Mixing matters – The FR-JET® modular mixer for nanoparticle formulation

Precise control over mixing is critical in nanoparticle manufacturing, especially for lipid nanoparticles (LNP), where hydrodynamics directly influence critical quality attributes (CQAs) (e.g., particle size, PDI, and encapsulation efficiency). Most existing systems struggle to maintain consistent mixing across formulations and scales. LEON's FR-JET® modular mixer overcomes these bottlenecks through engineering of purpose-built, predictable hydrodynamic conditions. Its design allows key hydrodynamic mixing parameters to be set and reproduced across scales, eliminating trial-and-error and ensuring reliable scale-up from R&D to GMP production.

The need for consistency

Nanoparticle-based drug delivery systems have become essential in modern pharmaceutical development, particularly for encapsulating small-molecule APIs and complex biologics like nucleic acids. From discovery through GMP manufacturing, developers face the challenge of ensuring formulation stability, tight control over CQAs, and batch reproducibility across scale.

In LNP production, these outcomes are tightly coupled to the dynamics of the mixing. LNPs form rapidly on micro- to millisecond timescales, where parameters such as solvent dilution, local turbulence, and micromixing govern nucleation and growth mechanisms.

Conventional mixing technologies often fail to deliver consistent hydrodynamic conditions as flow rate, formulation, or equipment size changes during process scale up. Small variations in jet momentum, residence time, or dilution kinetics can directly affect particle size, polydispersity index (PDI), and encapsulation efficiency.

Recognizing these limitations, the FR-JET® modular mixer was designed by LEON's technical team to enable a controllable confined hydrodynamic environment where key parameters can be precisely defined, predicted, and scaled.

Alternative Mixing Technologies and Their Limitations

Several approaches are commonly used in nanoparticle and LNP manufacturing, each with trade-offs in scalability, efficiency, and process control (

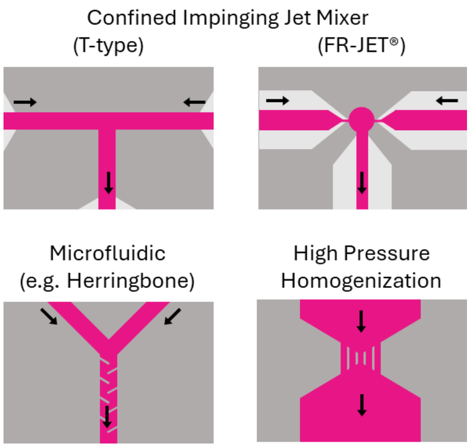

Fig. 1).

Microfluidic (MF) mixers

Microfluidic systems operate under laminar flow conditions, where mixing occurs predominantly through molecular diffusion. Some designs introduce secondary flow structures (e.g. herringbone grooves) to enhance mixing, but the overall turbulence remains low. MF mixers are ideal for low-volume formulations. However, they suffer from a high risk of clogging, poor throughput scalability, and limited adaptability to different formulation requirements.

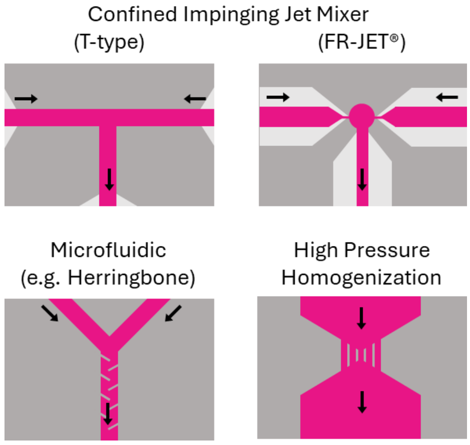

Fig. 1 Different types of mixers used in nanoparticle manufacturing (fluid path indicated in pink).

Confined Impinging Jet Mixers (CIJM)

CIJMs are widely used for scalable, bottom-up nanoparticle production. The most familiar version, the T-mixer, is often misclassified as a CIJM despite lacking a true mixing chamber. In T-mixers, two jets collide at a junction before expanding rapidly into downstream tubing. This setup produces abrupt shifts in energy dissipation rate (ε), mixing regime (Pe), and time scale of mixing (τ_{mix}) with changing flow rates, complicating scale-up and process transfer.

Classical CIJMs with fixed geometries and dedicated mixing chamber offer confined mixing zones but lack flexibility. Inlet nozzle and chamber dimensions are fixed, meaning any adjustment in flow changes hydrodynamics in a nonlinear and difficult to predict manner. This often results in extended development timelines and inconsistent scale-up performance.

High-pressure homogenization

This top-down method enables high-throughput manufacturing under GMP conditions but by definition introduces intense pressure and shear, which can degrade labile payloads like mRNA and siRNA. Fine-tuning of process parameters is essential to avoid shifts in product attributes, making development time- and resource-intensive.

> *Regardless of the system, one principle holds: mixing conditions dictate nanoparticle properties. Technologies that fail to stabilize key hydrodynamic parameters across scales inevitably produce inconsistent results.*

FR-JET® — Engineered Hydrodynamics in a Modular Platform

The FR-JET® modular mixer creates a stable and scalable hydrodynamic environment where mixing behavior is designed, not discovered. The system uses precision-machined pinhole inserts, producing consistent, well-defined jets, and a dedicated mixing chamber (the core).

Fig. 2 Flow regime inside the FR-JET® modular mixer (TFR = 60 mL/min; Non-solvent: purple; Solvent: blue).

