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Note

Preparation of uniform biodegradable microparticles using laser ablation

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Abstract

In an attempt to prepare uniformly sized biodegradable microparticles for controllable drug eluting and targeting characteristics, a novel technique by employing ultrashort pulse (USP) laser has been developed. This method involves pumping a drug–polymer solution through a small orifice creating a liquid stream. A USP laser constantly fires at the stream to cut it into discrete droplets and consequently solid particles can be obtained with monodisperse size distribution. Through mathematical modeling, volumetric flow rate, orifice size, laser spot size, and laser frequency were found as sole factors determining the size profile of the resulting microparticles. By choosing appropriate set of variables, monosized biodegradable microparticles with wide range of particle size may be prepared.

Keywords: Biodegradable; Microparticles; Drug delivery; Laser

Biodegradable polymer microparticles have been widely utilized as drug delivery systems in pharmaceutical formulations (Brannon-Peppas, 1995). A wealth of biodegradable polymers, such as poly(lactic acid) (PLA) and poly(lactic-*co*-glycolic acid) (PLGA), has been investigated to formulate microparticle-based drug carriers to date. Owing to their chemical natures, these biodegradable polymers are mainly fabricated into microparticles by physical methods, including emulsification (Arshady, 1991; Wu, 1995), spray-drying (Baras et al., 2000), and precipitation (Young et al., 1999). All these methods involve dissolving polymers into solution, disintegrating the solution into droplets, and subsequently removing the solvent to obtain solid particles. The droplet formation and the morphology of resulting solid particles depend on a variety of thermodynamic and kinetic factors, such as surface tension, local shear, etc. Thus, although these methods are relatively simple, they suffered a common drawback: poorly tunable particle size and broad size distribution.

In order to prepare biodegradable microparticles with strictly controlled size profile for designer drug eluting and targeting characteristics, efforts have been focused on generating liquid droplets with uniform size so as to monosized solid particles (Shiga et al., 1996; Ma et al., 1999; Varde and Pack, 2004). Among them, the methods for droplet disintegration by proactive factors are rather promising (Berland et al., 2001). In a typical process, a drug–polymer solution is ejected through a nozzle. Unlike conventional spray processes where the stream breaks up into random sized droplets due to Rayleigh instability (Taylor, 1950), the droplets are broken up mainly by modulated forces such as flow shear and acoustic excitation. Thus the size of droplets can be exactly controlled and the microparticles of uniform size can be formed. These methods are significant but the Rayleigh instability effect is still uncontainable in droplet formation. In addition, they generally are difficult to fabricate microparticles smaller than 10 μm due to the mechanical limitations. Toward the goal of developing methods that are free of uncontrollable environmental factors, we have developed a new technique based on laser ablation, which can fabricate uniform microparticles with a wide range of particle size

PLGA (85:15) was obtained from Birmingham polymers (Birmingham, USA). Poly(vinyl alcohol) (PVA, 88% hydrolyzed) and dichloromethane (DCM) were all purchased from Sigma–Aldrich. The ultrashort pulse (USP) Ti:Sapphire laser system (CPA-2010 model, Clark-MXR Inc., USA) employed in the experiment was mounted with a xyz lens manipulator to control the laser spot size and position on the sample.

Briefly, PLGA was dissolved in DCM (2–10 wt.%) and the solution was pumped through a glass capillary with a 10–100 μm opening. The modulated laser constantly fires at the ejected stream to cut it into discrete droplets. For very viscous solution, a coaxial airflow may be applied to assist the stream leave

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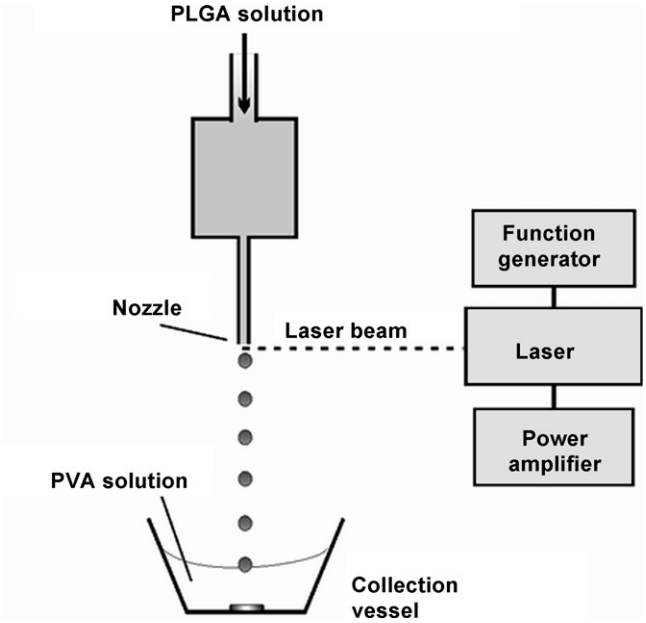

