Electrohydrodynamic Liquid Atomization of Biodegradable Polymer Microparticles: Effect of Electrohydrodynamic Liquid Atomization Variables on Microparticles

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ABSTRACT: The exploration of a method to tailor a biodegradable polymer into microparticles/nanoparticles with a desirable morphology and size may result in their enhanced performance as biomedical devices for drug delivery and simplify the preparation process. A modified electrohydrodynamic liquid atomization (EHDA) process is reported here for the preparation of poly(lactic-*co*-glycolic acid) (PLGA) microparticles. To understand systematically the EHDA method for the preparation of PLGA microparticles, PLGAs of four different molecular weights were electrosprayed under different conditions involving changes in the applied potential, liquid flow rate, polymer concentration, and solvent. The results show that the right concentration range of PLGA is key for electrospraying the spherical particles. A solution with a low-molecular-weight PLGA has a wider concentration range for electrospraying into spherical particles than a solution with a high-molecular-weight PLGA. At the concentration at which spherical particles are formed, the diameter of the as-sprayed particles is not affected substantially by the applied potential and PLGA molecular weight, but it increases monotonically with the liquid flow rate and PLGA concentration. Experimentation further demonstrated that low electric conductivity, a low dielectric constant, and a high vapor pressure of chloroform are favorable for controlling the EHDA process to obtain quasi-monodisperse particles. The addition of the solvent *N,N*-dimethylformamide with opposite solvent properties extremely disturbs the stability of the EHDA process and, at the same time, produces smaller and polydisperse particles. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 113: 526–534, 2009

Key words: biocompatibility; biodegradable; biomaterials; biopolymers; particle size distribution

INTRODUCTION

The synthesis and modification of biodegradable, biocompatible, and nontoxic polymers are of basic importance to biomacromolecular science. It is another substantial task to assemble biomacromolecules into a variety of vehicles, such as porous films,[1] ultrathin fibers,[2] microparticles, and nanoparticles,[3,4] for various potential applications. The processing of these polymers into microparticles/nanoparticles useful as vehicles for *in vivo* drug delivery has long been the focus of very intensive research. Current interest in preparing biopolymer particles is mainly based on a heterogeneous polymerization process (an emulsion,[5] suspension,[6] or supercritical fluid[7]) or a precipitation process in a nonsolvent.[8] Although these two processes lead to synthesized polymer particles with domains of different sizes, they induce a large particle size distribution. In addition, tedious preparation steps, such as the procedure of separating microparticles from solvents, usually need be carried out in these conventional methods.

Recently, electrohydrodynamic liquid atomization (EHDA), which is also called electrospraying, has been employed to generate biodegradable polymer microparticles.[9–11] Electrospraying is a unique process in which polymer particles can be produced with well-defined characteristics such as size, shape, and morphology. Because the formation of aim products requires only one step, it can rightfully be termed a microprocessing technique. In comparison with the conventional processes mentioned previously, electrospraying is a fast and simple process. Previously, Berklanda et al.[12] electrosprayed poly(lactide-*co*-glycolide) (PLG) microparticles of different sizes with a modified EHDA process. Meanwhile, Hong et al.[13] also reported quasi-monodisperse biodegradable polymer microparticles by separating droplets of different sizes.

Despite the advantages of this technique for polymer microparticle preparation, the characteristics of the electrostatic generation of well-defined

TABLE I
Molecular Weights of the Four PLGA Polymers

Sample	LA/GA	M_w	M_n	M_w/M_n
PLGA8k	8 : 2	8,300	5,100	1.63
PLGA17k	8 : 2	16,900	12,200	1.39
PLGA38k	8 : 2	38,300	27,900	1.37
PLGA73k	8 : 2	73,200	51,800	1.41

LA/GA = lactic acid/glycolic acid; M_n = number-average molecular weight; M_w = weight-average molecular weight.

microparticles are not completely understood. Although the EHDA process is simple, the conditions for controlling the EHDA variables to prepare desirable polymer microparticles are quite complex. These EHDA variables involve process parameters (e.g., the applied potential, liquid flow rate, and circumstance temperature) and system parameters (e.g., the liquid viscosity, conductivity, surface tension, and molecular weight of the polymer). The objective of this work was to systematically investigate the effects of some key EHDA variables, especially the molecular weight of the polymer, on the formation, morphology, and size of the as-sprayed microparticles by employing poly(lactic-co-glycolic acid)s (PLGAs) of relatively low molecular masses.

EXPERIMENTAL

Materials

PLGAs (lactic acid/glycolic acid = 8 : 2) with weight-average molecular weights of 8000 (PLGA8k), 16,900 (PLGA17k), 38,300 (PLGA38k), and 73,200 (PLGA 73k) were synthesized according to the literature.[14] The details of these polymers are summarized in Table I. Chloroform and N,N-dimethylformamide (DMF), purchased from Beijing Chemical Co. (Beijing, China), were analytical-grade and were used without further purification.

