Advancing Pharmaceutical Production: The Benefits of Flow Manufacturing for Nanomedicines

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Introduction

Nanomedicines are advanced pharmaceutical formulations or therapeutic agents that employ nanoscale materials to diagnose, treat, or prevent diseases. By leveraging the principle of nanotechnology, they enhance the performance, delivery, and safety of medical interventions. These systems are designed to interact with biological systems at the molecular level and can offer enhanced solubility, controlled release, and minimize adverse side effects. Nanomedicines are typically developed from three primary material classes (see Figure 1):

- Lipid-based systems (e.g., liposomes, lipid micelles, and lipid nanoparticles)
- Polymeric systems (e.g., micelles, dendrimers, polymeric nanoparticles)
- Metal or metal oxide-based systems (e.g., gold nanoparticles, iron oxide nanoparticles)

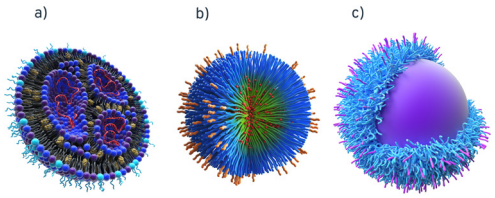


Figure 1. a) lipid-based nanoparticles (specifically LNP), b) polymeric nanoparticle, c) metal / metal oxide nanoparticle combined with organic coating.

Each class offers unique advantages tailored to specific applications, including cancer therapy, vaccine delivery, gene therapy, and diagnostic imaging.
Although the potential of nanoparticle-based drug delivery systems is well recognized, their successful integration into clinical practice requires addressing significant manufacturing challenges. Conventional synthesis methods often face issues such as batch-to-batch variability, limited control over particle properties, and poor scalability. Flow manufacturing represents a paradigm shift in nanomedicine production. Originally developed in petrochemical and chemical sectors, it is now gaining traction in pharmaceutical process development and manufacturing. This approach involves continuously pumping solutions through controlled junctions, enabling immediate reactions and product collection in a continuous mode. Although traditionally associated with covalent chemistry, flow technology is increasingly applied to nanoparticle self-assembly (particularly lipid and polymer systems) which is a new engine for translational nanomedicine. Unlike batch manufacturing, where materials are processed in discrete steps and the final product is obtained only at the end, flow manufacturing enables continuous production with tighter control and higher reproducibility. Its adoption has the potential to streamline efficiency, enhance scalability, and simplify global supply chains, establishing it as a leading emerging technology in the pharmaceutical industry.[1]

Advantages of flow manufacturing

The drug development process typically begins with milligrams or a few grams of material for primary testing. Production then scales quickly to tens of grams for in vivo toxicity studies. If the drug candidate progresses, the demand escalates to hundreds of grams for clinical trials, with the potential to eventually reaching several tons per year for successful pharmaceutical products. Such scale-up, across many orders of magnitude, is not trivial; thus, a robust and scalable initial synthetic route is essential for timely delivery. Scale-up is always a great challenge during the development of batch technologies, as the process behavior can show strong scale-dependence. Thus, the processes optimized on laboratory scale sometimes require thorough reoptimization, which might be challenging, since ensuring adequate supply for the clinical trials is the priority. In contrast, flow routes developed and optimized in the lab can often be scaled to production quantities with minimal reoptimization and without major changes to the production pathway [2].

Unlike batch manufacturing, where quality can vary between batches, flow manufacturing ensures consistent product quality with optional continuous inline quality control. After an initial start-up period, continuous processes reach a steady state, during which process parameters remain constant over time. Monitoring and maintaining these variables at fixed set points is much easier than managing the dynamic nature of batch operations [3].

Moreover, in flow systems, the reactants are continuously moving through small-diameter channels or tubes, which allows for much better control over heat transfer. The high surface-area-to-volume ratio in the flow reactors ensures more efficient heat transfer, enabling tight temperature control via rapid heating and cooling. This is particularly beneficial for exothermic or temperature-sensitive reactions. Additionally, flow reactors provide rapid and uniform mixing due to their continuous flow and well-defined geometries. This results in better mass transfer and more consistent reaction conditions throughout the process. In batch reactors, mixing can be uneven, leading to variations in product quality, while in flow systems, reactants are continuously introduced and mixed, ensuring a more homogeneous reaction environment [2].

These advantages underscore the growing importance of flow manufacturing in the future of pharmaceutical production in general and specifically for nanomedicines.

Flow technologies for nanoparticles

In recent years, significant advancements have been made in flow manufacturing technologies, resulting in the availability of a wide range of discrete flow components and modules, including pumps, mixers, reactors, and separation units. Moreover, there has been an increase in the commercially available flow systems. These systems can be employed for the production of various nanoparticles, including polymeric nanoparticles and lipid-based nanoparticles.

