

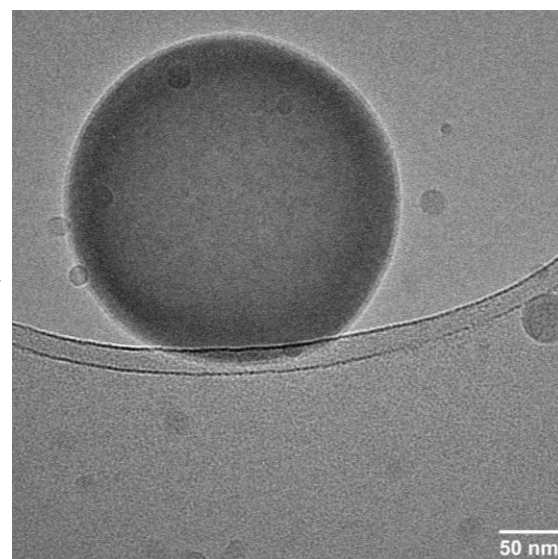
Perfluorocarbon Nanodroplet Production with TAMARA

Perfluorocarbon (PFC) nanodroplets (NDs) are promising ultrasound-responsive phase-change contrast agents for imaging and therapeutic applications. Upon reaching a specific acoustic pressure, their liquid PFC core undergoes **Acoustic Droplet Vaporization (ADV)** to form an echogenic gas bubble, enabling controlled ultrasound activation.

Precise control over **ND size, monodispersity, and composition** is essential for predictable and reproducible acoustic responses. While traditional fabrication methods can suffer from high polydispersity and batch-to-batch variability, **microfluidic mixing** enables highly controlled droplet size and formulation.

In this work, **lipid-shelled PFC NDs produced using TAMARA** were evaluated across different process and formulation conditions, including FRR, TFR, lipid concentration, and PFC core type and concentration. The impact of **PFC core composition on ADV thresholds** was also investigated.

Figure 1.
Representative
cryo-TEM image of
a PFP ND.



Highly monodisperse lipid-shelled PFC nanodroplets with tunable size, composition, and acoustic vaporization behavior were reproducibly produced using TAMARA.

This work was carried out by Ines Oberhuber and Simone Schürle (ETH Zurich), in collaboration with Romain Melich (Bracco Suisse SA), and supported by Sezen Gul and Yannick Mousli (Inside Therapeutics). The full study is published in Ultrasound in Medicine & Biology by Oberhuber et al.

Impact of process parameters on PFC ND properties

Perfluorohexane (PFH) NDs were produced using TAMARA with the staggered herringbone micromixer across different process conditions, varying the flow rate ratio (FRR, 2:1–10:1) and total flow rate (TFR, 2–10 mL/min), and their average size and polydispersity index (PDI) were measured by DLS.

Key findings

- **Increasing the FRR from 2:1 to 10:1 progressively decreased ND size**, likely because faster dilution of the organic phase triggers a nucleation burst, limiting individual droplet growth.
- **Increasing the TFR from 2 to 10 mL/min also resulted in smaller NDs**, consistent with increased shear stress within the microfluidic mixer.
- **Low PDI values (≤ 0.2)** were maintained across the tested conditions, demonstrating consistently high monodispersity.

TAMARA enabled predictable control over PFC nanodroplet size through process parameters while maintaining high monodispersity.

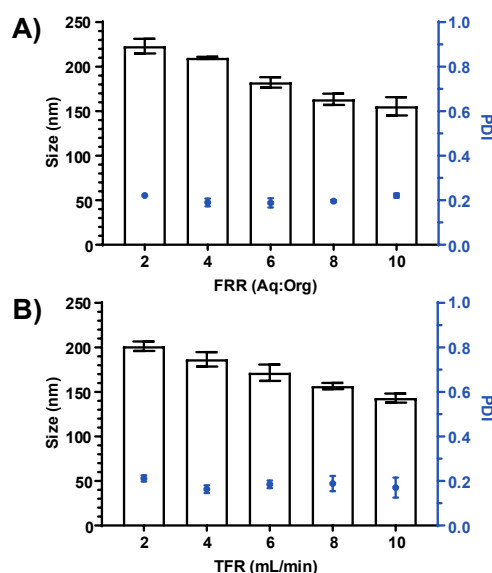
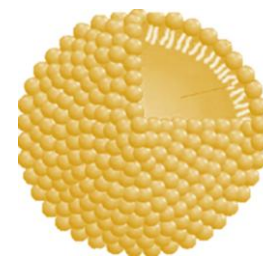


Figure 2. Size and PDI of PFH NDs produced using TAMARA at different (A) FRRs and (B) TFRs.

