Precision Engineering of Lipid-Based Nanosystems via Impingement Jet Mixing

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Introduction

Flash nanoprecipitation and emulsification by solvent diffusion, also known as the 'emulsification by the ouzo effect', are multi-component reactions commonly employed for large-scale production of drug-loaded lipid-based nanocarriers. In these processes, product properties and uniformity depend on effective mixing of various components under controlled conditions. In impingement jet mixers (IJMs), this is achieved by two fluid jets consisting of a water-miscible organic solvent and an anti-solvent colliding at a specific angle within a predefined geometry [1,2]. We studied the scalability of this process to higher throughputs while maintaining nanocarrier size and specific flow regimes.

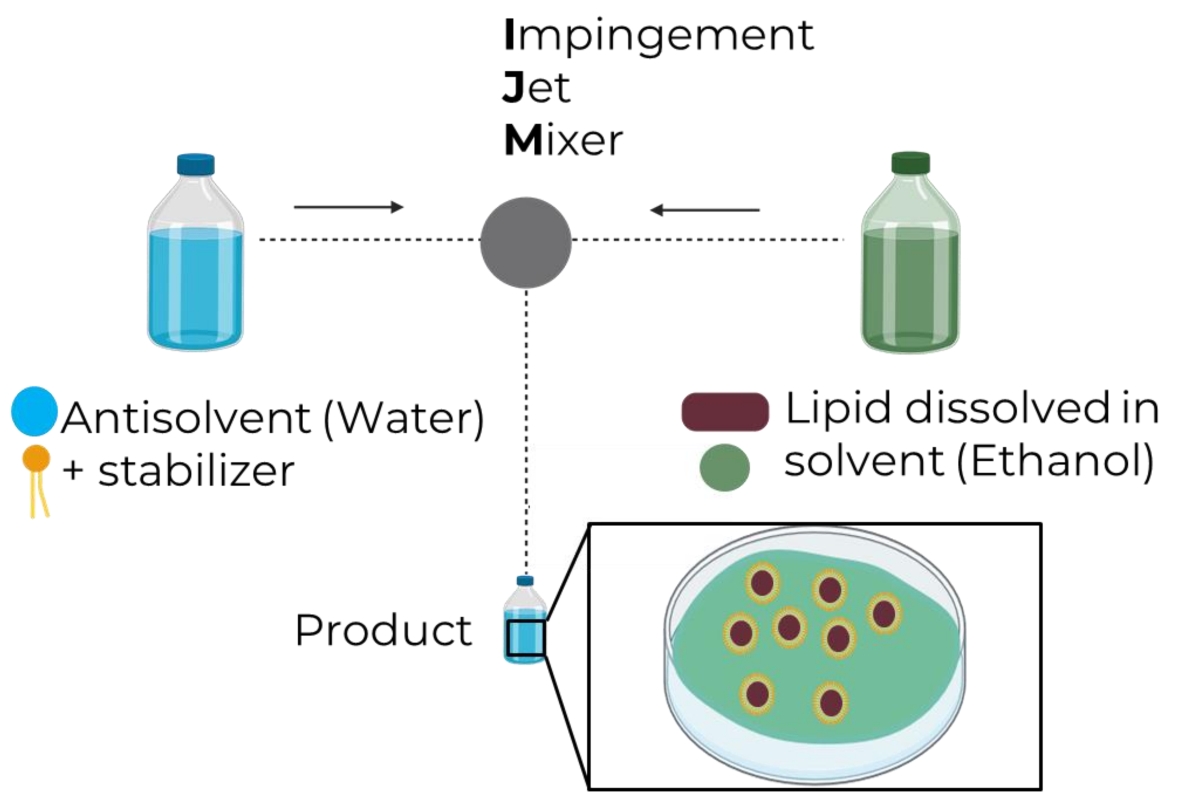
Materials

- 2 mg/ml Labrafac™ lipophile WL 1349 in ethanol (organic phase)
- 0.5 mg/ml Tween 80 in water (aqueous phase)

Methods

Investigation of the following aspects:

- Variation of the flow rates at a 1:1 (v/v) phase ratio within IJM 1 (smallest inner diameter)
  → Reynolds number 200 – 3400 (aqueous jet, see Fig. 1)
- Scale-up experiments while maintaining the same Re-number in IJMs with larger inner diameters (IJM 2-4)
- Size measurements via offline DLS and SR-DLS



