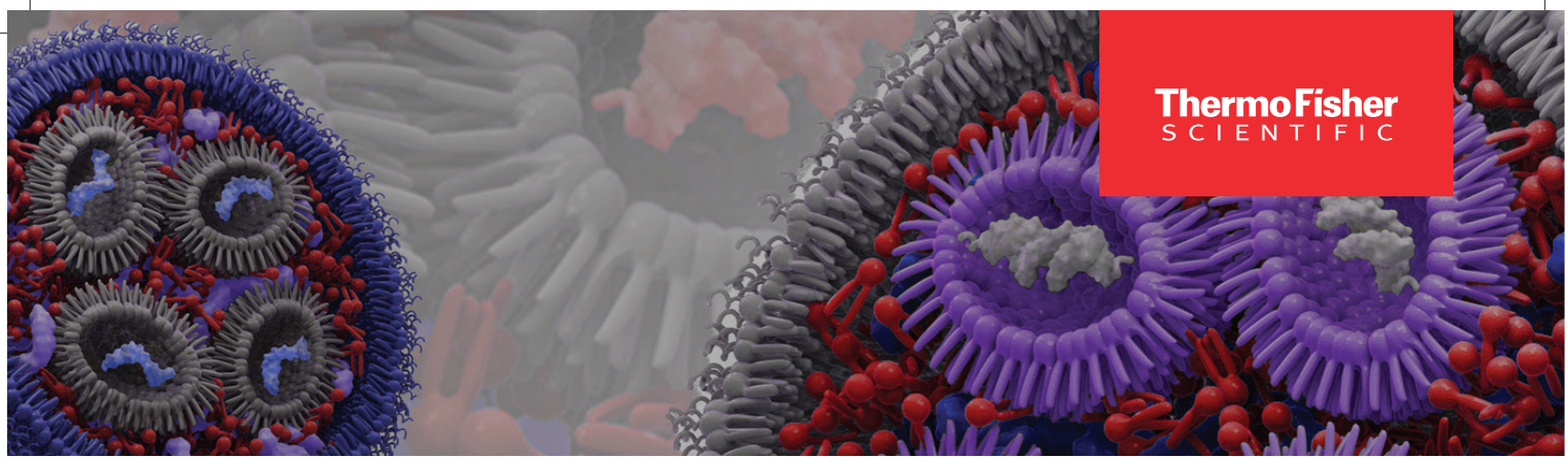

Cryo-TEM unlocks the potential of lipid nanoparticles for drug delivery

Lipid nanoparticles in drug development

Lipid nanoparticles (LNPs) are promising carriers for nucleic-acid-based therapeutics and vaccines. Their design and application depend on structural and morphological properties, influencing function, safety, and efficacy. Comprehensive characterization is crucial for designing effective LNP formulations. Cryo-transmission electron microscopy (cryo-TEM) plays a key role in assessing LNPs.

Advantages of cryo-TEM in LNP characterization

Traditional techniques like dynamic light scattering (DLS) and nanoparticle tracking analysis lack the resolution needed to visualize individual nanoparticle structures. Cryo-TEM allows researchers to observe LNPs in their native, hydrated state without staining or fixation, enabling:

- Accurate size and shape analysis that reveals size distribution and shape heterogeneity
- Encapsulation efficiency assessment that shows RNA loading and distribution
- Batch-to-batch consistency to minimize manufacturing variability
- Nano-structural insights that aid in optimizing formulation conditions
- Process optimization to help refine manufacturing techniques

Key takeaways

- Cryo-TEM enables nanoscale visualization of LNPs in their native state, which is critical for drug delivery research
- Structural insights from cryo-TEM help optimize LNP design for improved efficacy, safety, and RNA delivery
- Cryo-TEM supports scalable LNP manufacturing by comparing particle consistency across production methods
- Emerging therapies in cancer and metabolic diseases rely on cryo-TEM to assess LNP integrity and performance

Understanding structure-activity relationships of LNPs

Optimization of LNPs focuses on components like ionizable lipids, helper lipids, and PEG-lipids. Scientists at the University of Bristol and Leiden University used cryo-electron tomography (cryo-ET) to reveal distinct internal structures of LNPs, which are crucial for transfection efficiency.[1]

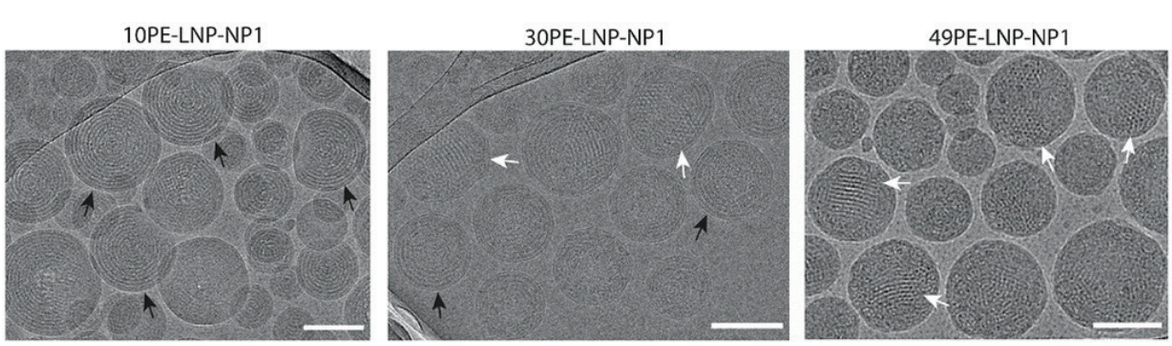

Figure 1. Representative cryo-TEM images of various lipid nanoparticle formulations. Black arrows highlight lamellar structures and white arrows indicate non-lamellar structures. Scale bar = 100 nm. Figure reproduced from Pattipeiluhu *et al.* under CC BY 4.0.