Examples of such commercially available systems for GMP manufacturing include:

Table 1. Examples of commercially available flow manufacturing systems

Vendor	System
Unchained Labs	Sunbather
Cytiva	NanoAssemblr
Knauer	NanoProducer
DIANT	LiFT

[1] note this is not an exhaustive list

These flow systems share several common features. They utilize either syringe pumps or high-pressure dosing pumps to continuously introduce reactants into the mixing chamber. They employ various types of mixing configurations that are designed to ensure efficient mixing and heat transfer, both of which are critical for the controlled formation of nanoparticles. Among these configurations are microfluidic chips (Figure 2a), where specific geometric parameters –such as etch depth, mixing patterns, and the number of mixing stations – significantly influence the process reproducibility and the quality of the resulting nanoparticles. Another example of mixing geometry that is employed in flow manufacturing is the impingement jet mixer, which facilitates the rapid mixing of two phases (solvent and anti-solvent), a key factor in the formation of lipid-based nanoparticles through the solvent-antisolvent precipitation method (Figure 2b).

In addition to the commercially available flow systems, with which Ardena has extensive experience, custom-built (in-house) flow systems can be tailored to specific process requirements. The flexibility and cost-effectiveness of these setups are particularly beneficial during the early stages of process development, enabling evaluation of the process compatibility with flow chemistry. Recently, we have explored the use of the multi-inlet vortex mixer (MIVM) for liposome manufacturing. Originally introduced by Prud'Homme et al., the MIVM is designed to enable flash nanoprecipitation at high flow rates [4], providing a scalable and reproducible method for manufacturing of wide range of nanoparticle including polymeric[5], lipid-based [6] and inorganic nanoparticles[7].

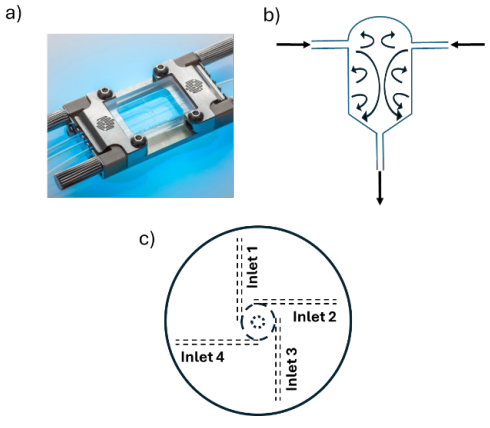


Figure 2. a) Microfluidic mixer employed in Unchained Labs Sunbather, schematic diagram of b) impingement jet mixer used in Knauer NanoProducer and c) MIVM

A case study using MIVM

The MIVM features four inlet streams and a central outlet, enabling the mixing of up to four distinct formulation streams (as illustrated in Figure 2c and Figure 3a). Its confined mixing geometry promotes rapid and turbulent mixing of two phases at high flow rates, essential for achieving flash nanoprecipitation. The MIVM operates on a vortex mixing principle, ensuring efficient micromixing is necessary for flash nanoprecipitation, with each inlet stream independently contributing to the vortex's momentum. As a result, varying flow rates can be applied to the lipid solution and anti-solvent streams 8. Two variations of this mixer are available, with maximum throughputs of 160 mL/min and 500 mL/min, respectively, demonstrating its suitability for large-scale nanoparticle manufacturing.

To evaluate the potential of the MIVM in manufacturing of lipid-based nanoparticles, an in-house flow setup was constructed, comprising high-pressure dosing pumps, the MIVM, PTFE tubing, and the necessary fittings (as depicted in Figure 3b). The main goal was to produce a liposomal formulation analogous to the Doxil formulation which is chemotherapy medication used for cancer treatment. The composition of this formulation is provided in Table 2. Various processing parameters were systematically evaluated to assess their effects on liposome size and size distribution, as indicated by the polydispersity index (PdI).

Table 2. composition of lipid-based nanoparticle used in the case study

Lipid component	HSPC	Cholesterol	mPEG-2000-DSPE
Molar ratio	1.075	725	1
Ammonium sulfate buffer			

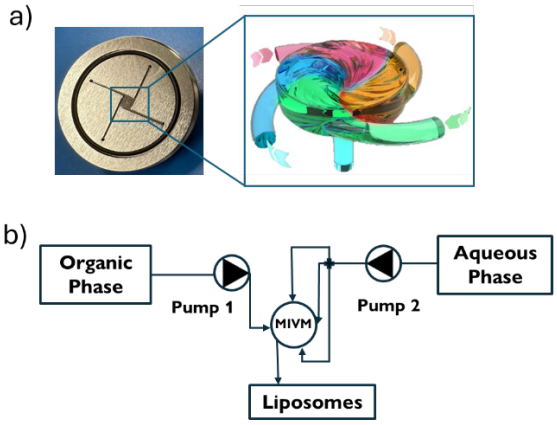
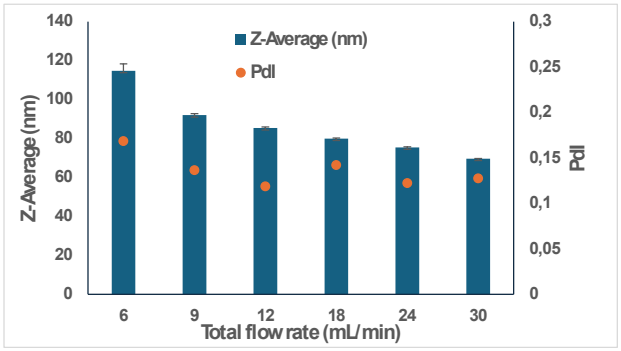


Figure 3. a) represents the internal view of MIVM and corresponding mixing. b) Schematic of the flow setup using MIVM.

Effect of total flow rate

The total flow rate was the first parameter evaluated, ranging from 6 mL/min to 30 mL/min, while maintaining a constant organic-to-aqueous phase ratio of 1:5. As illustrated in Figure 4, increasing the total flow rate led to a reduction in liposome size. This size reduction can be attributed to enhanced mixing at higher flow rates, indicating turbulent mixing (high Reynolds Number). Under these conditions, lipid nucleation predominates over the growth phase. However, further increasing the total flow rate from 9 to 30 mL/min did not result in a significant additional decrease in liposome size, as the system had already transitioned from laminar to turbulent flow. In addition, at all tested total flow rate, homogenous liposomes formed as confirmed by a PdI < 0.2.

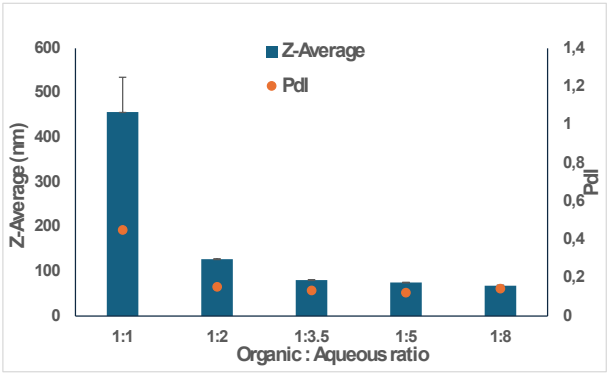
Figure 4. The effect of total flow rate on the liposome size and PdI.



Investigation of ratio of organic to aqueous

Next, we evaluated the effect of varying the organic-to-aqueous phase ratio from 1:1 to 1:8 while maintaining a constant total flow rate of 24 mL/min. As shown in Figure 5, increasing the organic-to-aqueous ratio resulted in the formation of smaller and more homogeneous liposomes. This suggests that a higher concentration of antisolvent promotes greater supersaturation, thereby facilitating the formation of smaller liposomes.

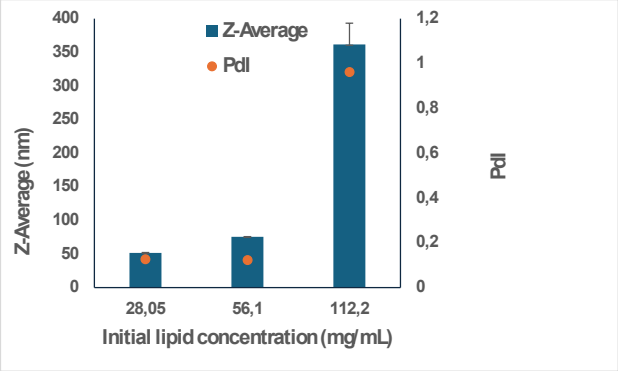
Figure 5. The effect of organic: aqueous ratio on the liposome size and PdI.



Impact of lipid concentration

Lastly, we assessed the impact of initial lipid concentration on both liposome size and PdI. By decreasing the lipid concentration, smaller and more homogenous liposomes formed indicating that at higher lipid concentration, liposome growth dominates the liposome size (Figure 6).

Figure 6. The effect of initial lipid concentration on the liposome size and PdI.



Conclusions

These findings validate the potential of flow manufacturing using a MIVM mixer for scalable production of lipid-based nanoparticles. The platform offers tunable control over critical parameters (flow rate, solvent ratio, concentration), ensuring consistency and reproducibility, which are essential for clinical and commercial nanomedicine production.

As pharmaceutical demand grows for complex, precisely engineered nanomedicines, flow manufacturing stands out as a transformative solution — not just for efficiency, but for enabling next-generation therapeutic platforms.

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