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ACCEPTED MANUSCRIPT

Design of a Small-Scale Multi-Inlet Vortex Mixer for Scalable Nanoparticle Production and Application to the Encapsulation of Biologics by Inverse Flash NanoPrecipitation

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Abstract: Flash NanoPrecipitation (FNP) is a scalable approach to generate polymeric nanoparticles using rapid micromixing in specially-designed geometries such as a confined impinging jets (CIJ) mixer or a Multi-Inlet Vortex Mixer (MIVM). A major limitation of formulation screening using the MIVM is that a single run requires tens of milligrams of the therapeutic. To overcome this, we have developed a scaled-down version of the MIVM, requiring as little as 0.2 mg of therapeutic, for formulation screening. The redesigned mixer can then be attached to pumps for scale-up of the identified formulation. It was shown that Reynolds Number allowed accurate scaling between the two MIVM designs. The utility of the small-scale MIVM for formulation development was demonstrated through the encapsulation of a number of hydrophilic macromolecules using inverse Flash NanoPrecipitation with target loadings as high as 50% by mass.

Keywords: Nanoparticles, Mixing, Protein Delivery, Peptide Delivery, Formulation, Particle Size, Polymeric Drug Carrier

Abbreviations:

FNP – Flash NanoPrecipitation
CIJ – Confined Impinging Jets mixer
MIVM – Multi-inlet Vortex Mixer
NP(s) – nanoparticle(s)
BCP – block copolymer
PS-PEG (PS-*b*-PEG) – poly(styrene)-*block*-poly(ethylene glycol)
PS – poly(styrene)
THF – tetrahydrofuran
Re – Reynolds Number (Equation 1)
iFNP – inverse Flash NanoPrecipitation
μMIVM – micro Multi-Inlet Vortex Mixer
$CHCl_3$ – chloroform
DMSO – dimethyl sulfoxide
HPLC – high-performance liquid chromatography
PS-b-PAA – poly(styrene)-block-poly(acrylic acid)
DLS – dynamic light scattering
CONTIN – algorithm name
PDI – polydispersity index
OVA – ovalbumin
HRP – horseradish peroxidase
MeOH – methanol
PAA – poly(acrylic acid)
SD – standard deviation

Introduction

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