THE SCIENTIFIC FRONTIERS

Popular Article

OPEN ACCESS

Medical Microbubbles- A gamechanger in drug delivery

Deepthi V[1], Pravin Maruti Madabhavi[2], Gobika S[3], M Bagavathi[4]

[1]PhD Scholar, Division of Pharmacology & Toxicology, ICAR- Indian Veterinary Research Institute, Izatnagar, Barielly, Uttar Pradesh, [2]Assistant professor, Division of Pharmacology & Toxicology, Shourabh College of Veterinary Science, Hindaun city, Rajasthan, [3]M.V.Sc, Animal Nutrition, TANUVAS, Assistant Professor, Animal husbandry Department, Vanavarayar Institute of Agriculture, Pollachi, Tamilnadu.

ARTICLE HISTORY

Received: November 10, 2025
Accepted: November 10, 2025
Published: December 1, 2025

Abstract

Bubbles can be found in many facets of our daily lives, such as soap bubbles, soft beverages, and the bubbles formed by ocean waves. But the innovation of medical microbubbles is having potential significance in therapeutics. Drug delivery has made significant strides, from taking care to prevent air emboli during injection to administering microbubbles as drug. Theranostics uses microbubbles in conjunction with ultrasound. This article provides a concise summary of how these microscopic bubbles were innovated, how they have come to dominate medication delivery in the future, emphasizing their mode of action and uses in gene therapy, cancer treatment and blood-brain barrier bridging.

Corresponding author's email: *deepthi99v@gmail.com*

DOI: https://doi.org/10.5281/zenodo.19676283

INTRODUCTION

Since its initial development to improve contrast in ultrasound (US) imaging, microbubbles (MB) have become the primary means of delivering medications. The unique characteristics of US waves may be effectively utilized to provide targeted therapy with reduced side effects, improved spatiotemporal control over drug dispersion, increased intratissue bioavailability of therapeutic chemicals and on-demand activation and a gene carrier.

FIRST GENERATION MICROBUBBLES

The initial generation of ultrasonic contrast agents were primarily shown as one-pass-only bubbles that contained air or gases with comparable densities, such as nitrogen, oxygen, etc. Due to the relatively high solubility of air components in physiological fluids (blood), air diffusion is the main disadvantage. The brief half-life of such bubbles in the bloodstream limited their use. For instance, the first microbubble, called Echovist (Bayer Schering Pharma, Berlin, Germany), was commercially accessible in 1991. It was made up of an air core covered in galactose shell, a sugar that is frequently found in food. The covering decreased bubble dissolution and inhibited coalescence.

SECOND GENERATION MICROBUBBLES

Due to their high molecular weight, low solubility and lower perfusion rate in water, sulfur hexafluoride or perfluorocarbons were used as gases for the core of the second generation of microbubbles. These microbubbles demonstrated a discernible increase in echogenicity and circulation time in the bloodstream. These microbubbles have a biodegradable phospholipid, polymer, or protein shell instead of a sugar coating.

MECHANISM OF ACTION

Cavitation

The bulk of the microbubbles are found along the blood vessel's midline, and their intravascular distribution is similar to that of red blood cells rather than plasma. Particularly in bigger vessels, this axial movement of the microbubbles within the vessel prevents the ligand and receptor from successfully interacting with the endothelium. Cavitation is a process that requires energy. Either inertial or stable cavitation could be the cause. The rhythmic movements of the MBs in stable cavitation cause shear stresses, microstreamings and localized pressure fluctuations, which temporarily but significantly increase the permeabilization of biological barriers (such as cell membranes). This improves pharmacodynamic efficacy and bioavailability by increasing the intratissue uptake of medicinal drugs. When the microbubbles collapse, violent microstreaming is created.

To encourage medication diffusion into different tissues and lesions, microstreaming could be used. Microjets and shockwaves are examples of powerful events produced by inertial cavitation. Although they are generally linked to high cell mortality, these high-speed acoustic impacts can produce temporary or permanent holes in cell membranes, causing localized tissue disruption that may also aid in medication uptake[1]. The intracellular transfer of medications, genes, or other therapeutic substances is thought to be facilitated by this method. Cell detachment and permanent membrane disruption are caused by irregular bubble collapse near the boundary, while viable membrane poration and enhanced drug absorption occur in cells farther away, according to Ohl and co-workers. The transcapillary transit of macromolecules or nanospheres co-delivered with microbubbles is increased by the local shock waves. Reactive oxygen species (ROS), are produced during pyrolysis when the sonosensitizers break down in the presence of intense heat from inertial cavitation. Through lipid peroxidation and other biological processes, the produced ROS can cause cancer cells to undergo apoptosis. In certain situations, such as cancer (immuno)therapy, where cell destruction does not jeopardize safety, it is very beneficial to induce cell death. However, preserving a high level of cell viability following sonoporation is still essential for other drug delivery applications, such as gene therapy.

