Nanocavity Polymer-Stabilized Microbubbles: A potential candidate for Enhanced Theranostic

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Abstract (300 word limit)

Background: Polymeric microbubbles are increasingly investigated as advanced theranostic agents for enhanced diagnostic imaging and targeted therapeutic delivery yet achieving their low polydispersity index and ability to retain shape under cryogenic conditions remain major barriers for consistent acoustic performance leading to clinical translation. While differential centrifugation and cryoprotective agents have been employed separately, their combined application for optimizing polymer-stabilized microbubble formulations has not been comprehensively investigated.

Methods:

In this systematic investigation, gas-core microbubbles were synthesized by applying controlled ultrasonication (20 kHz, 400W power output) to PVA-chitosan mixtures, forming nanocavity-stabilized shells. Produced microbubbles were systematically isolated into morphometrically uniform fractions using differential centrifugation. Cryoprotection was systematically achieved during snap-freezing and freeze-drying using 5% sucrose as cryoprotectant. Size distribution analysis was performed via MATLAB-assisted morphometry and bright-field microscopy. Hot-stage polarized light microscopy systematically investigated phase behavior during controlled thermal cycling (temperature range: -20°C to +40°C, heating rate: 2°C/min) to assess structural stability and acoustic performance parameters.

Results: Initial suspensions exhibited marked polydispersity with particle diameters ranging from submicron to >15 µm and polydispersity index (PDI) of 6.49. Post-centrifugation microbubble suspensions showed size distributions cantered around 1.85 µm, with PDI reduced to 0.20 and coefficient of variation of 33.1%. Addition of the 5% sucrose solution did not distort microbubble shapes at cryogenic temperature as sucrose solution achieved vitrification instead of crystallization during thermal cycling. Reconstituted microbubbles maintained structural integrity with preserved nanocavity architecture, retaining morphology and functionality for >3 weeks post-freeze-drying. Acoustic signatures were also performed that yielded good results.

Conclusions: The differential centrifugation of polymeric nanocavity bubbles reduced the PDI significantly from 6.49 to 0.20. Use of sucrose as cryoprotectant with PVA-chitosan microbubbles enhanced the lifespan while maintaining morphology. The approach transforms polydisperse populations into uniform systems with enhanced acoustic fidelity while preserving structural integrity through vitrification. The PVA-chitosan combination offers biocompatibility and superior preservation compared to conventional approaches, making it promising for clinical translation of ultrasound contrast agents.

Key words: Polydispersity Index, microbubble, chitosan, ultrasound, freeze drying.

Photograph

Image

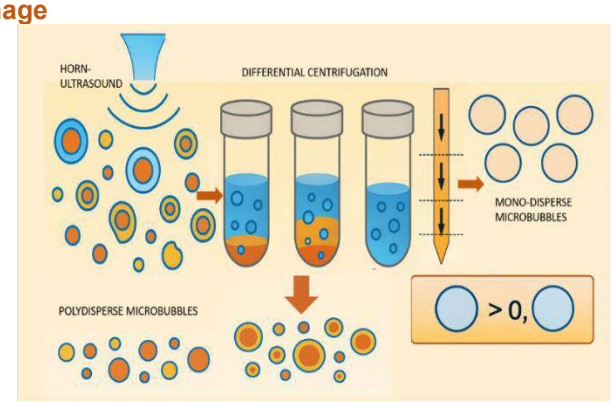


Figure.1. Cartoon showing origins of polydispersity during Differential Centrifugation.

Recent Publications (minimum 5)

1. Kumar, H.S., Kwa, S.H., Lee, K.H. (2017). "Rhodamine-6G based Highly Sensitive and Selective Chromogenic chemo sensor for Cu2+ ion in Aqueous Medium". International Journal of Management and Applied Science (IJMAS), 5(7), 27-31.
2. Kumar, H.S., Lee, K.H. (2021). "Synthesis, Photophysical Properties and Cytotoxicity of Rhodamine". Russian Journal of Bioorganic Chemistry, 47(3), 691-699. ISSN 1068-1620.
3. Malik, R., Pancholi, K., Melzer, A. (2016). "Microbubble–liposome conjugate: Payload evaluation of potential theranostic vehicle". https://doi.org/10.1177/1849543516670806.
4. Pancholi, K., Agbelusi, T., Kumar, H., Kumar, A. (2024). "Overcoming CD Spectroscopy Sample Preparation Challenges in Protein Structural Analysis for Biosimilars". Preprints, 2024010441. https://doi.org/10.20944/preprints202401.0441.v1.
5. Tan, M., Saini, G., Stanzione, M., Pancholi, K., Sampathkumar, H., Walker, M., Patterson, C., Vassalli, M., Naden, A., Magdysyuk, O., Armstrong, R., Kumar, A. (2024). "Polyetherureas as aqueous binders for Li ion batteries". ChemRxiv [Preprint].



Biography (150 word limit)

Ms. Harini Sampath Kumar has her expertise in biomedical technology and passion for improving health through innovative engineering solutions. Her multidisciplinary approach combines organic synthesis, microbubble generation, and polymer science to create new pathways for advancing healthcare diagnostics and treatment. She has built this expertise after years of international research experience across the UK, South Korea, UAE, Sweden, and India, spanning both academic institutions and industry settings.

Her foundation is based on translational biomedical research, bridging laboratory discoveries with clinical applications. Currently pursuing her PhD at Robert Gordon University, her work on microbubble-enhanced elastography for early detection of pre-cancerous oral lesions exemplifies her commitment to preventive healthcare. This approach is responsive to clinical needs and demonstrates her unique way of focusing on early intervention strategies.

With proven experience in project management, teaching, and cross-cultural collaboration, Ms. Kumar has successfully progressed multiple research projects simultaneously, resulting in peer-reviewed publications and innovative solutions for environmental sustainability and healthcare advancement has her expertise in evaluation and passion in improving health and wellbeing. Her open and contextual evaluation model based on responsive constructivists creates new pathways for improving healthcare. She has built this model after years of experience in research, evaluation, teaching, and administration both in hospital and education institutions. The foundation is based on fourth generation evaluation (Guba& Lincoln, 1989) which is a methodology that utilizes the previous generations of evaluation: measurement, description and judgment. It allows for value-pluralism. This approach is responsive to all stakeholders and has a different way of focusing.

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Notes/Comments: