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PLGA Micro-spheres

Formulation and size-tuning using the NanoAssemblr® Benchtop

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Abstract

In recent years, several methods have been developed for the production of microspheres composed of hydrophobic, biodegradable and biocompatible polymers for use as drug delivery vehicles for numerous therapeutic applications. However, these methods pose challenges in achieving target particle size and quality, maintaining batch-to-batch reproducibility, and process optimization for scale-up. The NanoAssemblr® platform is an automated microfluidics-based system that eliminates user variability and enables reproducible and scalable manufacture of nanoparticles and microspheres. Here, we report the use of the NanoAssemblr Benchtop to produce microspheres composed of poly(lactic-co-glycolic acid) (PLGA). This was achieved by controlling for formulation parameters and instrument parameters on the NanoAssemblr Benchtop. Using a partially water-miscible organic solvent, PLGA microspheres were manufactured at various sizes ranging 1 – 5 µm with a low span (narrow size distribution). In general, increasing the Total Flow Rate (TFR) led to a decrease in the size of PLGA microspheres. Modifying the aqueous to organic Flow Rate Ratio (FRR), on the other hand, did not influence microsphere size. Scanning electron microscopy (SEM) indicated a highly uniform and spherical morphology. Thus, we have successfully demonstrated the utility of the NanoAssemblr platform as a tool in the development of PLGA microspheres. These results also serve as guidelines for the manufacture of microspheres of alternative compositions.

Introduction

Over the last few decades, polymer microspheres consisting of biodegradable and biocompatible polymers such as PLGA have become increasingly attractive as drug delivery vehicles for a variety of active pharmaceutical ingredients (APIs) such as small molecules, peptides, proteins, and nucleic acids[1-3]. This interest has led to greater than 12 FDA-approved drugs with PLGA microspheres that are used to treat a range of indications including prostate cancer, type 2 diabetes, schizophrenia and alcohol dependence[2-3]. In addition, there is significant potential to use PLGA microspheres to develop vaccines against different pathogens such as hepatitis B, tuberculosis and malaria[4-5]. In many of these applications, the PLGA microspheres are administered by subcutaneous or intramuscular injection to create a localized depot of drug at the target site. It is important that the microspheres are of a sufficient size, usually on the microscale to form the depot and avoid migration to non-target tissue. In general, microsphere size is a critical attribute that impacts biodistribution, cellular interaction and API loading and release[4,6]. The use of biodegradable PLGA to form the microspheres allows for fine-tuning the degradation profile for long-term sustained release of the API at the target site thereby reducing administration frequency and improving patient compliance. Release of the API from the microspheres occurs over a long period of time through diffusion and hydrolysis and biodegradation of the polymer matrix[7,8].

There are several techniques reported for the manufacture of PLGA microspheres[6–10]. The single-emulsion technique is the most common method to produce PLGA microspheres loaded with a hydrophobic small-molecule API: Emulsification of a water-immiscible organic phase containing dissolved PLGA and drug with an aqueous phase containing stabilizer is achieved using sonication or high-shear mixing. This produces oil droplets which are heterogenous in size and so pressurization across an extrusion membrane is often implemented during or after the mixing step. Next, the PLGA microspheres are solidified by extraction of the organic solvent and isolated by filtration or spray-drying. The double-emulsion technique is a variation of this method used to encapsulate hydrophilic APIs[6]. The nanoprecipitation technique is an alternative method whereby PLGA is precipitated from a water-miscible organic solvent by bulk mixing with a large excess of an aqueous non-solvent[11].

These existing techniques have numerous drawbacks as they involve many time-consuming process steps and substantial operator intervention. In addition, it is difficult to generate microspheres of desirable size and quality, there is poor batch-to-batch reproducibility, and process scale-up is a substantial effort. Despite the fact that there are a large number of PLGA microspheres approved for clinical use, these challenges have limited their potential clinical impact. For example, it has been reported that a major impediment to development of generic drugs as competition to approved PLGA microspheres has been manufacturing complexity[2]. In addition, the discontinuation of the PLGA microsphere Nutropin Depot® by Genentech-Alkermes was due to high manufacturing costs[12]. Therefore, there remains an important need to improve the manufacture of PLGA microspheres.