Impact of formulation parameters on PFC ND properties

Lipid concentration (1–5 mg/mL; DPPC:DSPE-mPEG2000, 9:1 molar ratio) was systematically varied for PFH NDs, while PFC concentration (0–20 $\mu\text{L/mL}$) was evaluated for both perfluoropentane (PFP) and PFH-based NDs. Average size and PDI were measured by DLS.



Key findings

- Increasing the lipid concentration from 1 to 5 mg/mL decreased PFH ND size, likely because greater lipid availability promotes faster interfacial coverage of smaller PFC cores and limits droplet coalescence.
- Increasing the PFC concentration resulted in larger NDs for both PFP and PFH, likely due to the greater volume of hydrophobic core material relative to the available lipid.
- High monodispersity was preserved across all tested formulation conditions, with PDI values consistently ≤ 0.2 .

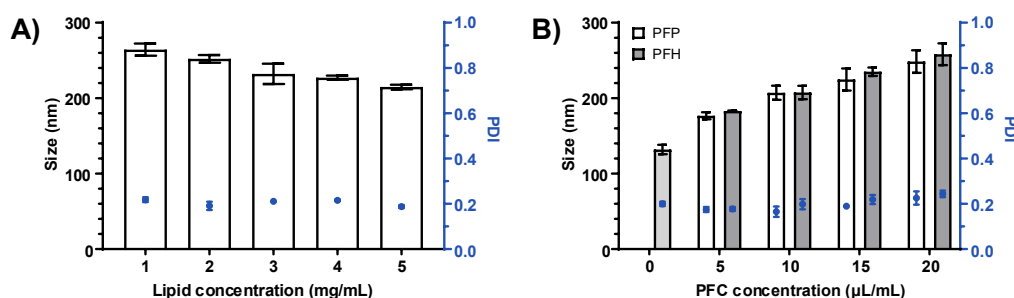


Figure 3. Size and PDI of NDs produced using TAMARA at different (A) lipid concentrations for PFH NDs and (B) perfluorocarbon concentrations for PFP and PFH NDs. 0 $\mu\text{L/mL}$ PFC condition represents lipid-based nanoparticles without a PFC core, i.e., liposomes.

TAMARA supported systematic adjustment of formulation parameters to tune PFC ND size while preserving highly monodisperse populations.

Influence of PFC core composition on ND ADV behavior

~200 nm NDs containing pure PFP or PFH cores, as well as mixed PFP:PFH cores, were produced using TAMARA. Mixed-core NDs with varying PFP:PFH ratios (75:25, 50:50, and 25:75) were evaluated to determine whether the ADV threshold could be progressively tuned between those of the pure PFP (100:0) and PFH (0:100) formulations.

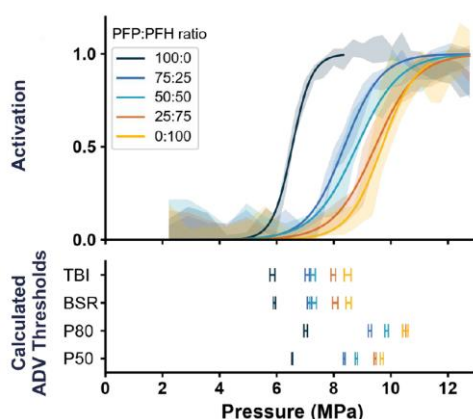


Figure 4. Effect of PFC core composition on ND vaporization behavior, showing activation curves and corresponding ADV thresholds for different PFP:PFH ratios.

Key findings

- Pure PFP NDs showed lower ADV thresholds than PFH NDs, consistent with the lower boiling point and higher volatility of PFP.
- Increasing the proportion of higher-boiling-point PFH progressively shifted the ADV threshold toward higher acoustic pressures.
- Mixed PFP:PFH cores enabled tuning of ADV thresholds between those of the two pure PFC formulations.
- The same composition-dependent trend was observed across the different ADV threshold definitions, demonstrating consistent modulation of vaporization behavior.

Precise control over PFC core composition using TAMARA enabled ADV thresholds to be systematically tuned at the formulation stage.

Conclusion

This application note demonstrates how TAMARA supports the **reproducible production and systematic optimization of lipid-shelled PFC nanodroplets**, providing:

- Highly monodisperse PFC NDs, with reproducible particle yields of $\sim 6\text{--}8 \times 10^{10}$ NDs/mL.
- Predictable tuning of ND size through process (FRR, TFR) and formulation (lipid and PFC concentrations) parameters.
- Production of pure and mixed PFC-core NDs, with varying PFP:PFH ratios allowing systematic tuning of ADV thresholds.

TAMARA enables rapid, reproducible production of lipid-shelled PFC NDs with tunable physicochemical and acoustic properties.



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Application Note on
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