Fig. 1. Schematic illustration of the particle fabrication apparatus equipped with an ultra short pulse (USP) laser for disintegrating jet stream into uniform droplets.

the tip and prevent beading at the tip. The droplets were collected by a large quantity of 1% PVA solution and then left overnight to harden by extraction of the DCM. The derived solid particles were centrifuged and lyophilized to obtain final products. For morphological examinations, the microparticles were analyzed by a Philips XL30 scanning electron microscope (SEM) after being fixed on a support and coated with gold. The particle size was also observed with an inverted light microscope and photographed in bright field mode. The particle size was measured by imaging software.

The schematic of the particle fabrication apparatus was illustrated in Fig. 1. With the system, a solution containing biodegradable polymers and drugs is pumped through a small orifice creating a straight liquid stream. An ultrashort pulse (USP) laser operated a defined frequency is focused at the central point of the liquid stream and close to the capillary tip. The laser periodically strikes at the stream and slices it into a sequence of monosized droplets. Once the droplets are formed and collected by a surfactant solution, extraction of the solvent leads to solid particle formation.

As shown in Fig. 2, the particles fabricated with the laser ablation method at specific conditions have an average size as small as 5 μm and a uniform size distribution (a 10 μm opening capillary was used and the laser spot sized was tuned to 20 μm). The microparticles assembled as loosed packed hexagonal arrays, indicting the high monodispersity of the particle size distribution. In the experiments, drugs can be readily incorporated in the particle by dissolving or forming fine emulsion in polymer solution (data not shown).A mathematic model has been developed in this work to understand the droplets formation mechanism. Assuming a straight removal (cut) of length equal to laser spot size and the same stream diameter (D_s) as the orifice size (Fig. 3A), the length of the sliced stream segment l

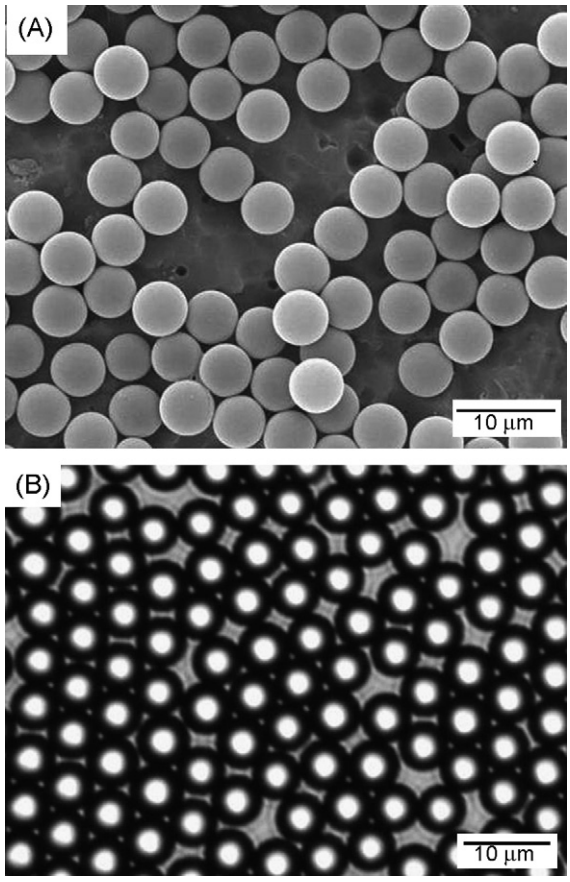

Fig. 2. The PLGA particles fabricated by the laser ablation technique. (A) A representative SEM image; (B) a representative light microscopic image.

is predicted to be:

$$l = \frac{4Q}{\pi D_s^2 f} - D_l \quad (1)$$

where Q is the stream volumetric flow rate, f the laser repetition frequency, and D_l the laser spot size (diameter). The particle size D_p then can be calculated as:

$$D_p = \sqrt[3]{\frac{6Q}{\pi f} - \frac{3}{2} D_s^2 D_l} \quad (2)$$

From above equations we can see that the particle size is theoretically determined by four factors solely: volumetric flow rate, orifice size, laser spot size, and laser frequency. The particle size as a function of varying volumetric flow rate and laser frequency was plotted in Fig. 3B. This figure illustrates that, for a certain laser frequency, a corresponding minimum volumetric flow rate is applied. The curves are sharp at the beginning, which means the particle size is sensitive to variation of the flow rate. Apparently, to create small particles, the combination of a small capillary tip, slow material flow speed, high laser repetition, or small laser spot size is recommended. However, several constrains have been applied. (1) The laser spot has to be bigger than the stream diameter to make a clear cut. (2) As a fraction of material will be lost due to laser ablation in the process, an

