Flow technique provides precise control over LNP formulation production

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Lipid nanoparticles (LNPs) are a type of drug delivery system that uses lipids to encapsulate and transport therapeutic agents, including drugs and genetic material, to targeted cells or tissues. They are increasingly recognised for their potential in overcoming challenges associated with conventional drug delivery, such as poor solubility, instability, and limited bioavailability.

As the use of LNPs has risen significantly in recent years this has brought with it a demand for precise control over formulation parameters. Among these, the flow rate ratio (FRR) and the total flow rate (TFR) are particularly critical, as they have been shown to significantly influence the physicochemical characteristics of the resulting particles, including size, polydispersity, and encapsulation efficiency [1]. This direct correlation between particle size and flow rate calls for accurate flow control systems to ensure uniform products and reproducible production methods, this is especially crucial in biotechnology and pharmaceutical production companies governed by strict regulatory requirements.

Conventional flow measurement technologies however exhibit several operational limitations in real-world applications. For example, Coriolis flowmeters often suffer from slow data accumulation rates, while volumetric flowmeters cannot be installed in-line, which is a key requirement in LNP production processes. Using the above stated flow measurement technologies risks giving incorrect flow readings, leading to batch-to-batch discrepancies.

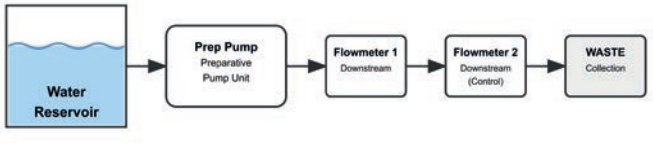

Figure 1: Traditional measurement setup with Flowmeter downstream of the pump

Methods for LNP production flow monitoring conventionally use flowmeters downstream of the pump (see *Figure 1*), usually one flowmeter per used pump. What seems to be logical, has however several drawbacks. First, by increasing the number of required connections on the high-pressure side of a system, this increases the possibility of undesired leakages which might go undetected. Also, this setup requires use of higher priced flowmeters capable of withstanding high pressures while keeping a constant performance. Lastly, operating at higher pressure increases the chances of flowmeter failure.

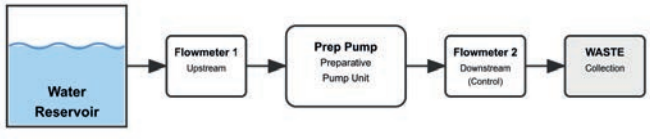

Figure. 2: Experimental Setup with Testa Preparative Flowmeter upstream of the pump.

To investigate a solution to these shortfalls, an experimental setup (*Figure 2*) utilising a Testa Analytical Preparative Flowmeter on the inlet side of the pump (upstream), rather than the conventional high-pressure outlet was studied. A second flowmeter was placed downstream of the preparative pump for both the traditional and experimental setup to function as reference for comparison reasons. A commercial Preparative HPLC pump, often employed in LNP production, was used in this study. Experimental data was collected for each setup at 4 flow rates commonly used in LNP production. A 10-minute continuous measurement was taken at each flow rate.

An overview of the flow measurements of Flowmeter 1 is shown in *Figure 3* below.

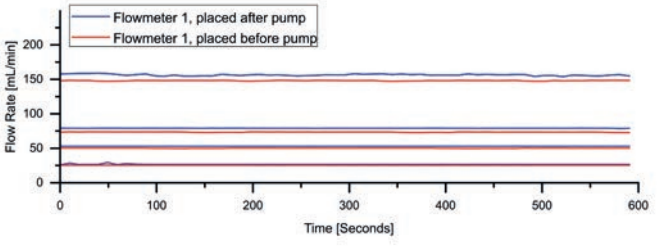

Figure 3: Flow measurement from Flowmeter 1 in both setup.

Comparing both flowmeters reveals that flow measurements at the pump inlet are virtually identical to flow measurements taken

at the conventional high-pressure side. Overall, the maximum deviation observed was less than 3% at the lowest flowrate, indicating that a preparative flowmeter with a lower flow range of up to 40 mL/min might be a precise, lower cost alternative for monitoring LNP formulation production.