Electrospraying

In a typical process, PLGA (0.5 g) was added to chloroform (10 mL) with magnetic stirring. After PLGA had dissolved completely, this solution was transferred into a glass syringe for electrospraying. The EHDA setup is shown in Figure 1. It consisted of a stainless steel capillary (i.d. = 0.5 mm) charged by a high-voltage supply (ES30P-5W, Gamma High Voltage Research, Inc., Ormond Beach, FL), a stainless steel ground electrode positioned at a desirable distance, and a collector positioned 15 cm away. A microfluidic syringe pump was employed to force and control the liquid contained in a glass syringe through the capillary.

In the regular EHDA, a structured Taylor cone was first formed at the exit of the needle, and then a liquid thread was issued from the vertex of the Taylor cone to form a cone-jet mode. The jet was unstable, breaking up farther downstream into droplets. Before deposition on the collector, the solvent evaporated rapidly from the droplets to form solidified products. All experiments were performed in air at the ambient temperature.

After the PLGA solution was electrosprayed, the resulting products were collected with aluminum foil and were dried in a vacuum desiccator for 3 days to remove the residual chloroform.

Characterization

The viscosity of the PLGA solution was measured with an NDJ-79 rotary viscometer (Shanghai Precision Instruments Co., Shanghai, China). The solution surface tension was analyzed with a ZJ-200A automatic interfacial tensiometer (Zhangjiajie Scientific and Technical Co., Zhangjiajie, China). The liquid electric conductivity was tested with a Delta 326 conductivity meter (Mettler–Toledo, Greifensee, Switzerland). The morphology and size of the sprayed products were recorded with a Shimadzu SSX-550 scanning electron microscope (Shimadzu, Osaka, Japan).

RESULTS AND DISCUSSION

Formation of the polymer microparticles

Unlike electrosprayed droplets consisting entirely of volatile small-molecule solvents, in which case the solvents will evaporate completely and thus the liquid droplets will disappear, droplets containing nonvolatile materials will produce micrometer/nanometer solid residues. Different nonvolatile materials under different conditions can produce solid residues with a variety of structures and
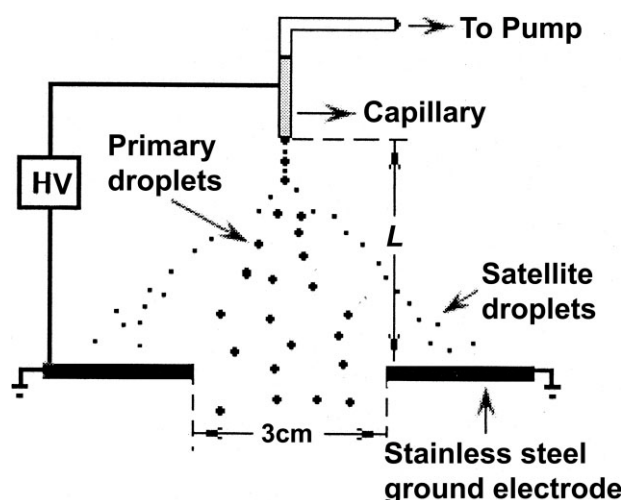

Figure 1 Schematic representing the configuration of the modified EHDA setup.
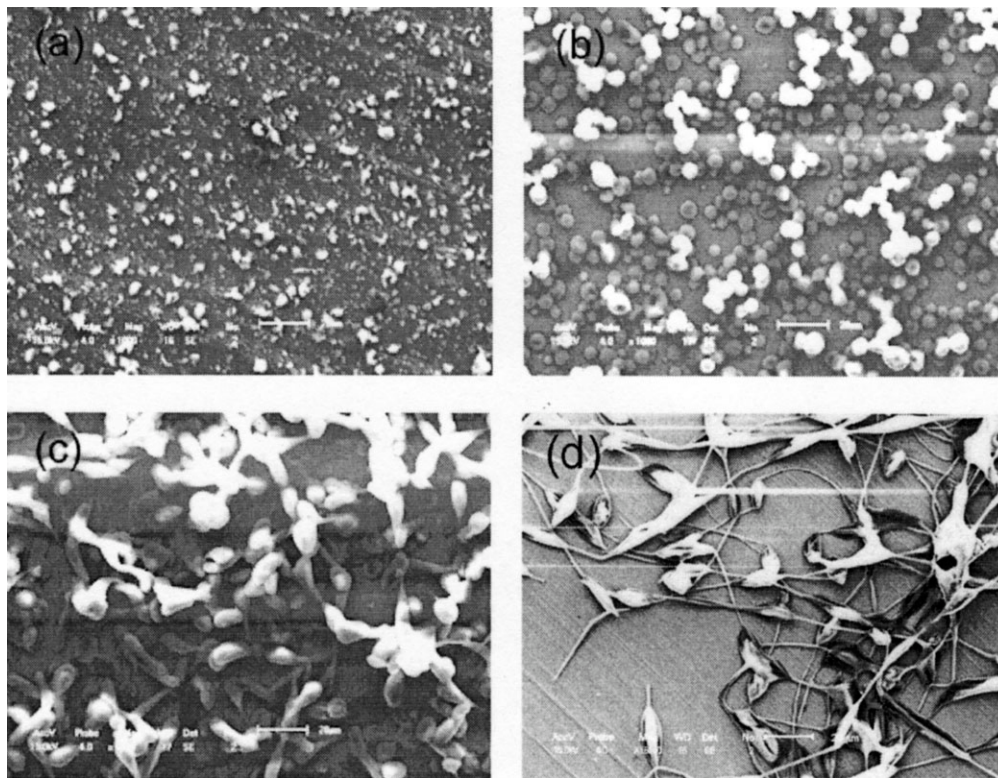
Figure 2 Changes in the PLGA concentration in chloroform solutions: (a) 2, (b) 5, (c) 8, and (d) 15 wt %. The scale bar is 20 μm.