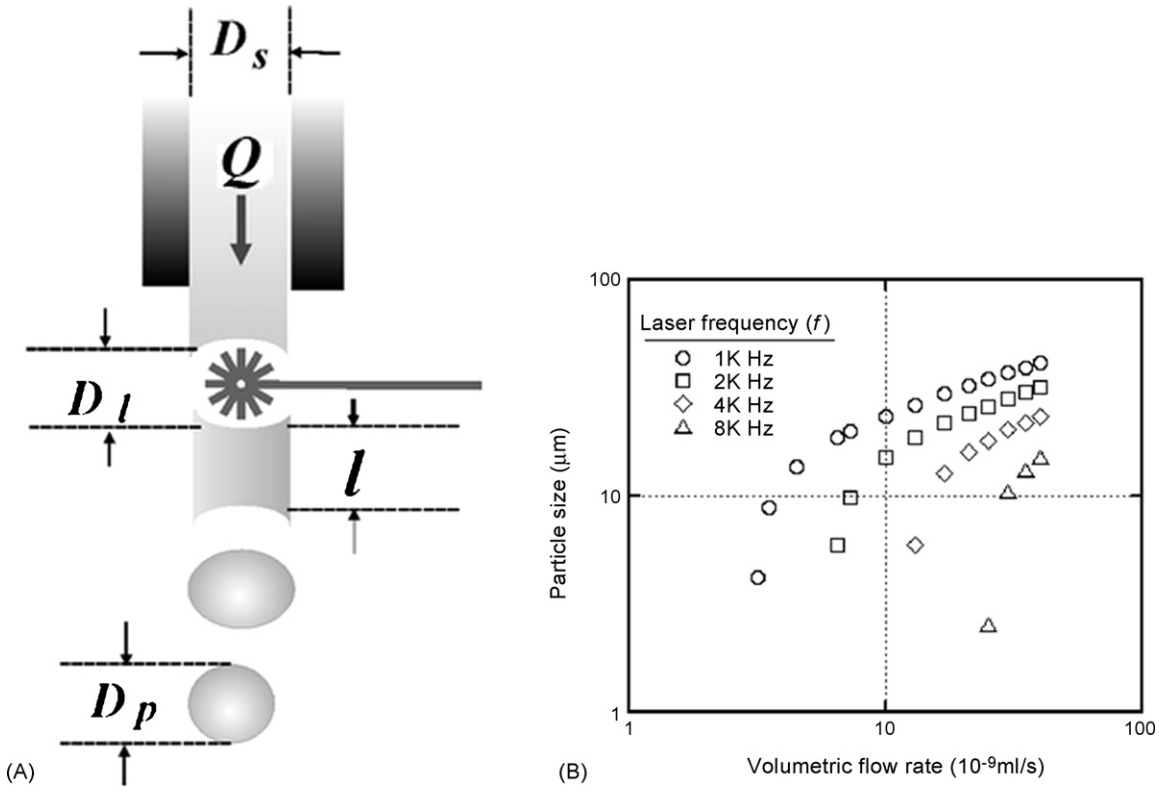

Fig. 3. (A) Schematic illustration of the particle generation mechanism and the variables controlling the resulting particle size. (B) Particle size as a function of volumetric flow rate and laser frequency. Ten-micrometer orifice size and 20 μm laser spot were applied and a 2 wt.% PLGA solution in DCM was used.

excessively high laser frequency will cause the vaporization of the entire stream whereas a low frequency will generate naturally formed droplets. (3) The fabrication of nozzle will become increasing difficult with decreasing orifice size under 10 μm. In terms of laser spot size, it is feasible to arrange the light intensity (Gaussian distribution) so that only the center of the spot is above the laser ablation threshold to match the orifice size.

The laser ablation technique developed in this work is promising in fabrication of uniformly sized microparticles with a wide range of particle size. The variables determining the microparticle sizes are all mechanical in nature, therefore can be easily tuned and strictly managed to obtain desirable particle size. Furthermore, the unique characteristics of the USP laser-based design provide several advantages for its application in microparticle fabrication: (1) owing to USP laser's extremely short pulse duration, upon focusing, the ablation of irritated materials on the liquid stream is almost instantaneously and virtually free of thermal effects such that no drugs incorporated in the droplets will be deactivated; (2) the ablation process is not dependent on the linear absorption at the laser wavelength; therefore the composition and physical properties of the processing materials have little influence to laser ablation performance; (3) this process does not require low viscosity liquidation. In fact, as long as the material can be extruded from the tip, microparticles can be made by this technique.

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