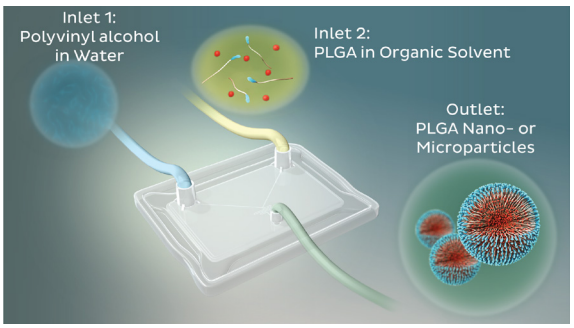

Figure 1: Microfluidic mixing for microsphere production. *NanoAssemblr technology enables rapid, time-invariant mixing of two liquids. A polar aqueous phase containing the stabilizer polyvinyl alcohol is mixed with polymer dissolved in ethyl acetate. Parameters such as Flow Rate Ratio (FRR) and Total Flow Rate (TFR) can be varied to dictate the size of the microspheres. The same microfluidic mixing technique has previously been used to generate PLGA nanoparticles using a fully miscible organic solvent.*

The NanoAssemblr microfluidic mixing technique has been demonstrated to produce a wide-range of liposomes, lipid nanoparticles and polymer nanoparticles with fine control over particle size and other quality attributes[13–19]. In addition, the technique is fast and easy to perform, it offers a high level of batch-to-batch reproducibility and it is inherently scalable. These benefits are achieved through precise time-invariant mixing of two solvent streams within a carefully engineered microfluidic channel (***Figure 1***). For example, we have previously reported on the use of the NanoAssemblr platform to reproducibly manufacture PLGA nanoparticles via nanoprecipitation with sizes ranging from 75 – 200 nm and a polydispersity index (PDI) of ~ 0.2 at volumes ranging from 2 – 280 mL[13–16, 20]. A water-miscible organic solvent with PLGA was combined with an aqueous solution containing stabilizer in the microfluidic mixer to form the PLGA nanoparticles. Fine size-tuning and low PDI was possible by controlling the rate of nanoprecipitation with different microfluidic mixing parameters.

In the current work, we were motivated to develop a substantially improved method for the production of PLGA microspheres that would address the need in the field. We demonstrate the use of the NanoAssemblr platform to produce PLGA microspheres by adaptation of the technique originally developed for PLGA nanoparticles. The influence of microfluidic mixing parameters such as Total Flow Rate (TFR) and Flow Rate Ratio (FRR) on the manufacture of microspheres was investigated by measuring particle size and span as critical attributes of particle quality. Scanning electron microscopy (SEM) was used to study the particle morphology and particle quality attributes.

The results clearly demonstrate the generation of high-quality PLGA microspheres that are tunable in size and are nearly monodisperse. This new method has all the advantages of the NanoAssemblr microfluidic mixing technology and overcomes many current challenges in PLGA microsphere manufacture.

Results

Previously, we have shown that for microfluidic mixing of PLGA in a water-miscible solvent, with water as an anti-solvent for PLGA, nanoparticles in the size range of 75 – 200 nm can be produced with a narrow PDI. The effect of various parameters such as FRR and TFR on the size and PDI of PLGA nanoparticles was studied systematically using the NanoAssemblr Benchtop[14–16], and the following trends were noted i) increasing the aqueous to organic FRR resulted in an increase in the particle size, and ii) increasing the TFR resulted in a decrease in the particle size. For a given set of operating parameters, microfluidic-assisted nanoprecipitation of PLGA was found to be highly robust, operator independent, and scalable[14–16].

To adapt this process to make larger microspheres, the solvent was changed from acetonitrile, which is completely water-miscible, to ethyl acetate which is partially water-miscible. Additionally, the concentration of the stabilizer (polyvinyl alcohol, PVA) was lowered from 2% to 0.1%. We have also used a high concentration of the polymer to favor the microsphere production. The effect of various parameters such as FRR and TFR on the size and span of PLGA microspheres was studied systematically using the laser-diffraction technique. We have also explored the process and user variability by testing three different formulation runs at fixed operating parameters and examined particle morphology by scanning electron microscopy (SEM).

THE EFFECT OF FLOW RATE RATIO

FRR is the ratio between the flow rates of the aqueous phase and the organic phase. For any period of time, it also represents the volume ratio at which the two phases are mixed. There were no significant differences between the mean sizes of microspheres (~ 2.3 µm) produced at three different FRRs (2:1, 4:1 and 6:1) at a fixed PLGA concentration of 50 mg/mL (5% w/v). This is different than the trend previously observed for PLGA nanoparticles. The key results are summarized in ***Figure 2***.