morphologies, including microbeads,[15] fibers,[16] and porous films.[17] In our experiment, because of the existence of nonvolatile PLGA, solid residues were obtained. The experimental results indicate that the structure and morphology of the sprayed residues are first determined by the solution concentration and molecular weight of the polymer. PLGA38k is used as an example for spraying. The results show

that chloroform solutions with different PLGA concentrations produce different morphologies. From Figures 2 and 3(a), we can see that a dilute PLGA solution (<2 wt %) produces polymer debris [Fig. 2(a)]. The right concentration of the PLGA solution (3–6 wt %) forms spherical PLGA particles [Fig. 2(b)]. When the PLGA concentration is higher than 8 wt %, tapered particles [Fig. 2(c)] and even ultrathin
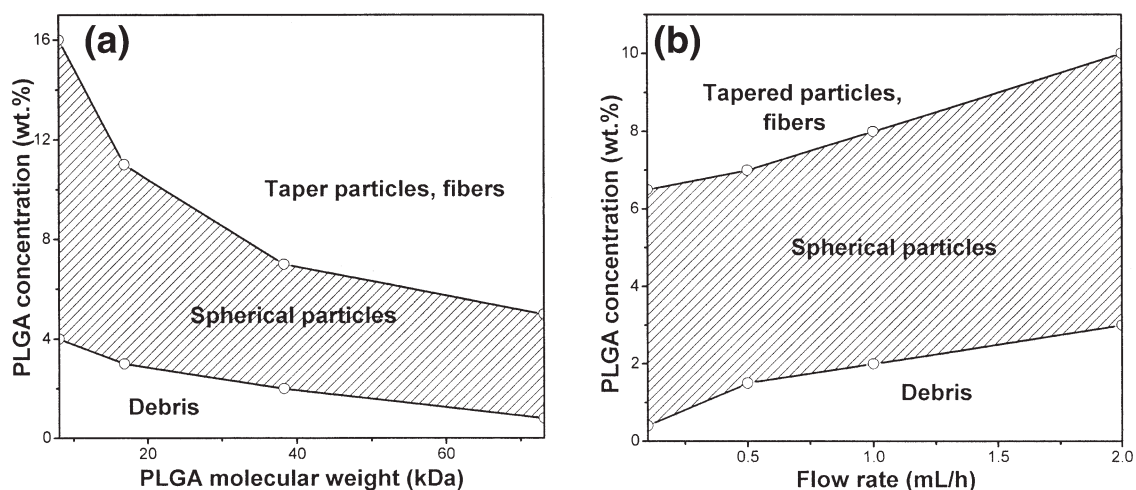

Figure 3 (a) Effect of the PLGA concentration and molecular weight on the production of spherical PLGA particles. The flow rate was fixed at 1.0 mL/h, and the applied voltage was set at 10 kV. (b) Effect of the liquid flow rate and PLGA38k concentration on the production of spherical PLGA particles.

fibers [Fig. 2(d)] emerge. Figure 3(a) shows that the influence of the PLGA molecular weight is also obvious. With high-molecular-weight PLGA, there is a weaker capability to produce spherical particles in comparison with low-molecular-weight PLGA (the concentration range of high-molecular-weight PLGA for producing spherical particles is narrower than that of low-molecular-weight PLGA). Figure 3(a) further shows that PLGA with a low molecular weight (e.g., PLGA8k) has a higher concentration (16 wt %) for producing spherical microparticles in comparison with high-molecular-weight PLGA (e.g., PLGA73k); in the case of PLGA73k, only when the PLGA concentration is lower than 5 wt % can the PLGA solution produce spherical microparticles.

Experiments indicate that the flow rate of the sprayed solution also affects the formation of polymer microparticles. As can be seen in Figure 3(b), for example, when a PLGA38k solution is sprayed at a low flow rate (0.2 mL/h), the concentration range for producing spherical particles is 0.4–6.5 wt %, and this range goes up (from 3 to 10 wt %) following an increase in the flow rate (2.0 mL).