Sonoporation

When MBs are triggered by US waves and oscillate close to cells or biological barriers, they increase their permeability into these barriers, which improves the penetration and extravasation of external substances. This process is known as sonoporation. A pore may be temporary or fatal. The size of the cargo that can be delivered is restricted by the pore's size. Ward and co-workers were the first to identify that the distance between bubbles and target cells affects how successful sonoporation is, and they found that the effectiveness quickly decreases as the spacing increases[2]. According to Zhou and co-workers, membrane poration is maximized when the bubbles come into direct contact with the membrane. It then rapidly decreases as the distance between the bubbles and the cells increases, halving at a distance equal to the bubbles size and disappearing entirely at a distance three times the bubbles size because even during the bubble's expansion phase, there was no contact with the cell membrane[3]. Yang et al. found a strong correlation between applied driving pressure and pore diameters[4]. Maintaining the peak negative pressure improves cavitation and sonoporation at lower ultrasonic frequencies, indicating the significance of wave amplitude. Pore resealing procedure following sonoporation and established that pore size has a significant impact on resealing.

Sonoluminescence

The production of light during the US-mediated cavitation effect at physiologically relevant temperatures is known as sonoluminescence. Microbubbles exposed to mild therapeutic US conditions experience a higher number of sonoluminescence events. Individual sonoluminescence occurrences, however, have a smaller amplitude. The domains of photodynamic therapy and sonodynamic therapy (PDT and SDT respectively) may benefit greatly from the production of sonoluminescence by microbubbles and ultrasound. The surrounding sensitizers may absorb the sonoluminescence from cavitating microbubbles, activating them. The chemical properties of the medication itself can be altered by ultrasound. According to reports, ultrasound can activate light-sensitive compounds like hematoporphyrins and harmless chemicals, which can kill cancer cells and prevent restenosis. Some substances, including cytosine arabinoside, and lidocaine, can make a person more sensitive to ultrasonic waves. Ultrasound activates sonosensitizers, which may function similarly to photosensitive agents but employ ultrasonic energy instead of light energy.

THERAPEUTIC USES

Blood-brain barrier

Microbubbles are the only known safe and non-invasive way to temporarily break the blood-brain barrier, and their spatiotemporal selectivity and reversible poration capabilities make them particularly useful for medication administration to the brain.

Microbubbles tumour therapy

Chemotherapy can be used as a neoadjuvant treatment, an adjuvant treatment or when the patient is not a good candidate for surgery or radiation therapy. Also, because the mechanism of action of certain anticancer treatments, such as radiotherapy or certain chemotherapeutics (doxorubicin (DOX), platinum complexes alkylating agents, topoisomerase inhibitors, camptothecins, and arsenic agents), depends on the production of reactive oxygen species and free radicals, tumor oxygenation is crucial. By detecting the strength of ultrasonic pressure waves and analyzing the pattern, the precise position of microbubbles (laden with magnetic nanoparticles) in cancer treatment can be found. Because microbubbles have antibodies on their surface that are particular to tumor tissue, they can concentrate in the tumor location.

Actually, the microbubbles reflect pressure waves of varying intensities than those found in bodily tissues. This enables the bubbles to rupture when necessary, releasing the drug content at the appropriate treatment location. To avoid treatment resistance, oxygen-filled microbubbles have been investigated to regulate damaged blood arteries and restore tumor oxygenation. The dissolved oxygen contained in the microbubble's core is released locally in the tumor vasculature through microbubble cavitation, and it can then diffuse into the tumor microenvironment (TME) to facilitate TME oxygenation. An oxygen supply can prevent tumor necrosis by keeping hypoxic cells alive for a longer amount of time. Therefore, it is beneficial for delivering nutrients and drugs to the tumor cells. Lastly, reoxygenating some TME (tumor microenvironment) regions encourages immune cell infiltration and activation, which may affect the TME's immunosuppressive properties. As demonstrated in the case of DOX, oxygen delivery also contributes to the normalization of the tumor microvasculature, which can ensure more efficient drug transport to the tumor.

