A scalable self-nano-emulsification approach to uniform nanocarriers

High-throughput production of uniform nanocarriers could drive biomedical breakthroughs, but remains challenging. Now an approach based on robust, scalable self-nanoemulsification driven by non-equilibrium surfactant partitioning is developed to synthesize diverse uniform nanocarriers at a rate of up to 5 l min^{-1}.

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The problem

Nanocarriers, such as nanodroplets, nanovesicles and nanoparticles, have facilitated advances in biomedicine[1–3]. However, current fabrication methods often yield polydisperse particles, require specialized equipment, and involve high costs, high energy consumption or excessive heat generation. Self-nanoemulsification offers a greener alternative, harnessing chemical potential gradients at non-equilibrium water–oil interfaces to induce molecular-level instability that spontaneously leads to the formation of uniform nanodroplets, which are convertible to other nanocarriers, such as nanovesicles and nanoparticles[4,5]. However, sensitivity to pH, temperature and humidity, along with low production rates, limits industrial scale-up. The sustainable, low-cost, high-throughput production of uniform nanocarriers therefore remains a challenge.

The solution

We developed a self-nanoemulsification process driven by interfacial instability induced by non-equilibrium surfactant partitioning that enables the scalable production of uniform nanodroplets. By initially dispersing oil-preferring surfactants in the aqueous phase, we created far-from-equilibrium conditions in oil–water–surfactant systems with a negative free-energy change ($\Delta G < 0$). This free-energy change drives rapid water-to-oil surfactant flux, enriching the surfactants at the interface to induce interfacial instability and spontaneous nanoemulsification (Fig. 1a). Using biocompatible pluronic surfactants (synthetic tri-block copolymers composed of polyethylene oxide (PEO) and polypropylene oxide (PPO) arranged in a PEO–PPO–PEO configuration), we elucidated how surfactant partitioning behavior, interfacial activity and molecular geometry influence this process. Finally, we further demonstrated the simplicity, robustness and versatility of the approach using diverse oil–water–surfactant systems and by creating a wide array of nanocarriers.

This approach enabled the liter-scale (5 liters) production of nanoemulsions through simple agitation, indicating the potential for scalabilty. Our findings show that molecular diffusion-driven surfactant flux induces interfacial instability, producing nanodroplets through repeated emulsification cycles (Fig. 1b). The final droplet size is governed primarily by the molecular structure of the surfactant (the chain lengths of the PEO and PPO blocks). Notably, this self-emulsification method achieved rapid nanoemulsion production with a polydispersity index below 0.1 at a rate of up to 5 l min^{-1}, surpassing the production rates of conventional methods by 2–3 orders of magnitude.

This process shows high robustness against a broad range of pH (~3–11) and temperature (~4–85 °C) variations, and good compatibility with more than 10 oil–water–surfactant systems. Furthermore, our approach enables the synthesis of diverse nanocarriers including micelles, vesicles, polymeric nanoparticles and metal–organic framework nanocrystals by using the resultant nanoemulsion droplets as templates to encapsulate the relevant precursors.

The implications

Our approach offers an alternative for nanocarrier production. The resulting nanodroplets can serve as nanoreactors or templates to produce various nanoparticles through self-assembly or polymerization. The key advantages of this strategy, including its simplicity, scalability, low cost, low surfactant concentration and low energy input, position it as a versatile platform for various applications, including drug delivery, diagnostics and cosmetics. Moreover, the dynamic partitioning of surfactants at water–oil interfaces could provide fundamental insight into non-equilibrium droplet systems, opening possibilities for studying out-of-equilibrium phenomena at the microscale.

Nevertheless, non-equilibrium surfactant partitioning is not universally applicable to all the oil–water–surfactant systems. Only systems that meet the criterion ($K_p > C_{o,0}/C_{w,0}$, where K_p is the partition coefficient of the surfactant, and $C_{w,0}$ and $C_{o,0}$ are the initial concentrations of surfactants in the water and oil phases, respectively) will induce the self-nanoemulsification. Moreover, water-in-oil nanoemulsions remain undemonstrated, as it requires further efforts to identify oil-soluble surfactants that prefer water. Extension of this strategy to ionic surfactant systems could further enhance its versatility.

