

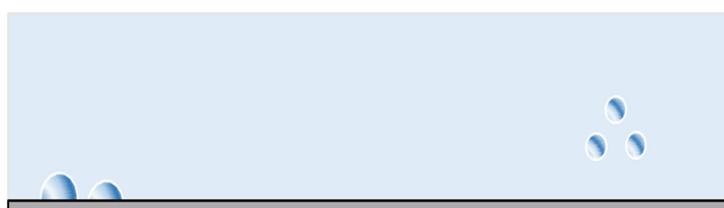
BÖLÜM 4

Nanobaloncuklar

Ahmet Doğan ERGİN¹

| GİRİŞ

Nanobaloncuklar, sıvı içindeki gazla dolu nano boyutlu parçacıklardır. Katı/sıvı arayüzündeki veya çözeltideki konumlarına göre sırasıyla yüzey nanobaloncukları (YNB) ve küme nanobaloncukları (KNB) olarak adlandırılırlar (1, 2) (Şekil 1). Küme nanobaloncukları, 1 μm 'den küçük boyutlara sahip küresel baloncuklar içeren yoğunlaşmayan gazlardır. Ayrıca bu baloncuklar ISO uluslararası standartlarına (ISO 20480-1:2017) göre ultra ince baloncuklar (UİB'ler) olarak da tanımlanırlar. Yüzey nanobaloncukları, küresel bir kapak biçiminde olan bir yüzey üzerinde bulunan gaz dolu baloncuklardır. Yüzey nanobaloncukları, genellikle on nanometre yüksekliğinde ve yüzlerce nanometre genişliğindedir (genellikle 100 ile 500 nm) (3).



Yüzey Nanobaloncukları (YNB)

Kümesel Nanobaloncuk (KNB)

Şekil 1. Yüzey ve küme nanobaloncukları

¹ Dr. Öğr. Üyesi, Trakya Üniversitesi, Eczacılık Fakültesi, Farmasötik Teknoloji AD., adoganergin@trakya.edu.tr, 0000-0002-9387-0085

ultrasonun tümör ablasyonunda etkinliğini artırmak veya kan pihtılarının tedavisinde trombolizde yardımcı olmak için kullanılabilir.

Nanobaloncuklar, çeşitli bilimsel disiplinlerde değerli araştırma araçları olarak hizmet eder. Akişkan dinamiği, akustik, malzeme bilimi ve yüzey olguları gibi alanları keşfeden çalışmalarında kullanılırlar. Bu baloncuklar, temel prensiplere ışık tutar, yeni teknolojilerin geliştirilmesine katkıda bulunur ve araştırmacıların mikro ve nano ölçekli fenomenleri incelemelerine olanak sağlar.

Mikro/Nanobaloncuklar, teşhis ve tedavi işlevlerini birleştiren teranostik yaklaşımların ortaya çıkmasına olanak sağlar. Görüntüleme yeteneklerini ve terapötik özelliklerini tek bir ajan içine entegre ederek, bu balonlar teşhislerin yapıldığı, tedavilerin uygulandığı ve tedavi yanıtlarının tek bir platform kullanılarak izlendiği kişiselleştirilmiş tip yaklaşımlarını mümkün kılar.

Genel olarak, mikro/Nanobaloncuklar, tıbbi görüntüleme, hedefe yönelik ilaç taşımacılığı, terapötikler, araştırma ve yenilikçi teranostik yaklaşımların geliştirilmesinde önemli bir rol oynamaktadır. Benzersiz özellikleri ve çok yönlü uygulamaları, sağlık sonuçlarının iyileştirilmesine ve çeşitli bilimsel alanlardaki bilgimizin genişletilmesine değerli araçlar sunar. Gelecekte birçok açıdan geliştirilmeye açık teknolojileri bünyesinde barındırır.

