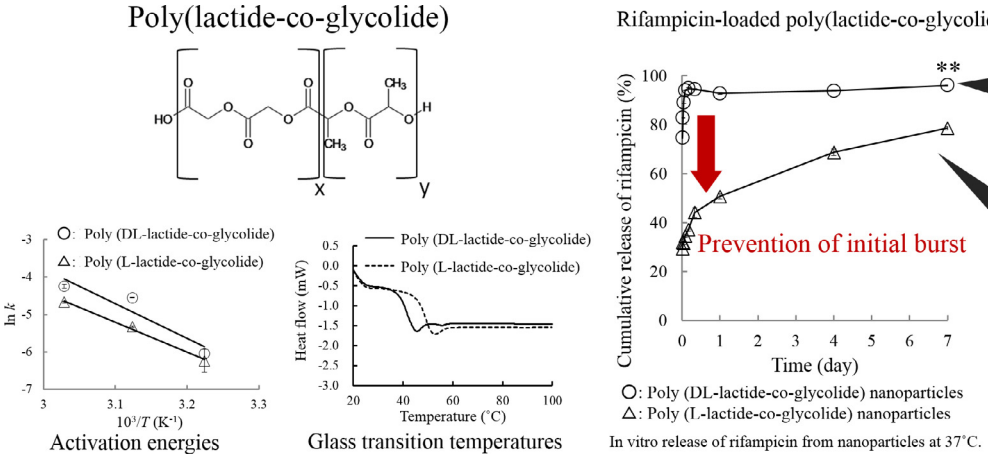
Effects of physicochemical properties of poly(lactide-*co*-glycolide) on drug release behavior of hydrophobic drug-loaded nanoparticles

Issei Takeuchi [a,b,c], Keishiro Tomoda [a,b,c], Ayaka Hamano [a], Kimiko Makino [a,b,c,*]

[a] Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641, Yamazaki, Noda, Chiba 278-8510, Japan
[b] Center for Drug Delivery Research, Tokyo University of Science, 2641, Yamazaki, Noda, Chiba 278-8510, Japan
[c] Center for Physical Pharmaceutics, Tokyo University of Science, 2641, Yamazaki, Noda, Chiba 278-8510, Japan

GRAPHICAL ABSTRACT



HIGHLIGHTS

- Poly(lactide-*co*-glycolide) of lactic acid/glycolic acid = 9/1 was synthesized.
- Glass transition temperature (T_g) of copolymers affected drug release behavior.
- T_g of poly(L-lactide-*co*-glycolide) was higher than poly(DL-lactide-*co*-glycolide).
- Poly(L-lactide-*co*-glycolide) prevented the initial drug burst from nanoparticles.

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ABSTRACT

Poly(lactide-*co*-glycolide) has been widely used and studied because of its biocompatibility and biodegradability. Many drug-loaded particles have been developed using this copolymer, however, information on its release behavior is lacking, especially for nanoparticles prepared using poly(L-lactide-*co*-glycolide). In this study, we used poly(DL-lactide-*co*-glycolide) (PLGA) and poly(L-lactide-*co*-glycolide) (PLLGA) with a 75/25 and 90/10 monomer composition of lactic acid/glycolic acid and molecular weights of 10,000. We determined the crystalline states, glass transition temperatures, and activation energies of the copolymers. Rifampicin-loaded PLGA7510, PLLGA7510, PLGA9010, or PLLGA9010 nanoparticles with 100-, 200- and 400-nm diameters were prepared, and *in vitro* release

* Corresponding author at: Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641, Yamazaki, Noda, Chiba 278-8510, Japan.
E-mail address: makino@rs.noda.tus.ac.jp (K. Makino).

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Activation energy
Rifampicin
Nanoparticle

tests were carried out in phosphate-buffered saline at 37 °C or 25 °C for a week. The cumulative release ratio of rifampicin from nanoparticles using poly(L-lactide-*co*-glycolide) as a drug carrier was significantly lower than the release ratio from nanoparticles using poly(DL-lactide-*co*-glycolide), since the glass transition temperature of poly(L-lactide-*co*-glycolide) was 7 °C higher than that of poly(DL-lactide-*co*-glycolide) at the same monomer composition. In addition, we found that the glass transition temperatures of the copolymers exerted a considerable influence on the initial release burst from the drug-loaded nanoparticles.

1. Introduction

Poly(lactide-*co*-glycolide) is a widely used and studied class of biodegradable polymers for pharmaceutical uses which are biocompatible and biodegradable [1]. Poly(lactide-*co*-glycolide) has shown immense potential as a drug delivery carrier and as a scaffold for tissue engineering; owing to its record in clinical uses, good degradation properties, and potential for sustained drug delivery, it is most commonly selected from a variety of available biodegradable polymers [2]. There are two types of poly(lactide-*co*-glycolide): Poly(DL-lactide-*co*-glycolide) (PLGA) and poly(L-lactide-*co*-glycolide) (PLLGA). These copolymers have been studied and their biocompatibility characteristics have been reported [3]. The advantages of PLGA nanoparticles have been demonstrated in transdermal treatments. PLGA improves permeability of medical agents, protects unstable agents within nanoparticles, controls the release ratio of active agent from the carrier, and can leverage iontophoresis techniques [4–9]. PLGA has also been used in studies of pulmonary drug delivery and treatment of tuberculosis [10–12].

