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# **FABRICATION OF MONODISPERSE POLY(DL- LACTIC ACID) MICROPARTICLES USING DROP MICROFLUIDICS**

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## **ABSTRACT**

Monodisperse poly(dl-lactic acid) particles with a diameter between 11 and 121  $\mu\text{m}$  were fabricated by drop microfluidics/solvent evaporation method using flow focusing glass capillary device. In the dripping regime, the ratio of droplet diameter to orifice diameter was in the range of 0.37–1.34 and was inversely proportional to the 0.39 power of the ratio of the continuous phase flow rate to dispersed phase flow rate.

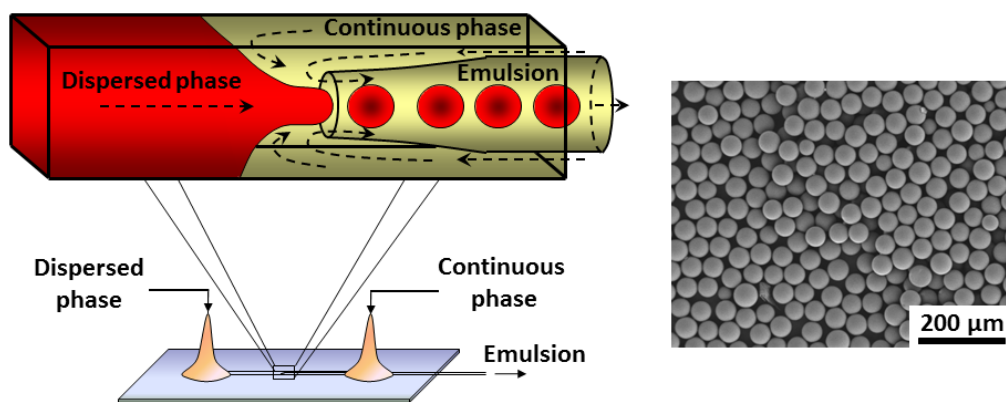
## **INTRODUCTION**

Biodegradable particles have been used for the encapsulation and controlled release of pharmaceutical actives, ultrasound and molecular imaging, fabrication of scaffolds, cell cultivation, etc. The most commonly used biodegradable synthetic polymers are poly(lactic acid) (PLA) and poly(lactic-co-glycolic) acid (PLGA), since they both have good biocompatibility and mechanical strength [1]. Monodisperse particles are favourable in drug delivery and ultrasound imaging because they exhibit predictable biodegradation rate, controlled drug release profile and acoustic response [2]. The conventional methods of droplet generation such as atomization processes, rotor/stator mixing and high-pressure homogenization result in polydisperse particles whose mean size cannot be precisely controlled. As a departure from traditional ‘top-down’ emulsification approach where small droplets are formed by reducing the size of larger droplets, a number of ‘bottom-up’ methods have been recently developed, where small droplets are directly formed by injecting one liquid through a micro -channel or -nozzle into another immiscible liquid. The purpose of this study was to investigate a novel approach to the fabrication of PLA microparticles based on flow focusing microfluidic device [3]. We have chosen borosilicate glass as a construction material for the device fabrication, because glass is more chemically robust than poly(dimethylsiloxane), does not swell, and has more stable surface properties.

## **MATERIAL AND METHODS**

The microfluidic device (Fig. 1 left), set on the stage of an inverted Leica DM-IRBE microscope, was connected to syringes containing the continuous and dispersed phases

via medical tubing. The dispersed phase consisted of a mixture of 5 % (w/w) poly(dl-lactic acid) (PLA) ( $15,000 \text{ g}\cdot\text{mol}^{-1}$ ), 95 % (w/w) dichloromethane (DCM) and 0.1–2 mM Nile red dye. The continuous phase was 5 % (w/w) aqueous solution of polyvinyl alcohol (87–89% hydrolyzed). Each phase was pumped into the device by a separate Harvard Apparatus PHD 22/2000 syringe pump. The droplet formation was recorded using a Phantom V5.1 high-speed camera at the rate of 800–2000 frames per second and frames were analysed using ImageJ v.1.44 software to estimate droplet diameter. The device was fabricated by inserting a round capillary with a tapered tip into the centre of a square capillary. To minimize wetting with DCM, the tip was treated with 2-[methoxy (polyethylenoxy) propyl] trimethoxysilane. Hypodermic needles were glued over both ends of the square tubing to act as tube connectors for the oil and water phase, while the exposed end of the round capillary served for sample collection.



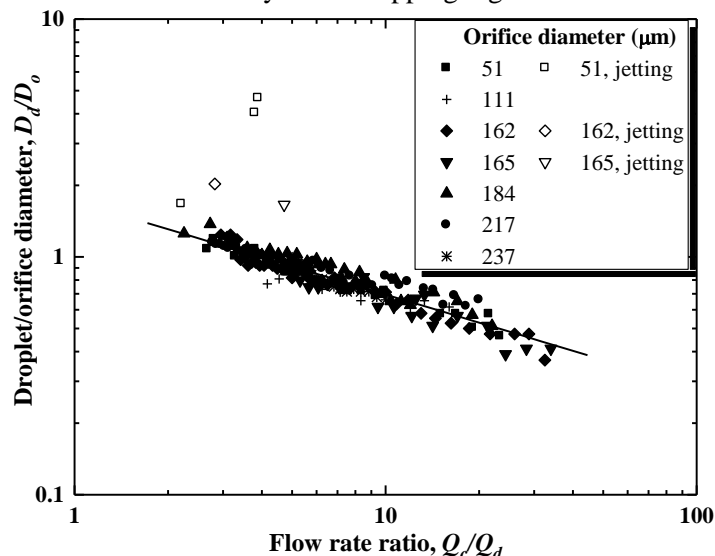
**Fig. 1.** Schematic diagram of flow focusing glass capillary device (left) and Scanning Electron Micrograph of  $23 \mu\text{m}$  poly(dl-lactic acid) microparticles (right).

## RESULTS AND DISCUSSION

Figs. 1 (right) is a Scanning Electron Micrographs of PLA particles showing a smooth surface with negligible porosity and spherical shape. After complete evaporation of DCM, the particle size was 2.7 times smaller than the size of the original droplets.

Fig. 2 is a log-log plot of drop diameters  $D_d$  scaled by the orifice diameter  $D_o$  versus ratio of volumetric flow rates of dispersed to continuous phase,  $Q_c/Q_d$ . Experimental data follows a linear trend with an equation of the best fit line:  $D_d/D_o = 0.23(Q_c/Q_d)^{-0.39}$ . Droplets formed in the dripping regime had diameters of  $1.34D_o > D_d > 0.37D_o$ . In dripping regime, the continuous phase flows through the orifice faster than the dispersed phase and the size of the droplets is determined by the balance between the drag of the continuous phase pulling the droplet downstream and interfacial tension force that resist the flow in the dispersed phase as pinch-off occurs. In jetting regime,

the dispersed phase flows faster than the continuous phase and it is the inertial force of the dispersed phase that must overcome the interfacial tension force. The uniform droplets were obtained only in the dripping regime.



**Fig. 2.** Droplet diameter/orifice diameter versus ratio of volumetric flow rates of dispersed to continuous phase. Open symbols are data points obtained under jetting.

## CONCLUSION

We have developed a novel method for production of poly(lactic acid) particles based on drop microfluidics in glass capillary devices and solvent evaporation. The size of the droplets formed in the microfluidic device has been closely controlled by phase flow rates and orifice size of the collection capillary. Our method is not limited to PLA and can be used to fabricate particles from a wide range of biodegradable material.

## Acknowledgment

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