Kaynaklar

1. Thi Phan KK, Truong T, Wang Y, Bhandari B. Nanobubbles: Fundamental characteristics and applications in food processing. *Trends in Food Science & Technology*. 2020;95:118-30.
2. Wang Q, Zhao H, Qi N, Qin Y, Zhang X, Li Y. Generation and Stability of Size-Adjustable Bulk Nanobubbles Based on Periodic Pressure Change. *Scientific Reports* 2019;9(1):1118.
3. Lohse D., X Z. Surface nanobubbles and nanodroplets. *Reviews Of Modern Physics* 2018.
4. Park B, Yoon S, Choi Y, Jang J, Park S, Choi J. Stability of Engineered Micro or Nanobubbles for Biomedical Applications. *Pharmaceutics..* 2020;12(11).
5. Lombard J, Biben T, Merabia S. Threshold for Vapor Nanobubble Generation Around Plasmonic Nanoparticles. *The Journal of Physical Chemistry C*. 2017;121(28):15402-15.
6. Johnson BD, Cooke RC. Generation of Stabilized Microbubbles in Seawater. *Science* 1981;213(4504):209-11.
7. Attard P. The stability of nanobubbles. *The European Physical Journal Special Topics*. 2013;223(5):1-22.
8. Yasui K, Tuziuti T, Kanematsu W. Mysteries of bulk nanobubbles (ultrafine bubbles); stability and radical formation. *Ultrason Sonochemistry* 2018;48:259-66.
9. Ljunggren S, Eriksson JC. The lifetime of a colloid-sized gas bubble in water and the cause of the hydrophobic attraction. *Colloids and Surfaces A: Physicochemical and Engineering Aspects* 1997;129-130:151-5.