thermo scientific

Tackling the challenge of endosomal escape

LNP mRNA complexes face challenges like inefficient endosomal escape. Scientists at Shenzhen Neocurna Biotechnology Corporation introduced a novel cationic polymeric micelle (cPM) for co-delivery with LNPs, improving endosomal escape and mRNA expression.[2] Cryo-TEM confirmed the structural integrity and morphology of the cPMs and LNPs.

Advancing the manufacturing of LNPs with accurate particle characterization

Developing scalable and reproducible methods for LNP production is challenging. Cryo-TEM enables detailed comparison of manufacturing methods, which facilitates optimization. Scientists at Leiden University and Johannes Gutenberg University introduced a cost-effective microfluidic platform for mRNA LNP synthesis, with cryo-TEM revealing smaller, uniform LNPs with ordered cores.[3]

New therapeutic approaches in cancer treatment and protein-replacement therapy

LNPs are explored for cancer and metabolic disease treatments. Researchers at the Icahn School of Medicine developed an LNP-RNA platform to target cancer, using cryo-TEM to visualize structural integrity.[4] Another study examined the impact of LNP composition on mRNA encapsulation and stability, with cryo-TEM showing distinct ultrastructures impacting function and stability.[5]

Conclusions

LNPs are complex systems requiring detailed analysis at the individual particle level. Cryo-TEM is essential for their development and characterization, ensuring the development of safer and more effective therapeutics.

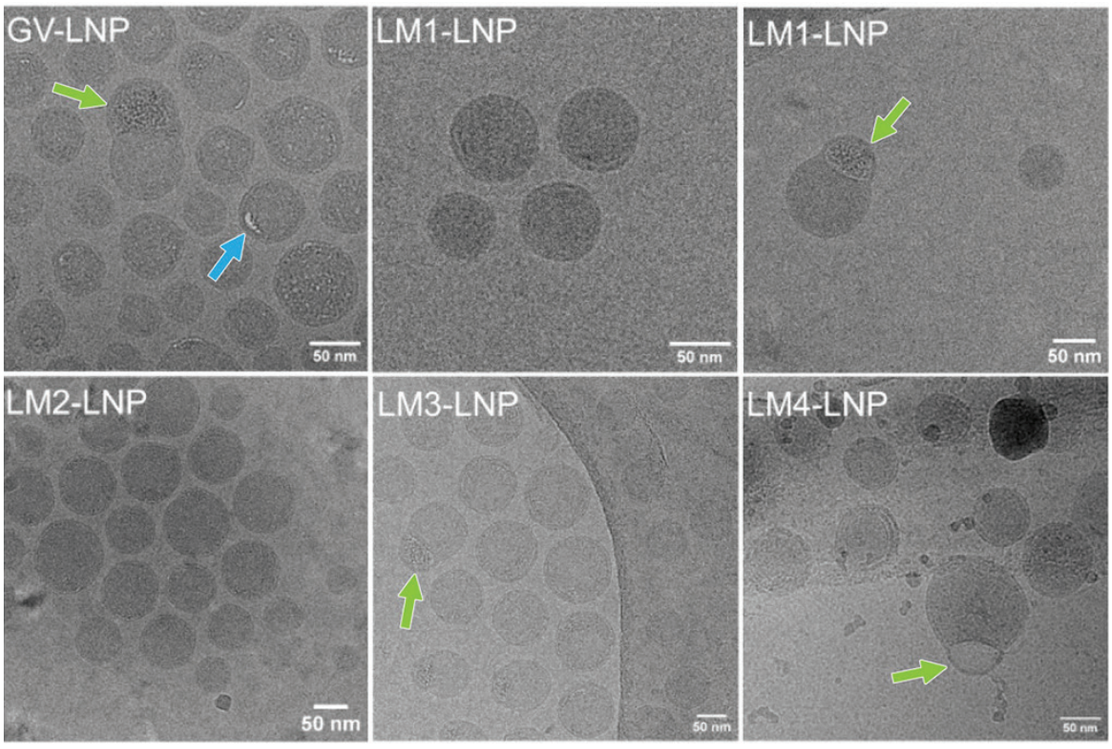

Figure 2. Cryo-TEM images of the various LNP formulations, with arrows highlighting specific structural features and irregularities, including "blebs" (green arrows) and internal defects (blue arrows).

References

1. Pattipeiluhu, R. *Nat Commun* 15:1303 (2024). doi: 10.1038/s41467-024-45666-5
2. Deng, S. *Vaccines* 13:25 (2025). doi: 10.3390/vaccines13010025
3. Johnson, NV. *Adv Healthc Mater* 13:26 (2024). doi: 10.1002/adhm.202401252
4. Xue, Y. *Nat Commun* 16:2198 (2025). doi: 10.1038/s41467-025-57149-2
5. Gambaro, R. *Pharmaceutics* 16:771 (2024). doi: 10.3390/pharmaceutics16060771s

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