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Liposome Nanoparticle Generation with Flow Focusing Microfluidic Device

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***Abstract*— Liposomal nanoparticles have many attractive features that make them a great candidate for usage in nanomedicine, drug delivery, biotechnology and nanotechnology. These nanoparticles can be chemically modified for targeting specific disease tissues or they can act as nanocarriers. Therefore, drugs can be encapsulated inside them. Microfluidic devices can provide a rapid and homogenous reaction environment with precise control over reagent addition. These Features make them an ideal platform for nanoparticle synthesis. In this work, the generation of nanoparticle liposomes by flow focusing microfluidic device was demonstrated. Our microfluidic device will provide a platform for continuous synthesis of liposomal nanoparticles with rapid synthesis capabilities.**

Keywords—Nanoparticle; Liposome; Microfluidics; Flow Focusing;

INTRODUCTION

Nanoparticles (NPs) are synthetic materials and have remarkable applications in medicine and biotechnology due to the unique way in which they interact with matter and their peoperties [1]. There are currently more than 35 US FDA-approved NPs, with a larger number in preclinical studies for therapy [2]. Nanoparticles have many attractive features that make them suitable for usage in nanomedicine. They can be chemically modified for targeting specific disease tissues, or for in vivo stability. Nanoparticles can also be used for therapy. Therefore, drugs can be encapsulated inside them and over time those drugs can be released in a controlled manner. The drug loaded liposomal nanoparticles can be used for treatment of various diseases such as cancer, inflammation, and infectious diseases. It is possible to use the nanoparticels for imaging purposes, they can provide higher contrast or higher brightness in comparison with the conventional small-molecule agents [1, 2, 3, 6, 7].

Microfluidic devices are able to rapidly mix reagents [4], provide homogenous reaction environments, control reaction temperature, and allow addition of reagents at precise time intervals. These features make the system suitable for nanoparticle synthesis. [5] Moreover, the simplicity and reproducibility of microfluidic device fabrication and handling small volumes with less expensive materials makes it an ideal platform for rapid synthesis and optimization of nanoparticles. In addition, by recent development in the field it is possible to carry out in-line characterization, feedback control, and continuous synthesis of nanoparticles that will contribute to the optimization and screening of libraries of nanoparticles. There are some evidence that by using microfluidic devices for nanoparticle synthesis a narrower size distributions, higher drug loadings, and improved batch-to-batch reproducibility can be achieved [8].

MATERIALS AND METHODS

Design of Experiment:

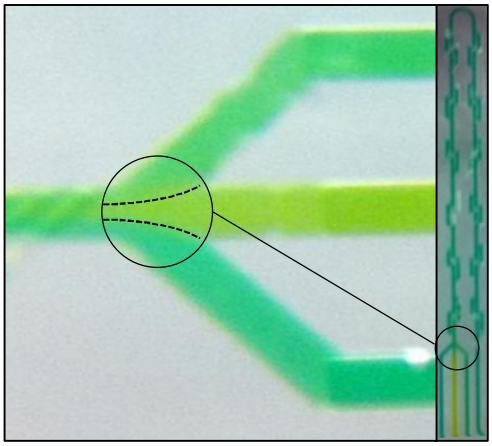

Fig. 1- Color microscopic image showing flow focusing ability of microfluidic channels by two emerging fluid streams. Food coloring dye was used for visualization purposes.

Flow focusing experiment: Mccormick food and egg coloring dye was injected to the microfluidic channels to show flow focusing ability of microfluidic channels and for visualization purposes. Fig 1 represents the flow focusing images obtained by color imaging of microfluidic channels.

Liposome Preparation:

Phosphatidylcholine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) was purchased from Avanti Polar Lipids, Inc. (Alabaster, AL, USA). Cholesterol (Ch) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Dulbecco's phosphate buffered saline (DPBS) was obtained from GIBCO. Stock solution of the phospholipids was prepared and was stored at −20 °C.

