The NanoAssemblr™ Platform: Microfluidics-Based Manufacture of siRNA Nanoparticles

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Nanoparticle Drug Development Process

Current nanoparticle manufacturing techniques limit innovation

- Poorly controlled processes
- Limited application for biologics (nucleic acids, proteins, peptides)
Microfluidics Enables Exquisite Process Control

Molecular Self-Assembly

- Control: laminar flow
- Nanoliter reaction volumes
- Rapid mixing: $\text{Time}_{\text{mix}} < \text{Time}_{\text{ppt}}$
- Low energy input
- Readily scalable
The NanoAssemblr™:
Microfluidics Enables Smarter Nanoparticles

- Enable rapid nanoparticle prototyping
- Remove process variability
- Robustly manipulate single variables
- Remove operator variability
- Enable seamless scale-up
The NanoAssemblr™: Rapidly Screen Formulation and Process Parameters
Simple Technology Transfer Between Users and Sites

siRNA-LNP (Cationic Lipid: DSPC: Cholesterol: PEG)

Automated instrumentation removes operator variability
Nanoparticle Drug Development Using the NanoAssemblr™

Rapid formulation and process development
Small Scale Formulation Development

Changing Composition

![Graph showing the effect of PEG-Lipid content on diameter and PDI.]

- **siRNA-LNP (Cationic Lipid: DSPC: Cholesterol: PEG)**

  - Diameter (nm)
    - 1.0
    - 2.5
    - 5.0

  - PDI
    - 0.00
    - 0.02
    - 0.04
    - 0.06
    - 0.08
    - 0.10

  - PEG-Lipid Content (mol %)
    - 0
    - 10
    - 20
    - 30

- **Removal of process variability allows for rational formulation optimization**
- **Robustly manipulate single variables in nanoparticle composition**
Removal of process variability allows for rational process optimization

- Robustly manipulate single variables in process

**Small Scale Process Development**

**Changing Process**

siRNA-LNP (Cationic Lipid: DSPC: Cholesterol: PEG)

![Graph showing the relationship between Flow Rate (mL/min) and Diameter (nm).](image)

- Flow Rate (mL/min): 0, 4, 8, 12, 16, 20, 24
- Diameter (nm): 100, 80, 60, 40, 20, 0

- Removal of process variability allows for rational process optimization
- Robustly manipulate single variables in process
Formulation & Process Manufacturability Assessment

Design of Experiment (DoE) variables

– Lipid Concentration
– Flow Rate
– Mixing Conditions
– Lipid:siRNA Ratio

Stable Results = Robust Process = Scalable Process
Nanoparticle Drug Development Using the NanoAssemblr™

Seamless process scalability makes small scale results more relevant
Continuous flow system:
✓ Rapidly achieves steady state
✓ Maintains particle quality with scale
✓ siRNA encapsulation efficiency > 94% in all fractions
Microfluidics as a Scalable Manufacturing Platform

Parallelization facilitates large volume production with *identical* reactor conditions.
Processing Final Drug Product

Final RNA Concentration = 0.96 mg/mL
siRNA Encapsulation Efficiency = 96%
Nanoparticle Drug Development Using the NanoAssemblr Platform

Conceptual Drug Product → Formulation → Process → Manufacturability → Scale-up → Final Drug Product
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The NanoAssemblr™ Platform
✓ Microfluidics-based nanoparticle manufacturing process
✓ Rationally engineered nanoparticle systems
✓ Automated instrumentation, precise process control, rapid prototyping
✓ Seamless scale-up

Come see the NanoAssemblr™ at BOOTH # 307

WE’RE HIRING

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Microfluidics Enables Manufacture of Potent LNP siRNA Systems

![Graph showing Relative FVII Protein Level (%) vs N/P Molar Ratio (Cationic lipid amine/ siRNA phosphate)]