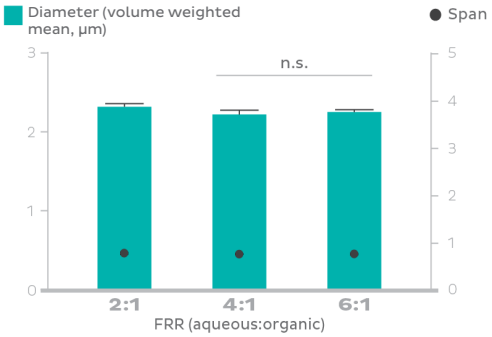

Figure 2: Increasing the aqueous to organic flow rate ratio does not affect microsphere size. *The microspheres were produced at three different FRRs (2:1, 4:1 and 6:1) at a fixed PLGA concentration of 50 mg/mL (5% w/v). Data points are the mean ± SD for 3 independent size/span measurements by laser-diffraction on 3 independent samples (n = 3). The horizontal bar indicates diameters that were not significantly different (P>0.05) by ANOVA followed by Tukey's multiple comparison test.*

Polymer	PLGA (50:50) ester term. 70-90 kDa
Aqueous Phase	0.1% w/v PVA in deionized water
Organic Phase	50 mg/mL polymer in ethyl acetate
Total Flow Rate (TFR)	12 mL/min
Flow Rate Ratio	As labeled (Aq:Or)

EFFECT OF TOTAL FLOW RATE

The TFR in mL/min dictates the mixing time and is the combined speed at which the two fluids are pumped through the NanoAssemblr microfluidic channels. Increasing TFR increases the mixing speed of the aqueous and organic phases and leads to smaller particles. For production of microspheres, the range of 8 – 20 mL/min was explored at a fixed PLGA concentration of 50 mg/mL (5% w/v). We were able to tune the size of the microspheres from ~5 - 1.5 µm particles by increasing the TFR from 8 – 16 mL/min. Further size tuning to ~ 1 µm was observed by increasing the TFR to 20 mL/min (data not shown). These results are consistent with the trend observed for production of PLGA nanoparticles, whereby increasing TFR results in smaller particles. The key results are summarized in ***Figure 3***.

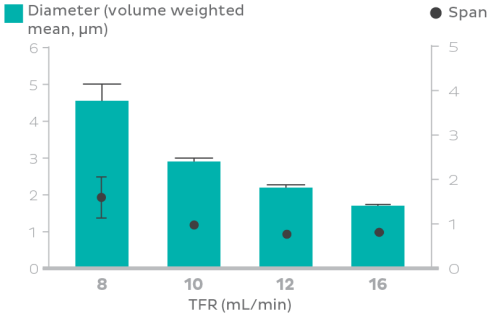

Figure 3: Increasing the Total Flow Rate decreases microsphere size. *The microspheres were produced at three different TFR (8, 10 and 12 mL/min) at a fixed PLGA concentration of 50 mg/mL (5% w/v). Data points are the mean ± SD for 3 independent size/span measurements by laser-diffraction on 3 independent samples (n = 3).*

Polymer	PLGA (50:50) ester term. 70-90 kDa
Aqueous Phase	0.1% w/v PVA in deionized water
Organic Phase	50 mg/mL polymer in ethyl acetate
Total Flow Rate (TFR)	As labeled
Flow Rate Ratio	2:1 (Aq:Or)

OPERATOR INDEPENDENCE

Operator independence was verified by producing PLGA microspheres using the NanoAssemblr Benchtop with a fixed set of operating parameters. Three different users manufactured the PLGA microspheres at an aqueous to organic FRR of 2:1 and a TFR of 12 mL/min at a fixed PLGA concentration of 50 mg/mL (5% w/v). The different users were able to reproduce particles with equivalent size and span, showing the robustness and reproducibility of the production method. The data is illustrated in ***Figure 4***.

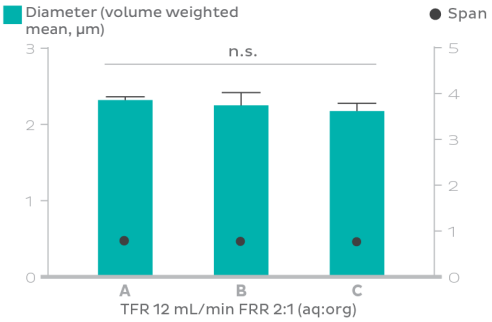

Figure 4: Microfluidic mixing is operator independent. *The microspheres were produced by 3 different users, over 3 different days using different stocks at a FRR of 2:1, a TFR of 12 mL/min, and at a fixed PLGA concentration of 50 mg/mL (5% w/v). Data points are the mean ± SD for 3 independent size/span measurements by laser-diffraction. The horizontal bar indicates diameters were not significantly different (P>0.05) by ANOVA.*

Polymer	PLGA (50:50) ester term. 70-90 kDa
Aqueous Phase	0.1% w/v PVA in deionized water
Organic Phase	50 mg/mL polymer in ethyl acetate
Total Flow Rate (TFR)	12 mL/ min
Flow Rate Ratio	2:1 (Aq:Or)

PARTICLE MORPHOLOGY

To augment the size and size distribution measurements obtained using laser-diffraction, select samples of microspheres were further characterized by scanning electron microscopy (SEM). The microspheres exhibited a highly spherical shape and a homogenous surface morphology. The size of the microspheres by SEM were also in agreement with the laser-diffraction measurements. The key results are summarized in ***Figure 5***.