Combining the information from mass spectrometry,[18–20] we believe that our results can be attributed to polymeric intermolecular entanglements, which play a key role during electrospraying. The intermolecular entanglements of PLGA are presented in two ways. One is the length of the polymer chain, and the other is the polymer concentration. In most mass spectrometry experiments, the tailored polymer has a high molecular mass, generally higher than a million. In this case, although the superdiluted polymer solution (<1%) is sprayed, polymer nanoparticles of tens of nanometers are sure to be produced. Unlike the mass spectrometry results, our results indicate that a low-concentration polymer solution fails to produce polymer particles. This fact demonstrates that longer the polymer chain is, the stronger the intermolecular entanglements are of the polymers. When the length of the polymer chain is longer than a critical value, polymer particles form. For example, in Figure 3(a) we can see that the line that compartmentalizes the polymer debris area and polymer particle area expresses the critical value of the polymer over which particles are formed. At the same time, our results also indicate that an increase in the polymer concentration can also produce polymer particles, demonstrating that a high polymer concentration can supply the deficiency of a low-length polymer chain. Once the amount of the polymers is increased in the droplets, the intermolecular entanglements are strengthened.

The solvent evaporation of electrosprayed droplets is in fact an effect of the polymer solution concentration. Teraoka[21] explained in detail the thermodynamic characteristics of polymer chains in polymer
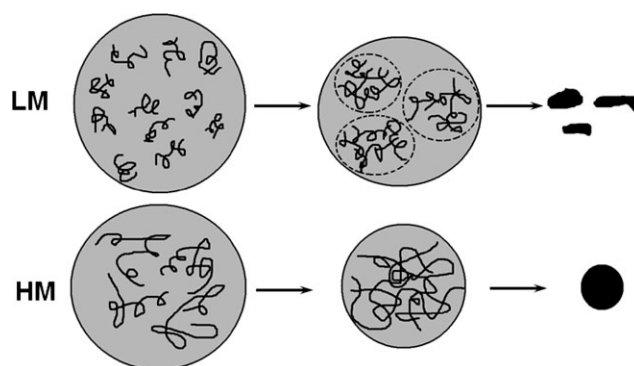

Figure 4 Schematic illustration of the effect of the polymer molecular weight on the electrosprayed products. LM denotes the low-molecular-weight polymer, and HM denotes the high-molecular-weight polymer.

solutions of different concentrations. According to Teraoka's theory, we can use a schematic illustration to explain the effect of the length of polymer chains on electrosprayed products. As shown in Figure 4, in the first stage, polymer chains are more or less separated from one another inside the electrosprayed droplets because of the dilute polymer concentration, no matter how long the polymer chains are. At this stage, these solutions are close to an ideal solution. After solvent evaporation, the polymer concentration increases. Polymer chains start to overlap and entangle, and at the same time, their mobility is greatly reduced. At this stage, in comparison with a polymer with a low molecular weight, a high-molecular-weight polymer has more entanglement points. Thus, the high-molecular-weight polymers can converge together to form a particle, but the polymers with low molecular weights will produce many new aggregative centers to form polymer debris.

