A Simple Confined Impingement Jets Mixer for Flash Nanoprecipitation

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ABSTRACT: Johnson and Prud’homme (2003. AICHE J 49:2264–2282) introduced the confined impingement jets (CIJ) mixer to prepare nanoparticles loaded with hydrophobic compounds (e.g., drugs, inks, fragrances, or pheromones) via flash nanoprecipitation (FNP). We have modified the original CIJ design to allow hand operation, eliminating the need for a syringe pump, and we added a second antisolvent dilution stage. Impingement mixing requires equal flow momentum from two opposing jets, one containing the drug in organic solvent and the other containing an antisolvent, typically water. The subsequent dilution step in the new design allows rapid quenching with high antisolvent concentration that enhances nanoparticle stability. This new CIJ with dilution (CIJ-D) mixer is a simple, cheap, and efficient device to produce nanoparticles. We have made 55 nm diameter β-carotene nanoparticles using the CIJ-D mixer. They are stable and reproducible in terms of particle size and distribution. We have also compared the performance of our CIJ-D mixer with the vortex mixer, which can operate at unequal flow rates (Liu et al., 2008. Chem Eng Sci 63:2829–2842), to make β-carotene-containing particles over a series of turbulent conditions. On the basis of dynamic light scattering measurements, the new CIJ-D mixer produces stable particles of a size similar to the vortex mixer. Our CIJ-D design requires less volume and provides an easily operated and inexpensive tool to produce nanoparticles via FNP and to evaluate new nanoparticle formulation. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:4018–4023, 2012

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INTRODUCTION

Nanoparticles have recently received enormous attention as a drug delivery tool.1–5 Flash nanoprecipitation (FNP) is a simple technique that is used to prepare polymeric nanoparticles with a high loading of hydrophobic compounds, including drugs.6–8 As shown in Figure 1,9 a hydrophobic drug and an amphiphilic block copolymer [e.g., polyethylene glycol-b-polyactic acid (PEG-b-PLA)] are codissolved in a water-miscible organic solvent [e.g., tetrahydrofuran (THF)], which is then impinged at high velocity against an antisolvent (water) to create turbulent mixing and high supersaturation. The supersaturation promotes coprecipitation of the hydrophobic drug and the hydrophobic block of the copolymer to form nanoparticles.10–13 Mixing and precipitation occur within milliseconds inside the small internal mixing chamber.

Johnson and Prud’homme6 first described FNP using a confined impingement jets (CIJ) mixer. In this design, a syringe pump was used to drive two opposing liquid streams (a and b in Fig. 1) at high velocity into the mixing chamber. Prud’homme and others6,7,14–17,33 have used this device to successfully make a variety of nanoparticles. The CIJ design was inspired by the simple T mixer that is commonly used to mix liquids or act as a chemical reactor.18,19 T mixers have also been used to mix monomers and oligomers for reaction injection molding.20–23

To avoid reducing the mixing efficiency (via one stream backing up the other), the two streams in
the CIJ mixer must operate at near equal moment-um. In practice, this requires approximately a 1:1 volume flow rate, limiting the highest achievable supersaturation level. To operate at unequal flow ratios, Prud’homme and coworkers developed a multi-inlet vortex mixer. In this design, the mixing chamber is connected to four inlets and the liquid streams meet at an angle as opposed to the head-on impinge-ment that is characteristic of the CIJ mixer. The vortex mixer can be applied to a wide range of solvent ratios and materials. However, the device is time con-suming to clean, and digitally programmed syringe pumps are usually required to control the inlet flow rates. In terms of operation, cleaning, and cost, the CIJ mixer is preferred. Nevertheless, the vortex mixer is able to achieve higher levels of supersaturation.

Here, we report a modified CIJ design, the CIJ with dilution (CIJ-D) mixer, that is simpler than the original Johnson and Prud’homme design, yet overcomes the limitation of 1:1 solvent ratio. To emphasize its simpler design and easier handling with equivalent function, we have compared the average size of β-carotene nanoparticles made using our CIJ-D mixer versus the vortex mixer.

DESIGN

Figure 2 shows the CIJ-D design. Two features distinguish it from the original CIJ mixer: hand operation and an antisolvent dilution stage. By using relatively small, low-friction syringes, turbulent flow can be achieved with simple, rapid hand motion, eliminating the need for syringe pumps. The small sample size and easy operation made the CIJ-D ideal for screening candidate formulations. A metal plate connects the two syringes to ensure simultaneous actuation. To increase the supersaturation, the outlet stream from the CIJ-D chamber immediately flows directly into a large volume of water.