Beyond these challenges, future work will focus on machine-learning-assisted construction of a library for oil–water–surfactant systems based on the partitioning characteristics and interfacial parameters of surfactant molecules. Such a library would broaden the impact of self-emulsification technology on nanocarrier production and accelerate its industrial translation.

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EXPERT OPINION

“This work reveals a powerful new mechanism for nanoemulsion production: a surfactant-flux-induced interfacial instability that leads to spontaneous emulsification. By exploiting nonequilibrium partitioning of surfactants at water–oil interfaces, the authors achieve unprecedented scalability — producing large quantities of monodisperse nanodroplets within seconds, without requiring extreme interfacial tension or complex equipment. The method’s robustness across diverse experimental parameters positions it as a transformative platform for sustainable, industrial-scale nanocarrier manufacturing.” **Daniel Bonn, University of Amsterdam, Amsterdam, The Netherlands.**

FIGURE

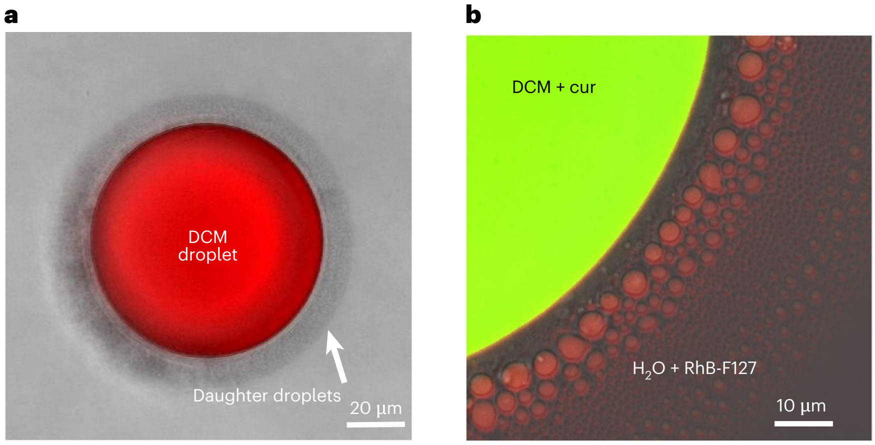

Fig. 1 | Non-equilibrium surfactant partitioning drives self-nanoemulsification. **a**, Confocal laser scanning microscopy image of the nanoemulsification process of an LR300-dyed dichloromethane (DCM; oil phase) droplet in water with 0.1 wt% surfactant F127 (water phase). The droplet generates numerous small daughter droplets around its surface under the continuous impact of the surfactant flux. **b**, Confocal laser scanning microscopy image of the nanoemulsification process of a curcumin (cur)-loaded DCM droplet in water with 0.1 wt% rhodamine B-labeled F127 (RhB-F127). The droplet generates daughter droplets that become progressively smaller through repeated self-emulsification cycles. © 2026, Cao, Q. et al.

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BEHIND THE PAPER

The high-throughput production of uniform nanocarriers remains a key challenge for the widespread industrial application of nanoparticles. We proposed that the non-equilibrium partitioning of surfactants in water–oil systems could induce interfacial instability and drive self-nanoemulsification. Early on in the project, we readily observed the self-nanoemulsification process through non-equilibrium surfactant partitioning, but struggled to uncover its underlying mechanisms. A systematic study then revealed that the surfactant partition coefficient, interfacial activity and molecular geometry are the key determinants. The most exciting moment came when we unexpectedly achieved 1 liter of nanoemulsions in just 1 minute, a breakthrough that spurred further scale-up to 5 liters and extension of the strategy to diverse nanocarriers. Our findings highlight the potential of this self-nanoemulsification strategy for industrial nanocarrier production. **N.-N.D. & W.W.**

FROM THE EDITOR

"Noteworthy aspects of this work include the mechanistic insight into the interfacial emulsification process, the precise control of the droplet size and polydispersity, and the application to multiple systems. We believe the fundamental study presented in this work will be of use in the design and scale up of soft-matter systems at the nanoscale for drug delivery and biomedical applications.” **Editorial Team, *Nature Chemical Engineering*.**