Results

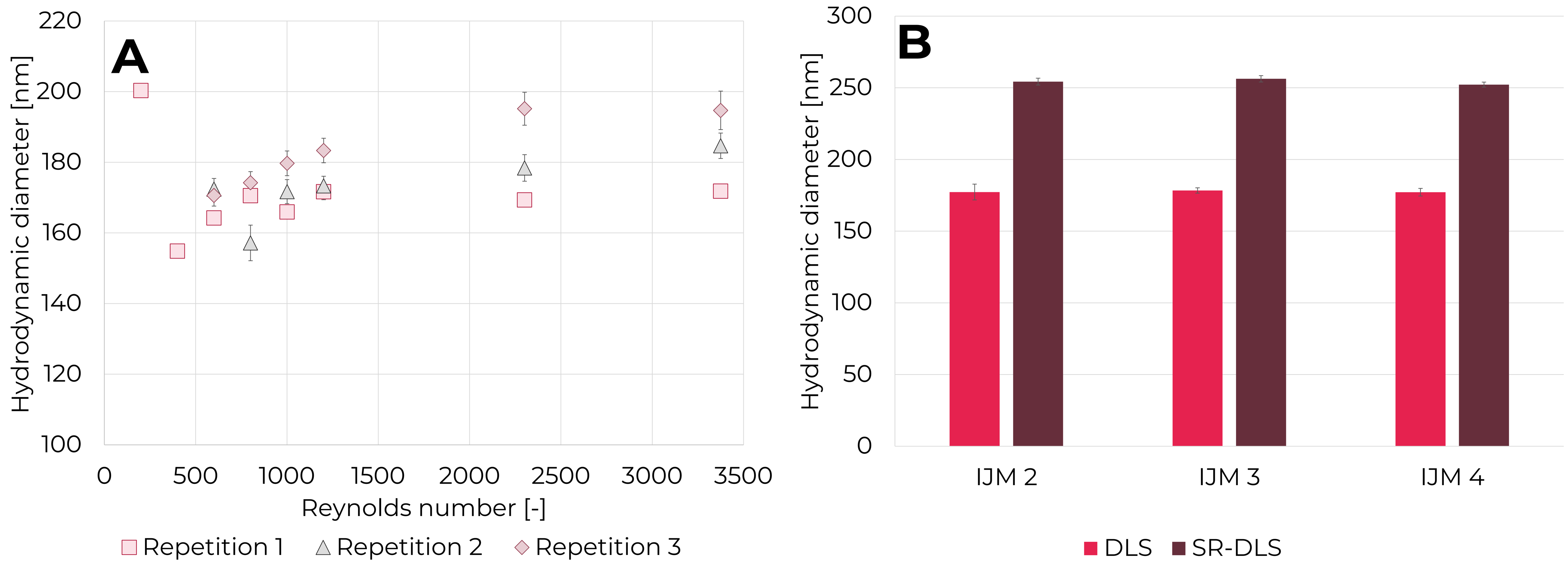


Fig. 1. **A** Results of the performed experiments in IJM 1 (Repetition 1 - 3) and **B** the scale-up runs in IJMs 2-4, measured offline via DLS after 1:100 dilution and via SR-DLS without solvent removal.

$$Re = \frac{\rho v l}{\eta}$$

ρ... Fluid density of aqueous phase [kg/m³]
v... Velocity of aqueous phase [m/s]
l... Inner diameter of IJM [m]
η... Dynamic viscosity of aqueous phase [Pa*s]

The flow rate variation experiments showed smallest droplet sizes at Re = 600 to 800, and no further size reduction at higher flow rates. The scale-up experiments were performed at Re=1000, being a good compromise between small droplet size, replicability and throughput.

The amount of lipid processed could be increased by a factor of five, while the droplet size was similar to the experiments performed with the smallest inner diameter. Offline SR-DLS and offline DLS results showed size deviations, which can be explained by the different light sources employed in both technologies, indicating the usability of SR-DLS as online PAT-tool for process control.

Conclusion and Outlook

In summary, our study demonstrates the feasibility of optimizing lipid-based nanocarrier production using impingement jet mixers (IJMs) through dimensionless analysis. The findings suggest the existence of favorable process regions, which can be predicted based on a limited set of rheological and material properties of the substances involved. These easily accessible characteristics enable the estimation of process parameters across different production scales and therefore facilitate scale-up .

References

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