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Assembly of Nucleic Acid-Based Nanoparticles by Gas-Liquid Segmented Flow Microfluidics

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ABSTRACT

The development of novel and efficient mixing methods is important for optimizing the efficiency of many biological and chemical processes. Tuning the physical and performance properties of nucleic acid-based nanoparticles is one such example known to be strongly affected by mixing efficiency. The characteristics of DNA nanoparticles (such as size, polydispersity, ζ-potential, and gel shift) are important to ensure their therapeutic potency, and new methods to optimize these characteristics are of significant importance to achieve the highest efficacy. In the present study, a simple segmented flow microfluidics system has been developed to augment mixing of pDNA/bPEI nanoparticles. This DNA and cationic polymer pair (plasmid DNA and branched poly(ethylenimine)) was chosen due to bPEI's well-known ability to spontaneously condense plasmid DNA. The system fabricated in this project utilizes silastic tubing (1.6 mm ID) as the reaction channels, nitrogen gas as the continuous phase, and the aqueous components as the dispersed phase. Drop flow has been characterized using UV/Vis spectrophotometry, and the relationships between continuous and dispersed phase flow and drop rate and size have been documented. Drops have been successfully formed using two different types of drop generation (cross-flow and co-flow). Physical properties of the nanoparticles were analyzed using dynamic light scattering (DLS) measurements and agarose gel electrophoresis. Biological performance of the nanoparticles was analyzed using DNase I protection, unincorporated bPEI quantitation, mammalian cell transfection, and cell viability assays. The nitrogen-to-phosphate (N/P) ratio (5 and 20), flow rate, and flow-path geometry (linear, serpentine, and coiled) have been explored for their effect on mixing and particle uniformity. The results show a significant decrease in nanoparticle size compared with bulk-mixed methods at an N/P ratio of 5 and an observable difference in nanoparticle properties and performance when adjusting the nature of mixing using the developed microfluidics system.

KEYWORDS

Microfluidics, mixing, nanoparticles, gene therapy, pDNA