The design dimensions for the CIJ mixing cham-

ber was recommended by Johnson and Prud’homme.

Two pathways lead to a small chamber with a con-

fined volume, where the organic solvent and water im-
pinge to create turbulence. A ratio of entrance channel length to diameter ($L/d_d$) = 6.1 was used to insure stable jets. The ratio of chamber height above the inlet nozzle to diameter is $H = 0.8D$, and the length to diameter ratio $H + Z = 2.0D$ was held constant to maintain geometric similarity upon scale-up. The chamber volume is 25 $\mu$L. The outlet tube runner length should be at least 10 times the outlet diameter $K/\delta > 10$, to create a pressure drop and to ensure that the chamber is filled with liquid during impingement.

Figure 3 shows the dimensions of our CIJ-D cham-

ber. The main body of the CIJ mixer was made of high-density polyethylene, with two inlets and adapters (IDEX Health & Science, P604, Middleboro, Massachusetts) fitted with threaded syringes, and one outlet adapter (IDEX Health & Science, P205-X). Two additional side openings resulted when horizontal jet pathways were drilled during manufacturing. These ports are sealed with threaded plugs (IDEX Health & Science, P203-X) during FNP experiments, but can be opened for thorough cleaning.

A typical procedure for making nanoparticles is as follows. β-Carotene was used as the generic hydrophobic molecule ($\log P = 15.5$, ACD model from www.emolecules.com). PEG-b-PLA (molecular weight: 5000-b-10,000 Da) was used as the
amphiphilic block copolymer. Twenty-five milligrams $\beta$-carotene and 25 mg PEG-\textit{b}-PLA were dissolved in 2.5 mL of THF and transferred to a 3 mL plastic syringe (Kendall, Tyco Healthcare, Mansfield, Massachusetts). Deionized water (2.5 mL) was loaded in a second 3 mL plastic syringe. A metal plate was placed on the top of the syringes to ensure simultaneous actuation, which occurred over a period of approximately 5 s. The comixed stream was immediately diluted into a bottom reservoir preloaded with 45 mL of deionized water. The final composition of the 50 mL dispersion was THF/H$_2$O = 5:95, containing 0.1 wt % of nanoparticles. Mass-average particle size and size distribution was determined by dynamic light scattering (DLS) (ZetaPALS, Brookhaven Instruments, Holtsville, New York; diode laser BI-DPSS wavelength of 659 nm, round cuvette) using regularized positive exponential sum (REPES) method, immediately after nanoparticles were prepared following the procedure of Zhu. The light intensity correlation function was collected at 25°C and a scattering angle of 90°.

**PERFORMANCE**

To test the CIJ-D mixer, nanoparticles were prepared following the typical procedure given above. DLS gave mass-average diameter of 38 nm with polydispersity of 1.6 and standard deviation of 6 nm for three measurements on three separately mixed samples. The particles were stable for several weeks. In other block copolymer and model drug studies, we have also used PEG-\textit{b}-PLA and PEG-\textit{b}-poly(lactic-co-glycolic acid) with a series of molecular weight (5000-\textit{b}-10,000 Da, 5000-\textit{b}-15000 Da, etc.) to make nanoparticles loaded with $\beta$-carotene. Zhu used hydrocortisone, paclitaxel, betulin, and their derivatives to test the capability of the CIJ-D mixer for preparing polymeric nanoparticles. Chow et al. assessed the CIJ-D mixer by making curcumin nanoparticles. Prud’homme and coworkers have used the CIJ-D mixer making polystyrene nanoparticles. They were successfully produced, reproducible in terms of size.

As mentioned above, the dilution stage allows high supersaturation while maintaining the 1:1 flow ratio of the impinging streams. In order to demonstrate the importance of the dilution stage, four groups of particles were made following the procedure described in the section Design but with differing dilution. For this study, we used pure $\beta$-carotene (no block copolymer) to make particles. These particles show good short-term ($\sim$4 h) stability because of the slightly negative surface charge as judged by zeta potential measurements.

In group 1, nanoparticles were made following the recommended procedure, immediate dilution into 45 mL water, THF/H$_2$O = 0.05. The resulting mass-average size was 55 nm. In group 2, nanoparticles were made without dilution. They were unstable, and aggregated to micron size in seconds. In group 3, dilution was delayed from $\sim$10 ms (residence time in the mixer and outlet tube) to 5 s. This also resulted in unstable microparticles (>$1\mu$m). In group 4, nanoparticles were made with immediate (10 ms) water dilution but less than 45 mL (e.g., 5, 10, and 25 mL or THF/H$_2$O = 0.33, 0.20, and 0.091). The particle sizes from group 4 are shown in Figure 4. None of them produced 55 nm nanoparticles, in contrast to the usual dilution, THF/H$_2$O = 0.05. Instead, all were much bigger, approximately 1400, 200, and 167 nm, respectively and eventually unstable. These experiments show that immediate dilution with a significant amount of water is indispensable to produce small and stable nanoparticles.