10. Kanematsu W, Tuziuti T, Yasui K. The influence of storage conditions and container materials on the long term stability of bulk nanobubbles — Consideration from a perspective of interactions between bubbles and surroundings. *Chemical Engineering Science* 2020;219:115594.
11. Yasui K, Tuziuti T, Kanematsu W, Kato K. Dynamic Equilibrium Model for a Bulk Nanobubble and a Microbubble Partly Covered with Hydrophobic Material. *Langmuir*. 2016;32(43):11101-10.
12. Vehmas T, L M. Metastable Nanobubbles. *ACS Omega*. 2021;6:8021-7.
13. Degens ET, von Herzen RP, Wong H-K, Deuser WG, Jannasch HW. Lake Kivu: structure, chemistry and biology of an East African rift lake. *Geologische Rundschau*. 1973;62(1):245-77.
14. Kyza GZ, Mitropoulos AC. From Bubbles to Nanobubbles. *Nanomaterials (Basel)*. 2021;11(10).
15. Theodorakis P, Che Z. Surface nanobubbles: Theory, simulation, and experiment. A review. *Advances in Colloid and Interface Science*. 2019;272:101995.
16. Michailidi ED, Bomis G, Varoutoglou A, Efthimiadou EK, Mitropoulos AC, Favvas EP. Fundamentals and applications of nanobubbles. Advanced Low-Cost Separation Techniques in Interface Science. *Interface Science and Technology* 2019. p. 69-99.
17. Zargarzadeh L, Elliott JA. Thermodynamics of Surface Nanobubbles. *Langmuir*. 2016;32(43):11309-20.
18. Peng H, Birkett GR, Nguyen AV. Progress on the Surface Nanobubble Story: What is in the bubble? Why does it exist? *Advance Colloid Interface Science* 2015;222:573-80.
19. Falzarano MS, Argenziano M, Marsollier AC, Mariot V, Rossi D, Selvatici R, et al. Chitosan-Shelled Nanobubbles Irreversibly Encapsulate Morpholino Conjugate Antisense Oligonucleotides and Are Ineffective for Phosphorodiamidate Morpholino-Mediated Gene Silencing of DUX4. *Nucleic Acid Therapy*. 2021;31(3):201-7.
20. Fix SM, Borden MA, Dayton PA. Therapeutic gas delivery via microbubbles and liposomes. *Journal of Control Release* 2015;209:139-49.
21. Unger EC, Porter T, Culp W, Labell R, Matsunaga T, Zutshi R. Therapeutic applications of lipid-coated microbubbles. *Advanced Drug Delivery Reviews* 2004;56(9):1291-314.
22. Yano Y, Hamano N, Haruta K, Kobayashi T, Sato M, Kikkawa Y, et al. Development of an Antibody Delivery Method for Cancer Treatment by Combining Ultrasound with Therapeutic Antibody-Modified Nanobubbles Using Fc-Binding Polypeptide. *Pharmaceutics* 2022;15(1).
23. Jugnot N, Massoud TF, Dahl JJ, Paulmurugan R. Biomimetic nanobubbles for triple-negative breast cancer targeted ultrasound molecular imaging. *Journal of Nanobiotechnology*. 2022;20(1):267.
24. Azevedo A, Etchepare R, Calgaroto S, Rubio J. Aqueous dispersions of nanobubbles: Generation, properties and features. *Minerals Engineering* 2016;94:29-37.
25. Favvas EP, Kyza GZ, Efthimiadou EK, Mitropoulos AC. Bulk nanobubbles, generation methods and potential applications. *Current Opinion in Colloid & Interface Science* 2021;54.
26. Pote AK, et al. State of Art Review on Nanobubbles. *Advanced Materials Letters* 2021;12:1-9.
27. Sekine S, Mayama S, Nishijima N, Kojima T, Endo-Takahashi Y, Ishii Y, et al. Development of a Gene and Nucleic Acid Delivery System for Skeletal Muscle Administration via Limb Perfusion Using Nanobubbles and Ultrasound. *Pharmaceutics*. 2023;15(6).
28. Banche G, Allizond V, Mandras N, Finesso N, Luganini A, Genova T, et al. Antimicrobial oxygen-loaded nanobubbles as promising tools to promote wound healing in hypoxic human keratinocytes. *Toxicology Reports* 2022;9:154-62.
29. Ma Y, Li J, Zhao Y, Hu B, Liu Y, Liu C. Nanobubble-mediated co-delivery of Ce6 and miR-195 for synergized sonodynamic and checkpoint blockade combination therapy with elici-