As drug delivery

The medication may be forced from the vasculature into or through the vessel wall by a ballistic impact when cavitation takes place. Additionally, since the drug carriers are essentially contrast chemicals, ultrasound can be used to track medication distribution. Generally speaking, this strategy will likely work best for highly active medications that don't need to be taken in large amounts to have a therapeutic effect. As an alternative, ultrasonography can be used to guide them to the tumor, where the medicine can be released when the bubbles are broken by the ultrasound waves. Medications can be integrated into the MB shell, implanted inside the shell, or connected to a carrier that is fastened to the MB. The US can then cause the release of the medications at the specified place. In situ, a sizable bubble (20–30 µm) will form, temporarily depositing in the microvasculature and blocking blood flow for 5–10 minutes. Preventing a rapid drug washout further improves the local medication efficacy[5]. According to Willmann and co-workers, it is normal to wait around 30 minutes between administering several bolus injections of the targeted microbubble. It is anticipated that the therapeutic effectiveness of drug-loaded microbubbles will be enhanced by raising the concentration of microbubbles produced. Upon ultrasonic activation, drugs are released quickly; nevertheless, the drug may affect the stability of the shell, and microbubble behavior and release may take place in regions such as the liver, spleen or lungs where microbubbles are trapped. Microbubble dosages should be high enough to allow for adequate bubble-cell interactions while being low enough to avoid the creation of massive bubble clusters, which can produce significant obstructions in vessels, distort the acoustic field, and decrease bubble-cell interactions.

As gene delivery

Without the introduction of exogenous microbubbles, ultrasound can be utilized to increase gene expression since it directly affects gene expression. Microbubbles are used to achieve a synergistic impact, and cavitation and ultrasound are likely mechanisms. It shows a gene being bound by a cationic (positively charged) microbubble. Their capacity to encapsulate nucleic acids inside the MB instead of attaching them to its surface makes them special. To sum up, MBs offer a promising method of delivering genes. The accelerated distribution of DNA across the cell membrane is likely made possible by the rapid oscillation of microbubbles on the cell surface, microstreaming, or shock waves caused by high acoustic pressures. Microbubbles are used as sonic "microjets" in site-specific, ultrasound-directed therapies, creating a microgene gun that enables macromolecules to successfully penetrate the vascular endothelial boundaries and reach the cytoplasm. Similar to systemic chemotherapy, the main challenge, in this case, is the ineffectiveness of gene delivery to cancer cells because of the tumor microenvironment and vasculature's distribution-limiting characteristics. Geers and co-workers found that inertial cavitation in microbubbles facilitates the direct cytoplasmic entrance of adeno-associated viruses that are adhered to the microbubble's surface without the need for endocytosis[6].

CONCLUSION

Several studies have provided insight into the mechanism underlying the operation of these ultrasonic responsive microbubbles and these discoveries have been applied to numerous real-world scenarios. This technique of drug delivery needs precise manufacturing protocols and delivery setups. Thus, for therapeutic microbubbles to become a revolutionary new technology in the pharmaceutical industry, much more research is still required. However, ultrasound guided microbubbles offers a promising insights for drug delivery development in medical applications.

REFERENCES

C.D. Ohl, M. Arora, R. Ikink, N. de Jong, M. Versluis, M. Delius, D. Lohse, Sonoporation from jetting cavitation bubbles, Biophys J 91 (2006) 4285–4295.

M. Ward, J. Wu, J.-F. Chiu, Experimental study of the effects of optison® concentration on sonoporation in vitro, 26 (7) (2000) 1169–1175.

Y. Zhou, K. Yang, J. Cui, J. Ye, C. Deng, Controlled permeation of cell membrane by single bubble acoustic cavitation, 157 (1) (2012) 103–111.

F. Yang, N. Gu, D. Chen, X. Xi, D. Zhang, Y. Li, J. Wu, Experimental study on cell self-sealing during sonoporation, 131 (3) (2008) 205–210.

J.K. Willmann, Z. Cheng, C. Davis, A.M. Lutz, C.H. Nielsen, Targeted microbubbles for imaging tumor angiogenesis : assessment of whole-body biodistribution with dynamic micro-PET in mice, Radiology 249 (2008) 212– 219.