Drug release from nanoparticles has been reported to involve an initial rapid release phase, followed by a relatively slow release phase, and the fraction of drug released in the initial burst usually depends on the nanoparticle composition or formulation. Generally, the mechanisms by which active agents can be released from a delivery system are a combination of diffusion of the active agent passing through the polymer that forms the controlled-release device, polymeric erosion, swelling, and degradation. It has been suggested that the release mechanism of drugs from PLGA nanoparticles may depend on diffusion kinetics and the PLGA surface and bulk erosion or swelling, since PLGA degradation is usually slow [13]. *In vitro* drug release behavior of 170–180 nm PLGA nanoparticles with entrapped *trans*-cinnamaldehyde and eugenol for antimicrobial delivery applications has been reported. The release profiles for both agents were biphasic, showing an initial burst in the first two h, followed by uniform release over time [14]. In addition, it has been reported that the drug fraction near or attached to the surface of the particle contributes to the initial burst [15]. Evaluation of *in vitro* release of dexamethasone from 20-μm PLGA microspheres found a triphasic release profile, with an initial burst followed by a lag phase and a secondary zero-order release phase [16]. This triphasic release profile is typical of PLGA microspheres [17]. The glass transition temperature (T_g) of PLGA was measured in that paper, but the relationship between the T_g value and drug release behavior was not discussed.

In this study, we prepared drug-loaded PLGA and PLLGA nanoparticles and measured the physicochemical characteristics of the copolymers to determine their influence on drug release behavior. Copolymers with the same molecular weight were used to observe the influence of monomer composition. Rifampicin (RFP), a semi-synthetic bactericidal antibiotic drug, was used as a hydrophobic model drug. There are already many reports focused on using PLGA to prepare RFP-filled microspheres and nanoparticles [18–23].

2. Materials and methods

2.1. Materials

PLGA with a molecular weight of 10,000 and a DL-lactic acid/glycolic acid monomer composition of 75/25 (PLGA7510), polyvinyl alcohol (PVA, degree of polymerization: 500), trehalose dihydrate ($C_{12}H_{22}O_{11}{\cdot}2H_2O$, purity ≥ 98%), DL-lactic acid ($CH_3CH(OH)COOH$, purity: 90%), tin(II) chloride dihydrate ($SnCl_2{\cdot}2H_2O$, purity ≥ 97%), and chloroform-d ($CDCl_3$, purity ≥ 99.8%, containing 0.05 vol% tetramethylsilane) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). PLLGA with a molecular weight of 10,000 and an L-lactic acid/glycolic acid monomer composition of 75/25 (PLLGA7510) was purchased from Taki Chemical Co., Ltd. (Kakogawa, Japan). L-lactic acid ($CH_3CH(OH)COOH$, purity: 90–92%) was purchased from Musashino Chemical Laboratory, Ltd. (Tokyo, Japan). Glycolic acid ($C_2H_4O_3$, purity ≥ 98%) was purchased from Nacalai Tesque Inc. (Kyoto, Japan). RFP ($C_{43}H_{58}N_4O_{12}$, purity ≥ 97%) was purchased from Sigma–Aldrich (St. Louis, MO, USA). All other chemicals were of the highest grade commercially available.

2.2. Synthesis of PLGA9010 and PLLGA9010

DL-lactic acid or L-lactic acid and glycolic acid were mixed at a molar ratio of 9:1 in a three-necked flask under nitrogen atmosphere. After stirring for 6 h at 140 °C and 4 kPa, a 4% (w/w) of tin(II) chloride dihydrate was added. The mixture was reacted at 165 °C and 1 kPa until its molecular weight became 10,000, which was measured using gel permeation chromatography (GPC). This polymer was dissolved in chloroform and purified by dropwise addition to diethyl ether. GPC (SIL-20A prominence, LC-20AD prominence, RID-10A, CTO-10ASvp, Shimadzu Co., Kyoto, Japan) was performed in chloroform with GPC columns (GPC K-803 and K-806, Showa Denko K. K., Tokyo, Japan). Molecular weights were calculated using polystyrene as the standard. All GPC measurements were carried out under the same conditions.

2.3. Measurement and characterization of copolymers

The ^1H NMR spectra were recorded in $CDCl_3$ on an FT NMR system (NNM-AL400, JEOL Ltd., Akishima, Japan). The solid-state form of the copolymers was confirmed by XRPD (RINT-Ultima 3, Rigaku Co., Ltd., Akishima, Japan). Molecular weights of copolymers were measured using GPC. The XRPD measurements were carried out in the standard measurement mode in the 2θ range from 10° to 50°. The scan speed was 2°/min and the counting step was 0.02°. X-ray source was CuKα, the accelerating voltage was 40 kV, and the current was 40 mA. Samples ground with a mortar and pestle were poured into a glass sample plate (0.2-mm depth). The T_g values of the copolymers were measured using differential scan-