Inside the spherical core, jets impinge in a confined chamber, where their kinetic energy dissipates under tightly controlled conditions (Fig. 2). The geometry of this chamber, together with the pinhole diameter and the flow rate, defines the hydrodynamic regime and allows engineers to model and control mixing outcomes across scales.

The modular design also supports asymmetric pinhole configurations (each pinhole using a different nozzle diameter). This uniquely allows stable and predictable jet momentum under typical LNP flow ratios such as 3:1.

By selecting pinhole and core combinations tailored to specific formulations, users can establish the optimal hydrodynamic regime from the outset, turning jet impingement and micromixing into tunable, design-controlled parameters and eliminating the trial-and-error common in traditional systems.

Whether operating at low or high flow rates, the FR-JET® preserves flow topology: two jets collide within a confined region, dissipate energy in a narrow turbulence zone, and flow downstream with consistent residence time, transforming hydrodynamics from a hardware side effect into an engineered property of the system.

Hydrodynamic Parameters and Their Influence on Particle Formation

The early moments of mixing, where solvent and solute rapidly interact, determine the final nanoparticle product characteristics. Each hydrodynamic parameter influences a specific step in the nucleation and growth process:

Reynolds Number (Re): Defines jet momentum and large-scale flow behavior. Higher Re typically produces deeper jet penetration and more energetic eddies, promoting the formation of smaller particles. However, Re must be interpreted in context with ε and τ_{mix} for accurate predictions.

Peclet Number (Pe): Indicates the balance between convection and diffusion. A high Pe ensures that solvent exchange initiates at the impingement zone, minimizing concentration gradients that could broaden particle size distribution.

Energy Dissipation Rate (ε): Measures how rapidly turbulent kinetic energy is converted into smaller-scale eddies. High ε shortens the solvent dilution timescale, enabling faster, more uniform nucleation. Lower ε allows more time for particle growth, which can lead to larger, less uniform particles.

Micromixing Time (τ_{mix}): Represents how quickly concentration fluctuations are eliminated. If τ_{mix} is shorter than the nucleation timescale, particles form under uniform, stable conditions. Longer τ_{mix} values indicate ongoing mixing during particle formation, leading to wider PDIs and inconsistent encapsulation. The dependency of τ_{mix} on FR-JET® configuration and total flow rate in a scale-up scenario is indicated in Fig. 3.

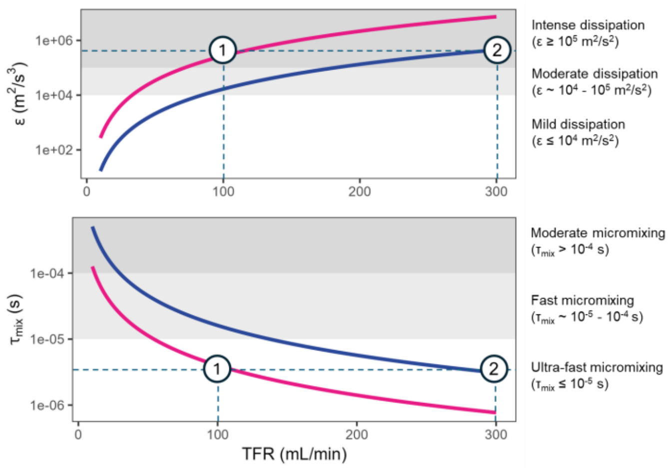

Fig. 3 Hydrodynamic operating regimes of the FR-JET® illustrated via global energy dissipation rate (ε, top) and micromixing time (τ_{mix}, bottom) as a function of TFR for two FR-JET® configurations (blue/pink). Higher dissipation (ε)

corresponds to stronger small-scale turbulent structures and greater deformation intensity. Together, ε and τ_{mix} describe the dynamic competition between turbulent energy input and local homogenization rates, which governs the molecular assembly pathway of mRNA-LNPs.

Together, these metrics form the hydrodynamic fingerprint of a mixer. A system that allows direct control over ε, Pe, τ_{mix}, and Re enables rational, reproducible design of LNP formulations, transforming process development from empirical to engineering-driven.

Scalability Without Compromise

In conventional fixed-geometry mixers, increasing flow rate typically intensifies mixing, reducing particle size and increasing polydispersity, an effect that complicates process transfer. The FR-JET® system decouples mixing intensity from throughput.

Because key process parameters are defined by pinhole and core geometry (the FR-JET® configuration), not the size or scale of the equipment, the FR-JET® is an ideal, flexible tool to scale from R&D to full-scale GMP production. The result is consistent product characteristics, regardless of batch size or equipment.

> *The FR-JET® mixer is used in all LEON's product portfolio, ranging from NANOscreen® and NANOlab® for early R&D and process development to NANOme® and NANOus® for GMP manufacturing.*

This approach simplifies scale-up to a process of hydrodynamic matching, removing the need for costly reformulation or system revalidation.

Enabling Robust, Scalable LNP Manufacturing

The FR-JET® modular mixer offers a new paradigm in nanoparticle and LNP production—one built on predictable, quantifiable hydrodynamics. By allowing developers to define and maintain the key mixing parameters that drive particle formation, it enables:

- Consistent particle size and narrow PDI
- High encapsulation efficiency
- Reproducible performance across scales
- Seamless transition from formulation to manufacturing

For CDMOs, biotech firms, and pharmaceutical manufacturers, the FR-JET® provides a unified platform that supports formulation exploration and large-scale production, without requiring redesigns or sacrificing control.

As mRNA and nanoparticle-based therapies advance toward commercial maturity, tools like the FR-JET®, embedded in LEON's comprehensive product portfolio, make it possible to scale intelligently, engineer predictability into process design, and meet rising industrial demands.

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