TAMARA: Development of a Simplified Microfluidic Nanoparticle Formulation System Tailored for Preclinical Stages

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ABSTRACT: Developing nanotherapies faces significant **formulation challenges**, as seen with RNA-LNP-based therapies, which account for over 500 formulations in development yet only four are FDA-approved. To address this, we have developed the **TAMARA nanoparticle formulation system**. Based on nanoprecipitation, TAMARA is a **user-friendly** platform that meets all **preclinical** needs, streamlining research in nanomedicine. TAMARA enables **rapid experimentation**, allowing screening of numerous formulations at very low volumes (<0.5 mL); and scales up to mL production for in vitro and in vivo experiments. It provides an ideal environment for exploring new therapies, enabling **high-quality**, efficient formulation of nanoparticles, including liposomes, mRNA-, siRNA-, ASO-loaded LNPs, and PLGA-based polymeric nanoparticles.

1 Problematic and objectives

Numerous methods are available for formulating lipid- and polymer-based nanoparticles; but they often result **in inconsistent nanoparticle quality** and are often extremely time-consuming.

Recently, controlled nanoprecipitation using **microfluidics** has emerged as a **leading method** in the early drug development steps thanks to its rapid process, low volume synthesis and precise control over critical nanoparticle attributes, such as size, polydispersity index (PDI), and encapsulation efficiency.

However, the adoption of microfluidic technology is limited by high costs and complexity, especially at low volumes.

To address these challenges, we developed TAMARA, a microfluidics-based nanoparticle formulation system designed to streamline preclinical development from screening to in-vivo and in-vitro.

This poster aims to introduce TAMARA's capabilities by:

- Comparing the 2 integrated micromixer designs: **Baffled** (A) and **Herringbone** (B)
- Exploring difference in formulated nanoparticle characteristics
- Assessing the platform's accessible volume ranges.

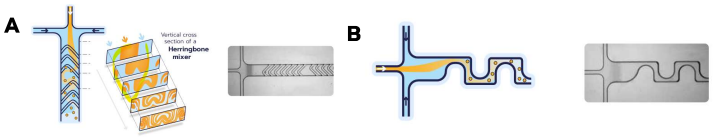

Figure 1. A) Herringbone mixer and **B)** Baffled mixer design, both working principle and magnified picture of the chip design taken by microscope.

2 Synthesis of organic nanoparticles with TAMARA

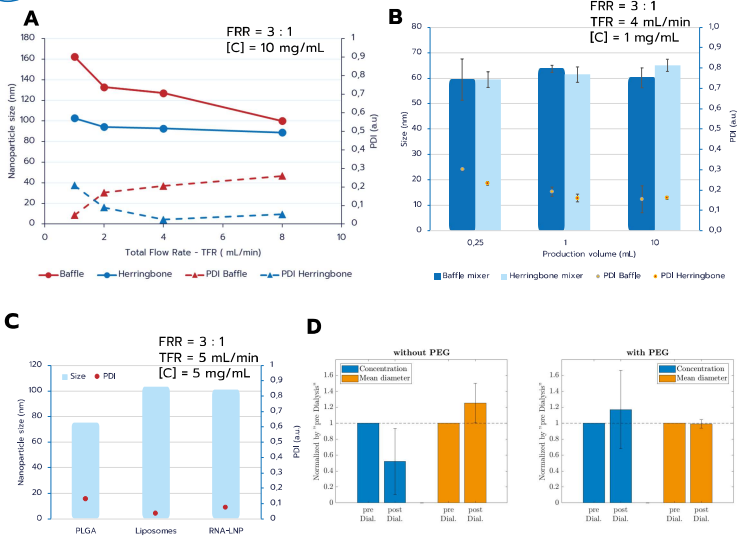

Figure 2. A) Size and polydispersity index (PDI) for PC : Cholesterol based liposomes produced at various Total Flow Rate (TFR) and **B)** repeatability at various production volumes, measured by DLS. Error bars represent standard deviation (n = 3). **C)** TAMARA allows the production of various type of organic nanoparticles, with high monodisperisty. **D)** Post-processing and composition of RNA-LNP impacts their concentration as well as stability, measured by Videodrop.

HIGHLIGHTS

- A **plug and play** microfluidics system for nanoparticle formulation
- Covering the requirements of most **preclinical development** stages
- Offering excellent level of **size control**
- PEG containing RNA-LNP physico-chemical characteristics are **stable up to a month** when stored at 4°C

3 Stability study of RNA-LNP produced with TAMARA

In this study, we have evaluated the stability of two different formulations of RNA-LNP by Interferometric Light Microscopy (ILM) using the **Videodrop** (Myriade), a GMP-compliant instrument providing NPs size and concentration characterization. As expected, storage at room temperature leads to a rapid destabilization of the RNA-LNPs and reduction in concentration while PEG-containing nanoparticles show increased overall stability overtime.

Higher TFRs lead to smaller yet less stable nanoparticles, with a decrease in concentration and rapid increase in size.

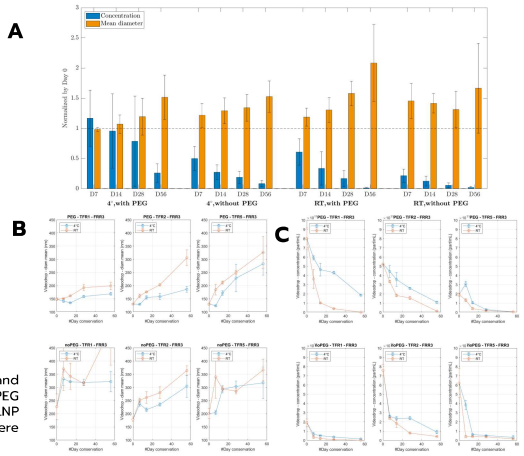

Figure 3. A) Relative evolution of RNA-LNP mean diameter and concentration at two different storage conditions and with and without PEG in the composition. **B)** Mean diameter and **C)** concentration of RNA-LNP produced with TAMARA at different total flow rates. All measurements were done by Videodrop.

CONCLUSIONS & PERSPECTIVES: The TAMARA nanoparticle formulation system demonstrates robust synthesis capabilities for both **lipid- and polymer-based nanoparticles**, ensuring excellent **batch-to-batch reproducibility** across scales. The flexibility in chip design enables a **wide range of nanoparticle sizes** with excellent polydispersity index (PDI) and stability, establishing TAMARA as a versatile and efficient platform for the preclinical development phase of nanomedicines.

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