Quasi-monodisperse polymer microparticles

Although experimental results have confirmed that PLGAs of relatively low molecular masses can be well sprayed into microparticles, the sprayed particles are polydisperse, as can be seen in Figure 5(a,c). Figure 5(c) shows that the size distribution of the PLGA microparticles is composed of two areas; that is, it is a bimodal particle size distribution. According to Tang and Gomez[22–24] and Hartman and coworkers,[25–27] droplets of three sizes—primary, satellite, and offspring—are easily produced in a volatile liquid spray. The primary droplets, originating from the jet diameter, are approximately equal to 2 times (1.89) the jet diameter.[28] The satellite droplets come from the breakup of the sprayed jet; there, the perturbation amplitude of the jet determines whether the satellite droplets can produce or not. The diameter of the satellite droplets is
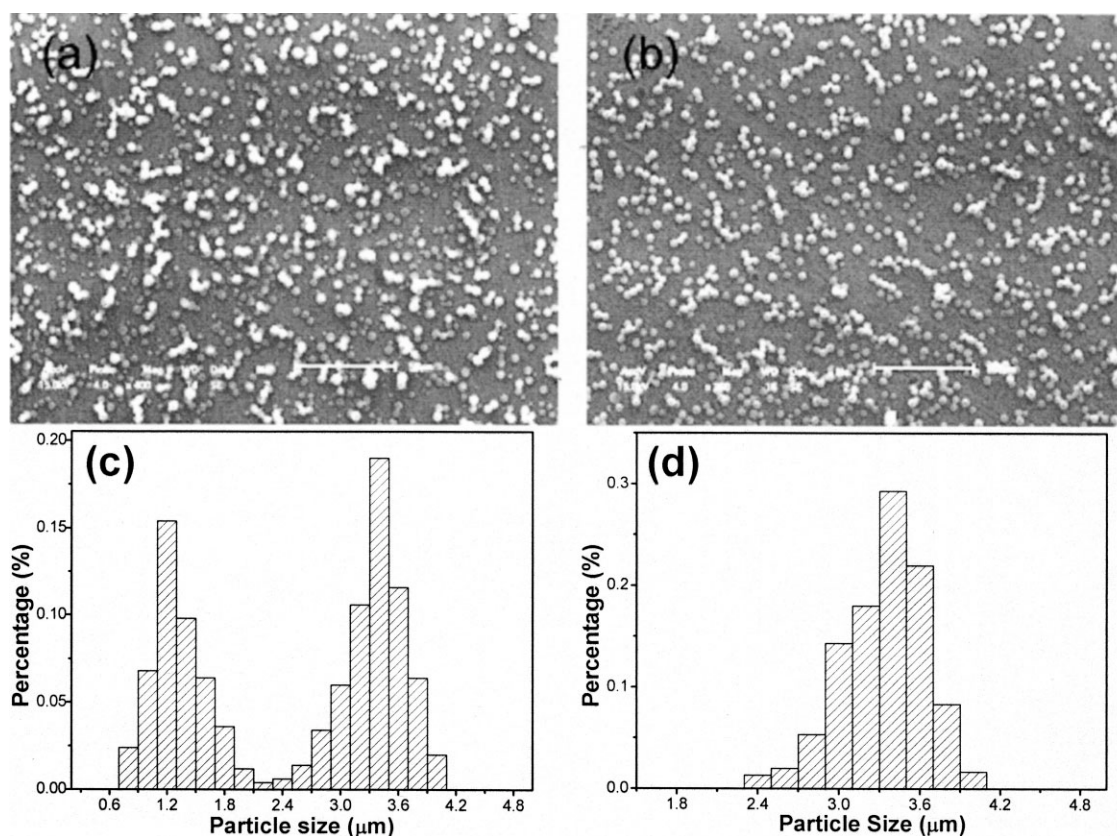
Figure 5 Scanning electron microscopy images and corresponding histograms of PLGA microparticles (a,c) before and (b,d) after size separation. The applied voltage was fixed at 10 kV, and the flow rate was 0.2 mL/h. The scale bar is 50 μm.

generally equal to one-half to one-fifth that of the primary droplets. The fission of the primary droplets produces the offspring droplets,[29,30] and their size is one-fifth smaller than that of the primary droplets. On the basis of this information, we can judge that these particles of different size distributions result from so-called satellite droplets (small size particles) and primary droplets (big size particles).[22–27]

Although PLGA microparticles of a bimodal size distribution are formed, size separation can be well performed. Tang and Gomez[22–27] observed that in a stable cone-jet mode, the spatial separation of the satellite droplets and primary droplets will occur soon after breakup by electrostatic inertia effects. That is, after the droplets disperse farther downstream, the spray can form two regions: an inner core of the primary droplets and an outer shroud of the satellite droplets (Fig. 1). On the basis of their observation, we used a steel plate with a 3-cm circular hole as a ground electrode. The distance from the capillary tip to the steel plate could be adjusted in the range of 4–6 cm so that the plate would intercept only the satellite particles. Figure 5(b,d) shows that the steel plate could effectively separate the satellite particles, leaving behind the quasi-monodisperse primary particles. Meanwhile, the electrosprayed particles intercepted on the ring shape steel plate

(ca. 50%) were also investigated. However, these particles were unavailable because a few primary particles were also intercepted and mingled with satellite particles.

Adjustment of the particle size

Experimental results show that the flow rate of the sprayed solution can control the size of the produced PLGA microparticles. We can see from Figure 6(a) that after a chloroform solution with 5 wt % PGA38k was sprayed at different flow rates, PLGA microparticles of different sizes were produced. When the solution was sprayed at a quite low flow rate (0.2 mL/h), the sprayed microparticles were 3.4 μm, and microparticles with a diameter of 12.2 μm were obtained after the flow rate went up to 3 mL/h. Anyway, the microparticle diameter increased monotonously in proportion to the flow rate. Interestingly, we find that the increase in the PLGA microparticle diameter with the flow rate obeys the following rule:

$$R \sim F^{1/2}$$

where R is the diameter of the microparticles and F is the flow rate. This result is consistent with Gañán-
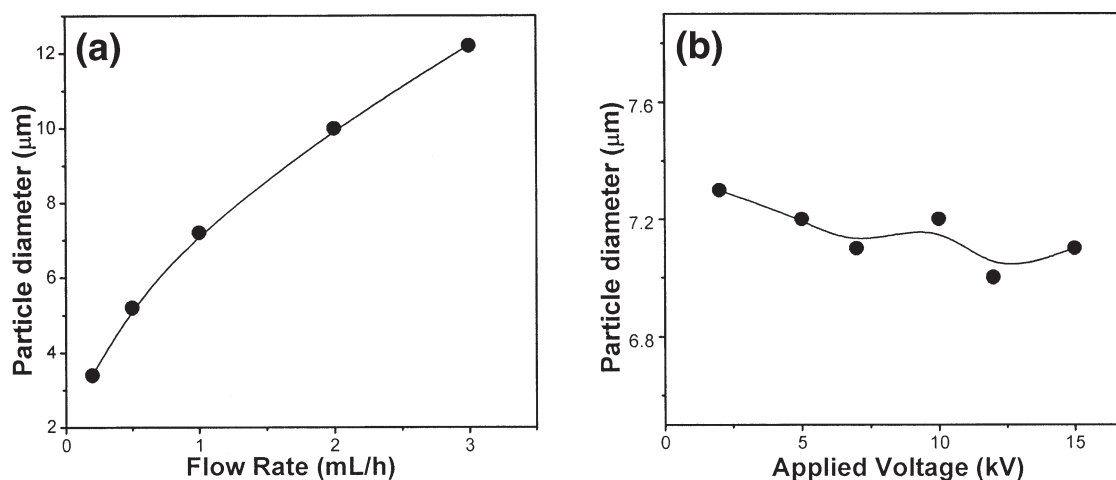
Figure 6 Changes in the microparticle diameters with (a) the flow rate of the sprayed solution (applied voltage = 10 kV) and (b) the applied voltage (flow rate = 1 mL/h).

Calvo's[31] results obtained with a volatile solvent. Our result suggests that the effect of the intermolecular entanglements of polymer chains on the diameters of the broken droplets can be ignored during jet breakup.

Within the applied voltage range that ensures a stable cone-jet mode, the effect of the applied voltage on the microparticle diameter has also been investigated, and the corresponding results are shown in Figure 4(b). We can see that the mean diameter of PLGA particles seems to not be substantially affected by the applied voltage. This result is in agreement with that of Tang and Gomez[24] and Harman et al.[27] When the applied voltage is higher than 15 kV, the whipping instability of the jet starts.

In addition, we also investigated the effects of the molecular chain length and concentration of PLGA on the microparticle diameters. The results indicate that the particle size and shape are not affected in substance by the polymer chain length [Fig. 7(a)] but increase in proportion to the PLGA concentration [Fig. 7(b)]. From these results we can speculate that at the moment of jet breakup, the concentration of PLGA in the jet is still quite dilute, and the intermolecular entanglements among the PLGA molecules are still very weak. To the end, only the droplet diameter and PLGA concentration can determine the diameter of the solidified particles.

Effect of the solvents

In the EHDA process, the physical properties of the liquid play key roles. These physical properties include the electric conductivity, surface tension,
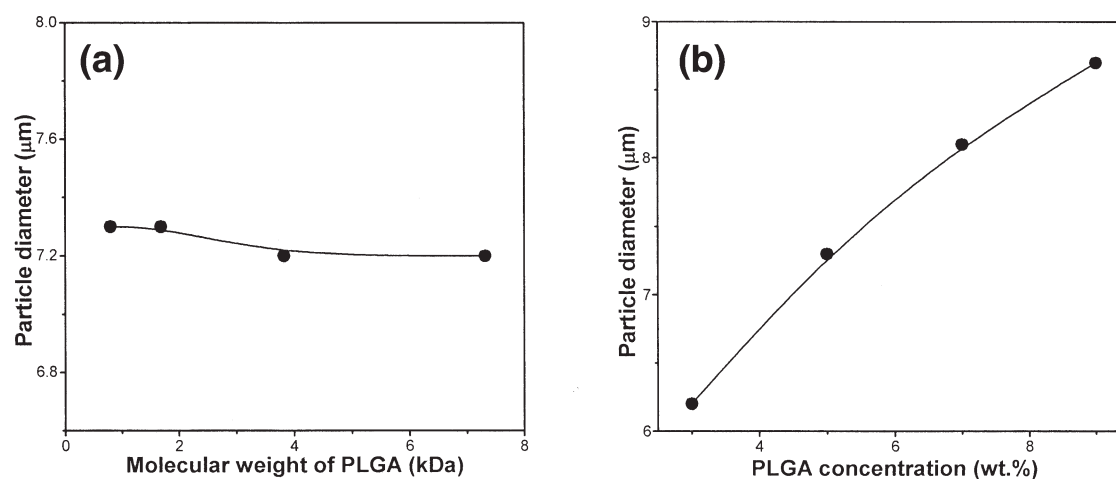
Figure 7 Effects of (a) the molecular weight of PLGA (all solutions containing 5 wt % PLGA were sprayed at 10 kV with a 1.0 mL/h flow rate) and (b) the PLGA concentration (the polymer was PLGA17k, and the polymer solution was sprayed at 10 kV with a 1.0 mL/h flow rate) on the particle size.