- tation of robust immune response in hepatocellular carcinoma. *European Journal of Pharmaceutics Biopharmaceutics* 2022;181:36-48.
- 30. Xu J, Salari A, Wang Y, He X, Kerr L, Darbandi A, et al. Microfluidic Generation of Mono-disperse Nanobubbles by Selective Gas Dissolution. *Small*. 2021;17(20):2100345.
 - 31. Schmidt BJ, Sousa I, van Beek AA, Bohmer MR. Adhesion and ultrasound-induced delivery from monodisperse microbubbles in a parallel plate flow cell. *Journal of Control Release*. 2008;131(1):19-26.
 - 32. Ma R, Nai J, Zhang J, Li Z, Xu F, Gao C. Co-delivery of CPP decorated doxorubicin and CPP decorated siRNA by NGR-modified nanobubbles for improving anticancer therapy. *Pharmaceutical Development of Technology* 2021;26(6):634-46.
 - 33. Eklund F, Alheshibri M, Swenson J. Differentiating bulk nanobubbles from nanodroplets and nanoparticles. *Current Opinion in Colloid & Interface Science* 2021;53.
 - 34. Ishida N, Inoue T, Miyahara M, Higashitani K. Nano Bubbles on a Hydrophobic Surface in Water Observed by Tapping-Mode Atomic Force Microscopy. *Langmuir* 2000;16:6377-80.
 - 35. Lou S-T, Ouyang Z-Q, Zhang Y, Li X-J, Hu J, Li M-Q, et al. Nanobubbles on solid surface imaged by atomic force microscopy. *Journal of Vacuum Science & Technology B: Microelectronics and Nanometer Structures* 2000;18(5).
 - 36. Alheshibri M, Qian J, Jehannin M, Craig VS. A History of Nanobubbles. *Langmuir* 2016;32(43):11086-100.
 - 37. Cavalli R, Bisazza A, Rolfo A, Balbis S, Madonnaripa D, Caniggia I, et al. Ultrasound-mediated oxygen delivery from chitosan nanobubbles. *International Journal of Pharmaceutics* 2009;378(1-2):215-7.
 - 38. Jin J, Li M, Li J, Li B, Duan L, Yang F, et al. Xenon Nanobubbles for the Image-Guided Preemptive Treatment of Acute Ischemic Stroke via Neuroprotection and Microcirculatory Restoration. *ACS Applied Mater Interfaces* 2021;13(37):43880-91.
 - 39. Liu Y, Miyoshi H, Nakamura M. Encapsulated ultrasound microbubbles: Therapeutic application in drug/gene delivery. *Journal of Controlled Release*. 2006;114:89-99.
 - 40. Wang T, Choe JW, Pu K, Devulapally R, Bachawal S, Machtaler S, et al. Ultrasound-guided delivery of microRNA loaded nanoparticles into cancer. *Journal of Controlled Release* 2015;203:99-108.
 - 41. Silindir M, Özer AY. Sterilization Methods and the Comparison of E-Beam Sterilization with Gamma Radiation Sterilization. *FABAD Journal of Pharmaceutical Sciences* 2009;34:43-53.
 - 42. Senthilkumar G, Aravind Kumar J. Nanobubbles: a promising efficient tool for therapeutic delivery of antibacterial agents for the *Staphylococcus aureus* infections. *Applied Nanoscience*. 2023;1:1-14.
 - 43. Baspinar Y, Erel-Akbaba G, Kotmakci M, Akbaba H. Development and characterization of nanobubbles containing paclitaxel and survivin inhibitor YM155 against lung cancer. *International Journal of Pharmaceutics*. 2019;566:149-56.
 - 44. Hamarat Sanlier S, Ak G, Yilmaz H, Unal A, Bozkaya UF, Taniyan G, et al. Development of Ultrasound-Triggered and Magnetic-Targeted Nanobubble System for Dual-Drug Delivery. *Journal of Pharmaceutical Science* 2019;108(3):1272-83.
 - 45. Argenziano M, Bessone F, Dianzani C, Cucci MA, Grattarola M, Pizzimenti S, et al. Ultrasound-Responsive Nrf2-Targeting siRNA-Loaded Nanobubbles for Enhancing the Treatment of Melanoma. *Pharmaceutics* 2022;14(2).
 - 46. Hsiao YH, Kuo SJ, Tsai HD, Chou MC, Yeh GP. Clinical Application of High-intensity Focused Ultrasound in Cancer Therapy. *Journal of Cancer*. 2016;7(3):225-31.
 - 47. Duan S, Guo L, Shi D, Shang M, Meng D, Li J. Development of a novel folate-modified nanobubbles with improved targeting ability to tumor cells. *Ultrasonics Sonochemistry*. 2017;37:235-43.