We also compared the sizes of these pure $\beta$-carotene nanoparticles made by the CIJ-D mixer to those made by a vortex mixer. Particle size was varied by varying...
the flow rate, $Q$. This was accomplished simply by changing hand velocity during mixing. Mixer efficiency is typically correlated with Reynolds number ($Re$), the ratio of inertial force to viscous force. The $Re$ was calculated by:

$$Re = \frac{\text{Inertial force} = \rho V^2}{\text{Viscous force} = \mu V/d} = \frac{\rho V d}{\mu} = \frac{\rho Q c}{\mu A}$$

where $\rho$ is the density of the fluid (kg/m$^3$); $V$ is the mean fluid velocity (s); $d$ is the stream inlet diameter; $\mu$ is the viscosity of the fluid (kg/m s); and $A$ is the pipe cross-sectional area (m$^2$), which in our case was the same for all inlets of a given mixer; and $Q_i$ is the volumetric flow rate (m$^3$/s) of the $i$th inlet stream.

For example, in CIJ mixing, $n = 2$ for two streams, $\rho$ is $1.0 \times 10^3$ kg m$^{-3}$ for H$_2$O or $8.89 \times 10^2$ kg m$^{-3}$ for THF at room temperature, $\mu$ is $1.0 \times 10^{-3}$ Pa s at room temperature for H$_2$O or $4.8 \times 10^{-4}$ Pa s for THF, and $d$ is $5 \times 10^{-4}$ m for the CIJ-D mixer.

The vortex mixer has four inlets, each with diameter $d = 1.45 \times 10^{-3}$ m. For all four streams, we assumed $\mu = 1.0 \times 10^{-3}$ Pa s and $\rho = 1.0 \times 10^{-3}$ kg m$^{-3}$ at room temperature because 90%H$_2$O/
10% THF has a similar kinematic viscosity to that of water.

The mass-average diameters shown in Figure 5 are averages of three measurements on three separately mixed samples prepared under the same conditions. The vortex mixing data were taken from Zhu. The error in the calculated Re comes from variation of injection time. In vortex mixing, errors are minor because the injection time is mechanically controlled by syringe pumps, but it is relatively large in CIJ-D mixing due to the uncertainty in timing of the hand motion. At the highest Re, the injection time of the CIJ-D mixer was $4.2 \pm 0.3$ s. 2.5 mL of solvents in two 3 mL syringes were used; thus, the flow rate was $1.2 \times 10^{-6}$ m$^3$/s. Considering this flow rate and the tubing dimensions (1 mm inside diameter and 15 mm long), the residence time in the chamber and outlet tube before dilution was approximately 10 ms. For Re $< 1000$, a syringe pump was used with the CIJ-D mixer because hand operation cannot be controlled well enough to create steady mixing over minutes.

The results in Figure 5 show good agreement between the new CIJ-D design and the vortex mixer. Because of the rapid injection, the CIJ-D can reach Re $> 4000$, twice the limit for the vortex mixer, and particle size of 30 nm, half the smallest size from the vortex mixer. At the same Re, particle size for the CIJ-D is slightly smaller.

A potential problem with hand operation of the CIJ-D mixer is the start-up of flow. The Re at the beginning of impingement will be lower because of the time required to accelerate the syringes. The same problem occurs with syringe pumps, but because the impingement time is longer, it is possible to discard the first part of the product. This start-up transient could lead to broader particle size distribution; however, we observed broad size distribution in both the CIJ-D mixer and the vortex mixer. For example, at Re $\approx 1750$ (shown in Fig. 5), DLS gave averaged size polydispersity indices of 0.5–0.8 for both samples.

CONCLUSION

A simple modification of Johnson and Prud’homme’s CIJ mixer has been used to make stable and reproducible nanoparticles. The addition of a dilution stage, uses very small volumes and is easy to operate and inexpensive, making it more effective for rapid screening of small quantities of new materials, via FNP, compared with the alternative mixers and other methods. It is especially attractive for evaluation of new drug formulations for their ability to produce nanoparticles.

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REFERENCES

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