TABLE II
Properties of Different Solvents at the Ambient Temperature and Pressure

DMF : chloroform	Surface tension (mN/m)	Viscosity (mPa S)	Electric conductivity (μs/cm)[a]	D_m[b]	P_m (kPa)[b]
0 : 100	33.9	0.57	0.01	4.8	21.0
100 : 0	34.5	0.37	0.51	36.7	0.49
10 : 90	33.8	0.42	0.10	8.0	18.95
30 : 70	34.1	0.48	0.19	14.4	14.85

[a] The minimum measure scale in our apparatus was 0.01 μs/cm.
[b] The dielectric constant (D_m) and vapor pressure (P_m) of the DMF/chloroform mixture solvents were obtained according to the following formulas:
$D_m = D_d \times S_d$ (%) $+ D_c \times S_c$ (%).
$P_m = P_d \times S_d$ (%) $+ P_c \times S_c$ (%).
D_d: dielectric constant of DMF.
D_c: dielectric constant of chloroform.
P_d: vapor pressure of DMF.
P_c: vapor pressure of chloroform.
S_d: volume percent of DMF in solution.
S_c: volume percent of chloroform in solution.

viscosity, dielectric constant, and solvent vapor pressure. Although their effects on the behavior of EHDA have been studied widely, the studied objects are volatile liquids. Little attention has been paid to liquids containing nonvolatile polymers and especially the correlation between the morphologies and sizes of the as-sprayed polymer products and the liquid properties. Our aim in this study was to investigate the changes in electrosprayed PLGA products with the properties of the solvents.

In this work, the sprayed PLGA solutions were very dilute. This means that the solvent was the predominant ingredient, and the liquid physical properties were dominated by the solvent. For example, in the aforementioned solvent/polymer system, chloroform dominated the physical properties of the sprayed solutions. To change the properties of the sprayed solutions, another solvent, DMF, extremely different from chloroform but capable of dissolving well in PLGA and chloroform, was selected. Table II shows that DMF has higher dielectric constant and electric conductivity values but lower vapor pressure values than chloroform. A mixture of DMF with chloroform greatly changes the properties of chloroform. In an experiment, 5 wt % PLGA38k solutions in which the DMF/chloroform solvent concentration was changed from 0 to 30% were electrosprayed at different flow rates ranging from 1.0 to 0.2 mL/h. Figure 8(a,d,g) shows that when no DMF is added, quasi-monodisperse PLGA microparticles can be obtained with the modified EHDA process. However, the addition of DMF drastically changes the EHDA process and the electrosprayed PLGA products. We observed that when the solutions contained 10% DMF, the electrosprayed process was extremely unstable, and this resulted in the formed jet

swinging in the electric field. Sometimes, the multijet even emerged. The cone-jet model cannot be controlled, and the modified EHDA process is also not suitable for monodisperse particle preparation. This conclusion is further proven by the electrosprayed results, as can be seen in Figure 8. In electrosprayed products from a solution with 10% DMF [Fig. 8(b,e,h)], we can see that the particles are polydisperse despite the use of the filter steel plate. In comparison with the previous particles with a bimodal size, these particles do not show any statistical size distribution rule. At the same time, these as-sprayed particles also have a far smaller diameter than those electrosprayed from the pure chloroform solution. For example, different PLGA solutions were electrosprayed at 0.2 mL/h, and the diameters of the PLGA particles decreased greatly with an increase in the DMF ratios from 0 to 10 to 30% [Fig. 8(g,h,i)]. These results suggest that coulombic fission occurs during the EHDA process. That is, following the evaporation of the solvent, the droplets start to shrink, and the charges at the surface of the droplets get closer. When the coulombic repulsion exceeds the surface tension, the droplets explode in a jet-fission mode, thereby producing a set of small progeny particles and some residue particles from each primary particle. In addition, from Figure 8 we can see that after the increase in the DMF ratio and the solution flow rate, adherence of the electrosprayed particles occurs [Fig. 8(b,f)]; even polymer stains are produced when a solution with 50% DMF is electrosprayed at a flow rate of 1.0 mL/h [Fig. 8(c)].

