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Matrix assisted pulsed laser evaporation of poly(D,L-lactide) thin films for controlled-release drug systems

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Abstract

We report the successful deposition of the porous polymer poly(D,L-lactide) by matrix assisted pulsed laser evaporation (MAPLE) using a KrF* excimer laser (248 nm, $\tau = 7$ ns) operated at 2 Hz repetition rate. The chemical structure of the starting materials was preserved in the resulting thin films. Fluence played a key role in optimizing our depositions of the polymer. We demonstrated MAPLE was able to improve current approaches to grow high quality thin films of poly(D,L-lactide), including a porosity control highly required in targeted drug delivery.

Keywords: Controlled drug release; Porous polymers; Thin films; Matrix assisted pulsed laser evaporation

1. Introduction

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a pre-designed manner [1–5]. The release of the active agent may be constant over a long period; it may be cyclic over a long period, or it may be triggered by the environment or other external events [6–8]. The purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing [9]. Other advantages of using controlled-delivery systems include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance [10]. While these are significant advantages, one cannot overlook the potential drawbacks of the process: the possible toxicity or non-biocompatibility of the materials used; undesirable degradation by-products; any surgery required to implant or remove the system; potential patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations [11]. There is a need for developing novel techniques for controlled and sustained drug delivery. Key issues may include: (i) development of drug formulations that will facilitate the absorption of insoluble compounds and macromolecules, leading to improved bioavailability and release rates, (ii) control of dosage, and (iii) development of effective methodologies to manufacture drug formulations into coatings (i.e., thin films) with controlled amount, morphology, and surface properties in order to improve handling, dispersion, and absorption [12–14]. Thin polymer films can be deposited by a variety of techniques that differ widely in complexity and applicability. Selection of the thin-film processing technique depends on the physico-chemical properties of the polymer, film quality requirements,

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and the specific substrate to be coated [15,16]. In the search for a universal approach to producing high quality thin polymer films, a new vapor deposition technique, matrix assisted pulsed laser evaporation (MAPLE), has emerged. The patented process [17], developed at the Naval Research Laboratory in Washington, DC, can generate high quality polymeric, organic, and biomaterial films on many types of substrates. Specific to MAPLE is the use of a cryogenic composite target of a dilute mixture of the polymer to be deposited and a light absorbent, high vapor-pressure solvent matrix. Ideally, the incident laser pulse used for MAPLE initiates two photothermal processes in the matrix, evaporating the frozen composite target and releasing the polymer into the chamber. Because of the low concentration of polymer 1–5 wt.% in the composite target, the simultaneous action of the evaporation gently desorbs the polymer or biomaterial. The photon energy absorbed by the solvent is converted to thermal energy that causes the polymer to be heated but the solvent to vaporize. The polymer molecules attain sufficient kinetic energy through collective collisions with the evaporating solvent molecules, to be transferred in gas phase. By careful optimization of the MAPLE deposition conditions (laser wavelength, repetition rate, solvent type, concentration, temperature, and background gas and gas pressure), this process can occur without any significant polymer decomposition. MAPLE [18–20] has proved capable of producing with minimal processing completely, or continuously, coated drugs of high encapsulation efficiency [21,22]. Basically, a core drug is encapsulated with a thin layer of a coating material, such as a surfactant or a biodegradable polymer. The coating may be applied to slow down the rate of active component release, improve dispersion/flow properties, or increase absorption into the systemic circulation.

The process has several advantages [23–26] over conventional techniques. MAPLE allows fast processing with runtimes on the order of minutes. A variety of coating materials can be employed, making it possible to produce films of organic and inorganic biomaterials. It is a dry, solvent-less technique that can be conducted under sterile conditions. Drug agglomeration/adhesion can be minimized by applying coatings that affect the bonding nature and electrostatic charge on the surface. Capsule formation by depositing coatings onto the drug surface makes it possible to control drug release kinetics by (a) the diffusion of the drug though the polymer coating or (b) degradation of the biodegradable polymer coating and release the core drug material [27].

Getting the right amount of drug into the right tissue or organ and keeping it there for a sufficient period of time is where most therapies could be improved. MAPLE can help solve this problem by producing new once-a-day delivery systems in therapeutic areas.

Poly(D,L-lactide) is a polymer derived from the optically active D and L monomers of polylactide. The chemical structure of this biodegradable polyester is shown in Fig. 1. Owing to its amorphous nature, poly(D,L-lactide) degrades faster than polylactide, the homopolymer of L-lactic acid. It is also more likely to exhibit a homogeneous dispersion of the active species within a monophasic matrix. Poly(D,L-lactide) degradation

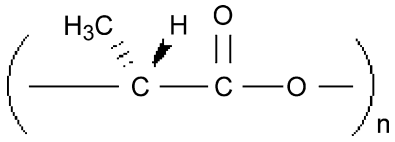

Fig. 1. Poly(D,L-lactide) chemical structure.

occurs via chain scission, during which polymer chains are cleaved to form oligomers and then monomers. The erosion process can be described as the loss of oligomers and monomers leaving the polymer film. The degradation of these lactide-based polymers and other hydrolytically degradable polymers depends on chemical composition crystallinity, and hydrophilicity [28]. MAPLE may be used to develop drug-polymer thin-film coatings in medical implants for controlled and sustained release. In this study, we demonstrate MAPLE as an alternative novel thin films processing technique for organic biomaterials.

2. Experimental

2.1. Materials

Poly(D,L-lactide) was commercially obtained (Sigma–Aldrich, St. Louis, MO). The manufacturer's listed molecular weight is 75,000–120,000. To create a suitable MAPLE target matrix, the poly(D,L-lactide) was solvated into a 2% solution with ethyl acetate.

2.2. MAPLE—experimental conditions

MAPLE depositions of poly(D,L-lactide) were performed using a pulsed excimer KrF* laser (λ = 248 nm, τ_{FWHM} = 7 ns, pulse repetition rate = 2 Hz, laser fluence = 400–900 mJ/cm^2). The incident angle of the laser beam was of 45° with respect to the target surface. The target–substrate distance was maintained at 4 cm, and the spot area was kept at 4 mm^2. Prior to deposition, ~5 ml of the solvated fluid was pipetted into the target holder and frozen by immersing in liquid nitrogen (LN). The copper target holder was placed on a homemade cryogenic rotating assembly that was maintained at a temperature of ~173 K using a copper holder connected to a LN reservoir. The target was rotated at a rate of 0.4 Hz during film deposition. The number of subsequent laser pulses was within the range of 1300–15,000. In all experiments double polished Si⟨1 1 1⟩ substrates were used. A control set of films were prepared by drop casting in order to provide comparison data.

2.3. Characterization methods

All of the MAPLE thin films were characterized by Fourier transform infrared spectroscopy (FTIR), atomic force microscopy (AFM), and optical microscopy (OM). FTIR spectra of poly(D,L-lactide) thin films and structures were recorded with a Nexus 470 apparatus (Thermo Nicolet Corporation, Madison, WI, USA) with 8 cm^{-1} resolution. The AFM micrographs of the poly(D,L-lactide) thin films were made with a Nomad atomic