48. Chen H, Zhou X, Gao Y, Zheng B, Tang F, Huang J. Recent progress in development of new sonosensitizers for sonodynamic cancer therapy. *Drug Discovery Today* 2014;19:502-19.
49. Åslund AKO, Berg S, Gadel Hak SH, Mørch Y, Torp SH, Sandvig A, et al. Nanoparticle delivery to the brain--By focused ultrasound and self-assembled nanoparticle-stabilized microbubbles. *Journal of Controlled Release* 2015;220:287-94.
50. Cavalli R, Bisazza A, Giustetto P, Civra A, Lembo D, Trotta G, et al. Preparation and characterization of dextran nanobubbles for oxygen delivery. *International Journal of Pharmaceutics* 2009;381(2):160-5.
51. Fournier L, de La Taille T, Chauvierre C. Microbubbles for human diagnosis and therapy. *Biomaterials*. 2023;294:122025.
52. Su C, Ren X, Nie F, Li T, Lv W, Li H, et al. Current advances in ultrasound-combined nanobubbles for cancer-targeted therapy: a review of the current status and future perspectives. *RSC Advances* 2021;11(21):12915-28.
53. Hernot S, Klibanov AL. Microbubbles in ultrasound-triggered drug and gene delivery. *Advanced Drug Delivery Reviews*. 2008;60:1153-66.
54. Agessandro Abrahao A, Meng Y, Llinas M, Huang, Y., Hamani C, Mainprize T, et al. First-in-human trial of blood-brain barrier opening in amyotrophic lateral sclerosis using MR-guided focused ultrasound. *Nature Communications*. 2019.
55. Endo-Takahashi Y, Kurokawa R, Sato K, Takizawa N, Katagiri F, Hamano N, et al. Ternary Complexes of pDNA, Neuron-Binding Peptide, and PEGylated Polyethyleneimine for Brain Delivery with Nano-Bubbles and Ultrasound. *Pharmaceutics*. 2021;13(7).
56. Chan MH, Chen W, Li CH, Fang CY, Chang YC, Wei DH, et al. An Advanced In Situ Magnetic Resonance Imaging and Ultrasonic Theranostics Nanocomposite Platform: Crossing the Blood-Brain Barrier and Improving the Suppression of Glioblastoma Using Iron-Platinum Nanoparticles in Nanobubbles. *ACS Applied Material Interfaces*. 2021;13(23):26759-69.
57. Fix SM, Koppolu BP, Novell A, Hopkins J, Kierski TM, Zaharoff DA, et al. Ultrasound-stimulated phase-change contrast agents for transepithelial delivery of macromolecules, toward gastrointestinal drug delivery. *Ultrasound in Medicine & Biology*. 2019;45:1762-76.
58. Moyer LC, Timbie KF, Sheeran PS, Price RJ, Miller GW, Dayton PA. High-intensity focused ultrasound ablation enhancement in vivo via phase-shift nanodroplets compared to microbubbles. *Journal of Therapeutic Ultrasound*. 2015;3:7.
59. Meloni MF, Livraghi T, Filice C, Lazzaroni S, Calliada F, Perretti L. Radiofrequency Ablation of Liver Tumors: The Role of Microbubble Ultrasound Contrast Agents. *Ultrasound Quarterly*. 2006;22(1).
60. Perera RH, Solorio L, Wu, H., Gangolli M, Silverman E, Hernandez, C., et al. Nanobubble Ultrasound Contrast Agents for Enhanced Delivery of Thermal Sensitizer to Tumors Undergoing Radiofrequency Ablation. *Pharmaceutical Research* 2014;31:1407-17.
61. Durham PG, Dayton PA. Applications of sub-micron low-boiling point phase change contrast agents for ultrasound imaging and therapy. *Current Opinion in Colloid & Interface Science*. 2021;56.
62. Unger E, Porter T, Lindner J, Grayburn P. Cardiovascular drug delivery with ultrasound and microbubbles. *Advanced Drug Delivery Reviews* 2014;72:110-26.
63. Xie F, Tsutsui JM, Lof J, Unger EC, Johanning J, Culp WC, et al. Effectiveness of lipid microbubbles and ultrasound in declotting thrombosis. *Ultrasound Medical Biology* 2005;31(7):979-85.
64. Unger E. Nanobubble-Enhanced Sonothrombolysis: From Benchtop to Bedside. *Therapeutic Ultrasound* 2006.
65. Paproski R.J, Forbich A, Hitt M., Zemp R. RNA Biomarker release with ultrasound and phase change nanodroplets. *Ultrasound in Medicine & Biology* 2014;1-10.