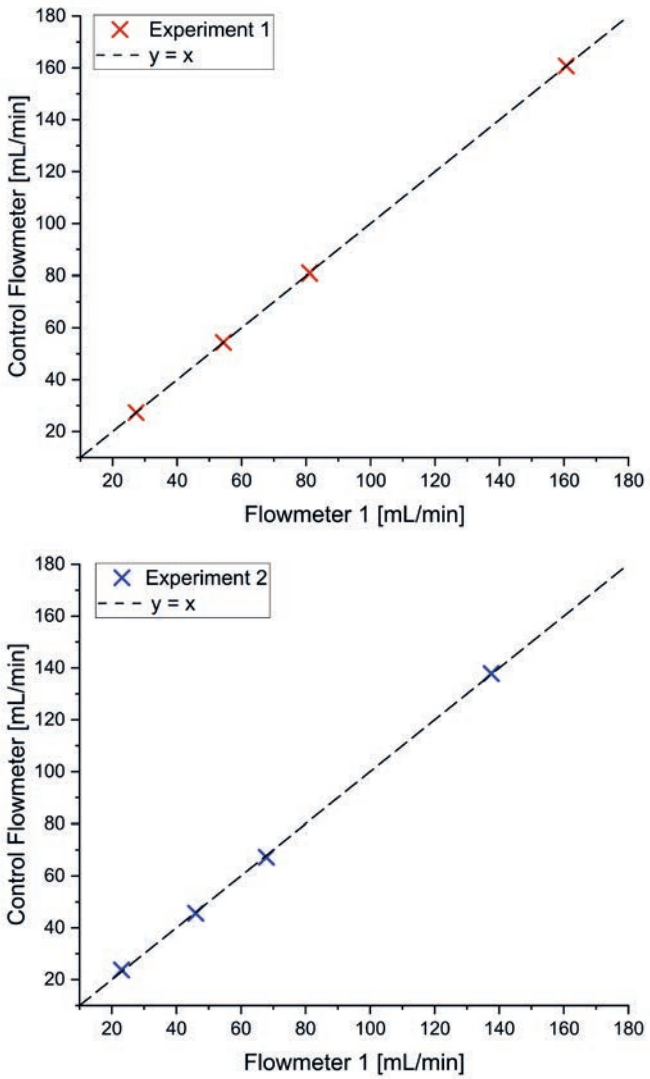

Figure 4: Comparison of flowmeter readings in Experiments 1 and 2. Each point shows a pair of simultaneous readings.

This study confirms that positioning a Testa Analytical preparative flowmeter upstream delivers identical data compared to conventional high-pressure setups, while eliminating the complications that come with high-pressure environments. An additional benefit of this real time monitoring setup is its ability to detect micro air bubbles and pause the system before they reach the pump and the system. This unique capability can eliminate system downtime and the expense of product rejections that arise from unexpected air bubbles.

In this study, the Testa Analytical preparative thermal flowmeter demonstrated its suitability for LNP production monitoring applications. Its non-invasive inline installation capability provides real-time measurement without disrupting flow patterns, while its broad solvent compatibility addresses the diverse buffer and solvent requirements in LNP production. Additionally, the dedicated flowmeter software which is compatible with many Chromatography Data Systems (CDS) ensures reliable data collection and traceability. Overall, the implementation of this system enhances LNP formulation production reliability and regulatory compliance, which altogether results in reduced operational costs.

Conclusion

This study demonstrates that Testa Analytical preparative thermal flowmeters provide superior measurement capabilities compared to traditional high-pressure monitoring approaches. The flow measurement approach presented minimises the possibility of costly process revalidation while achieving reproducible, scalable, and audit-ready LNP production. This methodology addresses fundamental challenges in process parameter control, system reliability, and regulatory compliance.

References

1.Roces CB, Lou G, Jain N, Abraham S, Thomas A, Halbert GW, Perrie Y. Manufacturing Considerations for the Development of Lipid Nanoparticles Using Microfluidics. Pharmaceutics. 2020 Nov 15;12(11):1095.

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