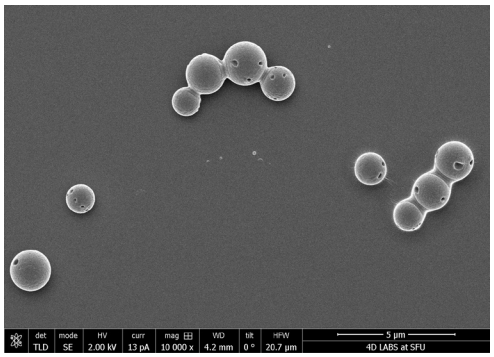

Figure 5: Scanning electron micrographs of PLGA microspheres. *Representative SEM image of PLGA microspheres produced with a FRR of 2:1, a TFR of 20 mL/min and a PLGA concentration of 50 mg/mL (5% w/v). The microspheres exhibit spherical shape with sizes between 1.2 - 1.9 µm. Scale Bar = 5 µm. All samples were washed 3x by centrifugation and resuspended in deionized water, dispersed on a Si chip, allowed to dry, and sputter coated with 5 nm Iridium. This image has previously been published[20].*

Polymer	PLGA (50:50) ester-term. 70-100 kDa
Aqueous Phase	0.1% w/v PVA in deionized water
Organic Phase	50 mg/mL polymer in ethyl acetate
Total Flow Rate (TFR)	20 mL/ min
Flow Rate Ratio	2:1 (Aq:Or)

Discussion

There has been an increasing interest in particulate systems comprised of FDA-approved polymers such as PLGA for wide range of biomedical and pharmaceutical applications. PLGA microspheres enable entrapment and delivery of several diagnostic and therapeutic small molecules, peptides, proteins and nucleic acids. Emulsion or nanoprecipitation methods can be employed to generate microspheres. However, these bulk methods are not reliable and suffer from poor reproducibility, and they are difficult to scale for manufacturing. Also, these techniques fail to produce well-defined microspheres with narrow size distribution. When considering the nanoprecipitation reaction, factors such as polymer solubility, polymer concentration, viscosity of the medium, choice of stabilizer/surfactant, concentration of surfactant, and choice of dispersing solvent play crucial role in the rate of solidification of a given polymer and the final size characteristics. For example, increasing the concentration of PLGA in the organic phase, and having a low surfactant concentration typically results in faster solidification and larger particles.

In this work, some of these key variables were used to optimize the development of nearly monodisperse microspheres of PLGA on the NanoAssembler Benchtop. This was achieved by controlled microfluidic mixing of PLGA in ethyl acetate with an aqueous solution of 0.1% PVA. Ethyl acetate is a partially water-miscible solvent. During fast, highly-controlled NanoAssemblr mixing conditions, the PLGA solubility rapidly decreases, resulting in larger microspheres which have low polydispersity. By increasing the TFR, the size of the PLGA microspheres could be fine-tuned to smaller particles. We have observed an additional subset of sub-micron sized particles at a TFR of 20 mL/min (data not shown). This indicates there may be a specific window of TFR required to get well-defined monodisperse microspheres. Increasing the TFR increases the mixing speed of the aqueous and organic phases. This increase in mixing speed typically results in smaller particles and has been observed for multiple different nanoparticles and microparticles[13-20]. Interestingly, we have seen that the change in the volume ratios of water to ethyl acetate via the FRR does not affect size. This could provide an opportunity to produce microspheres at higher concentrations without affecting the critical quality attributes. This is a particular benefit at large manufacturing scales where maximizing production yield and reducing batch size are important.

We have recently reported on the production of PLGA microspheres using PLGA from an alternative supplier and a different sizing measurement. The PLGA was ester terminated 50:50 PLGA from PCAS (Longjumeau, France) and the particles were characterized using dynamic light scattering (DLS, Malvern NanoZS). In the current work, we have focused on optimizing the PLGA microsphere production and size characterization using laser-diffraction (Malvern Mastersizer) which is better-suited for measuring particles in the micron range. In both of these studies, the polymer composition was the same, but was obtained from two different vendors. Although a direct comparison of experimental conditions across the studies was not possible (due to the polymer batch/vendor differences and due to the measurement technique difference), the findings were consistent. This is another clear indicator of the robustness of this new technique for PLGA microsphere production.