These electrospraying results in essence can be attributed to the addition of DMF, which greatly enhances the electric conductivity and dielectric
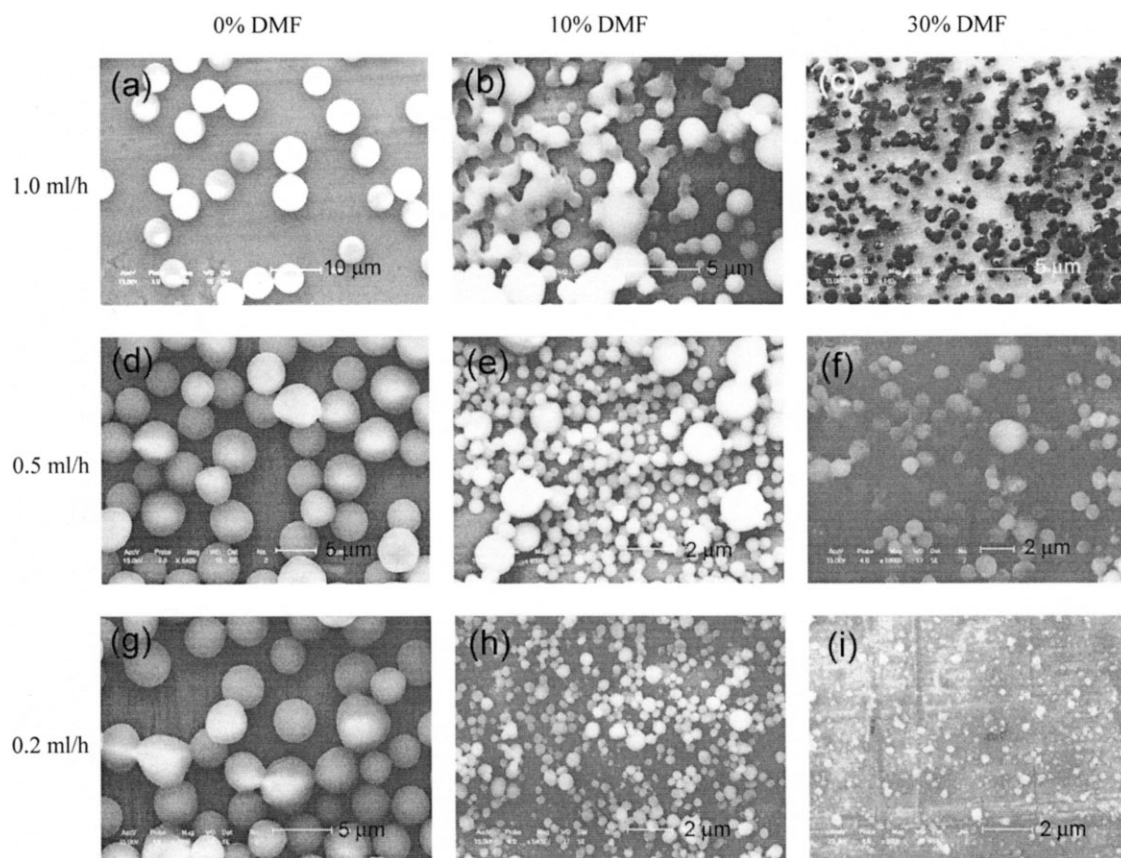
Figure 8 Scanning electron microscopy images of PLGA38k products electrosprayed from 5 wt % PLGA solutions with different DMF/chloroform ratios (0, 10, or 30%) at different liquid flow rate (1.0, 0.5, or 0.2 mL/h). The applied voltage was fixed at 10 kV.

constant of the sprayed solutions and lowers their solvent vapor pressure (Table II). The high electric conductivity and dielectric constant trigger jet whipping instability and endow the liquid jet with more surface charge, which accelerates the jet thinning. On the other hand, because of the decrease in the solvent vapor pressure, the thinning time of the jet is prolonged. As a result, the cone-jet model and jet stability cannot be controlled, and at the same time, smaller droplets are produced. In the pure chloroform solution, the solvent in general will evaporate rapidly to solidify droplets after the jet breaks up into droplets. In this process, the rapid solidification of droplets increases the force of intermolecular entanglement, which impedes the droplet fission. However, the increase in the droplet surface charge and the decrease in the liquid vapor pressure weaken the force of PLGA intermolecular entanglement. During droplet shrinking, the coulombic repulsion will exceed the droplet surface tension. Finally, the droplets explode to produce many small offspring particles. These results suggest that the use of solvents with high conductivity, a high dielectric constant, and a low vapor pressure is undesirable

for controlling the EHDA process to electrospray monodisperse particles.

CONCLUSIONS

The results of our studies have demonstrated that the concentration and molecular weight of PLGA are requirements for electrospraying spherical particles. PLGA molecules with a relatively low molecular weight have a wider concentration range for producing spherical PLGA particles than high-molecular-weight PLGA. Under the conditions of electrospraying spherical particles, the diameter of PLGA particles is affected largely by the liquid flow rates and the PLGA concentration but is not substantially affected by the applied potential and molecular weight of PLGA. The solvent properties also play important roles in determining the fate of as-sprayed PLGA products. A stable EHDA process, that is, the so-called cone-jet mode, can be established only with low electric conductivity, a low dielectric constant, and a high vapor pressure of a solvent such as chloroform, and subsequently, quasi-monodisperse particles can be obtained with a modified EHDA

process. The addition of a solvent with the opposite solvent properties destroys EHDA stability and produces smaller and polydisperse particles. In summary, this work provides a simple technique and relatively systematic results with respect to the fabrication of biocompatible and biodegradable polymer particles.

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