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Liposomes was prepared by injecting a lipid mixture into the center channel of the microfluidic device and phosphate buffered saline (with different concentration) was injected to the other microchannels. Schematic presentation of device setup is shown in Fig 2. The PHD 2000 Infuse/Withdraw syringe pump was used to introduce different mixtures with different flow rates to the microfluidic device. The variation of the flow rate and mixture ratio of reagents will influence the formation of nanoparticles. Zeiss Microscope that is equipped with a stage, and software was used for image acquisition and

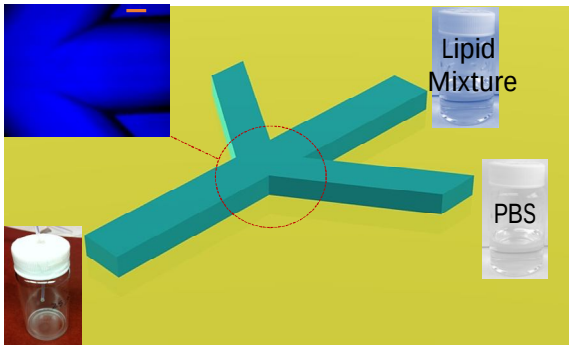

Fig. 2. Schematic presentation of microfluidic flow focusing device for nanoparticle generation with feeding microchannels and obtained liposome shown in the outlet (Inset: optical microscopy image of the microchannels, scale bar 50 µm).

analysis. Dynamic light scattering (DLS) measurements was performed by employing 90Plus zeta sizer for measuring the hydrodynamic diameter of the liposome nanoparticles. This procedure can be done by dilution of the sample in 3 ml cuvette. Obtained liposomal nanoparticles were analyzed by DLS measurement and obtained results are presented in Fig. 3.

RESULTS AND DISCUSSIONS

Flow focusing in microfluidic device allows for rapid mixing of reagents in the microchannels in a controlled manner. In our experiments, we have observed that by keeping the central channel flow rate constant and increasing the side microchannel flow rates. The length of flow focusing region (the dashed line in Fig.1) will decrease. This implies that by increasing the side channel flow rate we are squishing the central channel flow stream harder. Therefore, the central stream width will decrease. Moreover, we have studied the nanoparticle liposome generation. For our purpose, we used the DPPC with flow rate of 50 µL/min in central channel and Dulbecco's phosphate buffered saline with flow rate of 300 µL/min in side channels. After collecting the nanoliposome samples from the outlet of microfluidic device, we ran the DLS measurements five times for our samples. However, only three of them are presented here for brevity. Table 1 represents the DLS measurement results for the obtained liposomal nanoparticle sample. The average effective diameter was 354 (nm) and polydispersity was 0.308. The DLS graphs are shown in Fig. 3 A and B. We have also varied the flow rate in the side microchannels and kept the central channel flow rate constant. Therefore, we have decreased the flow rate of side channels to 200 µL/min. The obtained results are shown in Fig. 3 C and D. By increasing the flow rate in side channel, we obtain smaller nanoparticles by keeping all the variables constant.

CONCLUSION

In this paper, the generation of nanoparticle liposomes by flow focusing microfluidic device was demonstrated. Our microfluidic device will provide a platform for continuous synthesis of liposomal nanoparticles with rapid synthesis capabilities. First, the concept of flow focusing microfluidic device was demonstrated. Then, the effect of the variation of the flow rate on the liposomal nanoparticle size distribution was shown. In our studies, we have shown that by increasing the flow rate in side channel, we obtain smaller nanoparticles by keeping all the variables constant.

DLS MEASURMENT RESULT FOR LIPOSOME NANOPARTICLES

Run	Nanoparticle size and Polydispersity		
	Effec. Diameter(nm)	*Half width(nm)*	*Polydispersity*
1	319	171	0.288
2	346	196	0.321
3	376	213	0.305

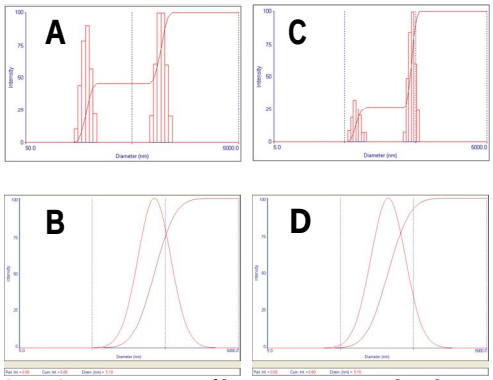

Fig. 3. DLS measurements of liposome nanoparticles obtained for two samples (A, C) Size distribution of lipid nanoparticles vs. intensity (B, D) Size distribution of lipid nanoparticles vs. number.

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