Conclusions

We have demonstrated the production of PLGA microspheres using NanoAssemblr technology. This work also highlights how the microfluidic nanoprecipitation technique using the NanoAssemblr platform is easily adaptable for production of nearly monodisperse nanoparticles as well as microspheres of customizable sizes. The microfluidic-based mixing was able to reproducibly formulate PLGA microspheres with sizes ranging from 1 – 5 µm with low spans. The size of the PLGA microspheres was tunable by varying the Total Flow Rate. We have also shown robust production that is operator independent. These results provide general guidelines for the production of microspheres using different polymer systems. The NanoAssemblr Benchtop can be used to enable rapid optimization of formulations with specific characteristics such as optimal drug release. Hence, the NanoAssemblr platform is an attractive solution for accelerating the development and large-scale manufacturing of polymer-based microspheres for the controlled delivery of active pharmaceutical ingredients.

Materials & Methods

MATERIALS

Ester-terminated PLGA (50:50 Poly (DL-lactide-co-glycolide, molecular weight 70,000 - 90,000, 0.55 - 0.75 dL/g) was obtained from LACTEL Absorbable Polymers, AL, USA. Poly(vinyl alcohol) (PVA) (molecular weight ~31,000, 87-89 mol% hydrolyzed) and ethyl acetate were obtained from Sigma-Aldrich, USA (St Louis, MO).

MICROSPHERE PREPARATION

PLGA microspheres were prepared using the NanoAssemblr Benchtop. PLGA polymer dissolved in organic solvent ethyl acetate at 5% w/v was rapidly mixed with an aqueous phase containing 0.1% w/v PVA as a stabilizer. Flow Rate Ratios (FRR) and Total Flow Rate (TFR) were varied to manufacture microspheres at various process conditions. Detailed formulation conditions are given in a table format accompanying the figures. The initial and final waste volumes were set at 0.25 and 0.05 mL, respectively. Formulation volume was 2 mL. Post cartridge sample was collected in a 15 mL sample collection tube containing 6 mL of de-ionized water (4 times dilution). Samples were then dialyzed against 1 L deionized water using a dialysis bag (MWCO – 12-14 kDa) for 24 h replacing the dialysis medium twice in the first 4 h.

PARTICLE SIZE MEASUREMENTS

Microspheres were characterized for their hydrodynamic size and size distribution. Measurements were taken using a laser-diffraction particle size analyzer (Mastersizer Hydro 2000SM, Malvern, UK) at 25 °C with Milli-Q water as the dispersant. The Mastersizer works on the principle of Mie scattering of laser light by the particles in solution. Microspheres were first diluted to get an obscuration value in the right range. Briefly, 0.5 – 1 mL of the formulation was added to a 120 mL sample chamber containing deionized water with 2 drops of 2% Tween 20. An obscuration percentage in the range of 5-15% was used for collecting the data. Volume weighted mean value (D[4,3]) is considered as the hydrodynamic diameter, and the width of the distribution is expressed as span. Span of the distribution is defined as (d0.9-d0.1)/d0.5, where d0.9, d0.5, d0.1 are the volume weighted sizes below the 90, 50, and 10th percentile of the particle population, respectively.

SCANNING ELECTRON MICROSCOPY

The size and morphology of the microspheres was characterization by scanning electron microscopy (SEM). Dialyzed samples were centrifuged (3000 x g, 10 min), the supernatant was removed, and the pellet was resuspended in deionized water. This was repeated for a total of 3 washes. Then, 2 µL of a 1 mg/mL solution was dispersed on a silicon chip (University Wafer, 2", (100), PRIME), and allowed to dry under fume-hood for 30 minutes. The dried sample was then coated with 5 nm Iridium for improving conductivity using a Leica EM ACE600 sputter coater. SEM analysis of the resultant sample was performed using a FEI Helios NanoLab 650 SEM/FIB system. The electron beam conditions were 13 pA at 2 keV.

STATISTICAL ANALYSIS

All samples were prepared in triplicate (n=3). Size measurements were performed 3 times for each sample. Statistics were determined using Graph Pad Prism software. Horizontal bar indicates data were not significantly different ($p > 0.05$) by one-way ANOVA followed by Tukey's post-hoc test where indicated.

Related Material

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