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Microbubble Drug Delivery System

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A B S T R A C T

Combining microbubble agents with therapeutic substances or administering them in conjunction with pharmaceutical agents (such as plasmid DNA for transfection) is how ultrasound assisted medication delivery and activation is carried out. This has been accomplished in a number of model systems both in vitro and in vivo. Clinical investigations for the targeted acceleration of thrombolytic enzyme function using ultrasound and microbubbles. A step toward the

implementation of targeted, individualized diagnostics and therapy will be provided via microbubble targeting and an ultrasound-assisted microbubble-based drug delivery system. A common, affordable, non-invasive, real-time, and secure theranostic modality used in preclinical research and clinical settings for anatomical, molecular, and therapeutic imaging is ultrasonic. Another aspect of the novel ultrasound molecular imaging application has been made possible by the development of non-targeted and molecularly-targeted ultrasound contrast agents. Ultrasound is a non-invasive treatment tool that may localize mechanical and thermal effects in addition to diagnosing and tracking disease processes at the molecular level. We got an overview of the use of ultrasound and microbubbles in the microenvironment of tumour tissue for medication administration and immune system activation. Ultrasound imaging has consistently shown interest in the use of microbubble contrast agents for general tissue identification and perfusion. Microbubbles have exceptional detection sensitivity and only require a modest dosage when used as contrast materials. Due to targeting ligands on their surface, microbubbles can selectively gather in areas of interest when vascular endothelium receptor molecules rise. In animal models, selective contrast imaging of inflammation, ischemia-reperfusion injury, thrombosis, and angiogenesis has been achieved. Ultrasound-assisted drug delivery and activation has been achieved in a variety of model systems both in vitro and in vivo by co-administering pharmacological agents (such plasmid DNA for transfection) or by combining microbubble agents with therapeutic substances. Targeted thrombolytic enzyme function acceleration using ultrasound and microbubbles has already been the subject of clinical studies. Microbubble targeting and ultrasound-assisted microbubble-based drug delivery devices will be a step toward the deployment of targeted, customized diagnostics and therapies.

Keywords: Microbubble, Thrombolyticenzyme, Plasmid DNA, Microspheres, Blood capillaries, Ultrasonography

INTRODUCTION

"Microbubble" describes as microspheres that are packed with air or gas and suspended in a liquid carrier phase, which frequently occurs when air or gas is injected. Surfactants are added to the liquid phase to control the stability and surface properties of the bubble. Because microbubbles are usually smaller than red blood cells, they can enter even the smallest blood capillaries and, when ultrasound is applied, release drugs or genes that are imbedded on their surface. Size of the microbubble make it easier for medication delivery mechanism. Gas included in the microbubble is surrounded by a membrane that may consist of biocompatible biopolymers,polymers, surfactants,protein ,lipids or its combination..Microbubbles carry a drug or gene until a specific area of interest reached, and then ultrasound is used In general, there are numerous uses for microbubbles. However, in the biomedical field, they are mostly used as diagnostic instruments in combination with ultrasonography to do molecular imaging of many organs, including cancer. These are also proposed for delivering genes and medications to targeted regions in conjunction with other methods. Microbubbles are often between 0.5 and 10 micrometers in size to burst the microbubbles, causing site specific delivery of active materials. Because perfluorocarbon-filled microbubbles are stable enough to circulate in the vasculature as blood pool agents, they act as transporters of these agents until they reach the region of interest. The microbubbles can then be ruptured at this site on the skin's surface using ultrasound to release the medication locally. The systemic use of both drug concentrations alone and lesser medicine concentrations is then made possible by this technique. In addition to their well-known application as contrast agents for diagnostic ultrasound, microbubbles have been demonstrated to be an effective technique for the targeted administration of genes and drugs.Drugs are added to the microbubbles in a number of ways, such as via binding to the microbubble shell or attaching site-specific ligands.

Table 1 - Example of microbubbles:

Name	Gas	Shell
Optison	Perfluropropane	Albumin
Albunex	Air	Albumin
Sonazaoid	Perfluropropane	Lipid
Levosist	Air	Fattyacid

Microbubble Formulation

1. Shell composition: microbubbles covered in phospholipids

The thin, soft shell of these microbubbles (3-5 nm) offers superior acoustic response for contrast imaging.

• Microbubble coated with proteins:

This has a natural protein layer that is thicker and stiffer (15-150 nm).

• Microbubbles coated with polymers:

These consist of a thick, rigid coating of biodegradable, natural, or synthetic polymers that ranges in thickness from 50 to 500 nm.

2. Gas composition: The stability of microbubbles is significantly influenced by the gas composition. It is made up of the gasses PF6 and SF6.

3. Size and microbubble volume dose: Different acoustic responses are caused by the different components of microbubbles, such as the shell, gas core size, concentration, and suggested dosage.

4. Techniques to regulate the process of microbubble size distribution:

Defferential centrifugation techniques and microfluidic devices.

Mechanism For Target Drug Delivery of Microbubbles

- The violent collapse of microbubbles called inertial cavitation. Two potential methods for delivering genes and medications are emerging. A direct delivery of materials attached to microbubbles without the use of ultrasound contrast agents is the second method. The first is ultrasound-mediated microbubble destruction, which is predicated on the cavitation of microbubbles brought on by ultrasound application. In order to improve drug delivery with ultrasound (photodynamic therapy), a neutron beam (boron neutron capture therapy), and a magnetic field (targeted accumulation of magnetic drug carrier in the tissue), microbubbles in the insonified field lower the peak negative pressure required. a few methods for breaking up microbubbles.

Cavitation: Inertial cavitation is the violent collapse of microbubbles.

- Acoustic radiation forces: Ultrasound can cause microbubbles to tunnel through soft tissue and squeeze through the endothelium by translating them in the direction of the ultrasound wave.
- Sonoporation: By creating holes in a surrounding surface with ultrasound and microbubbles, permeability across natural barriers is increased.

Basic characteristics of a micro bubble

1. An increase in the gas pressure inside

2. The production of free-radical ions and the creation of nanobubbles are caused by an increase in ion concentration near the gas-water interface.

The main goal of drug delivery and targeting is to improve therapeutic activity in the sick area while reducing unwanted side effects, such toxicity, in the healthy tissues. Recently, research combining drugs with an externally applied "trigger" has gained more attention. This technique regulates medication activity and/or deposition in the targeted area using mechanical energy or an external energy field, such as light near the magnet. One mechanical energy source that has been utilized to improve the delivery of drugs and therapeutic genes is ultrasound irradiation.

The use of ultrasonic waves as a "controlling" field for medications has several advantages. Nanomedicine, which capitalizes on the unique properties of nanoparticles, has revolutionized the detection and treatment of neurological diseases. One of the numerous nanotechnological advancements that

shows promise in overcoming the blood-brain barrier (BBB) and enhancing the precision and efficacy of therapeutic treatments is ultrasound-mediated drug delivery using micro- and nanobubbles.

This paper explores the principles, current clinical uses, challenges, and possible future directions of ultrasound-mediated drug delivery devices for the treatment of stroke, brain tumors, neurodegenerative diseases, and neuroinflammatory disorders. Additionally, a comprehensive analysis of how nanomedicine affects neurological conditions is given, along with a discussion of ongoing clinical trials and potential advancements in the field.

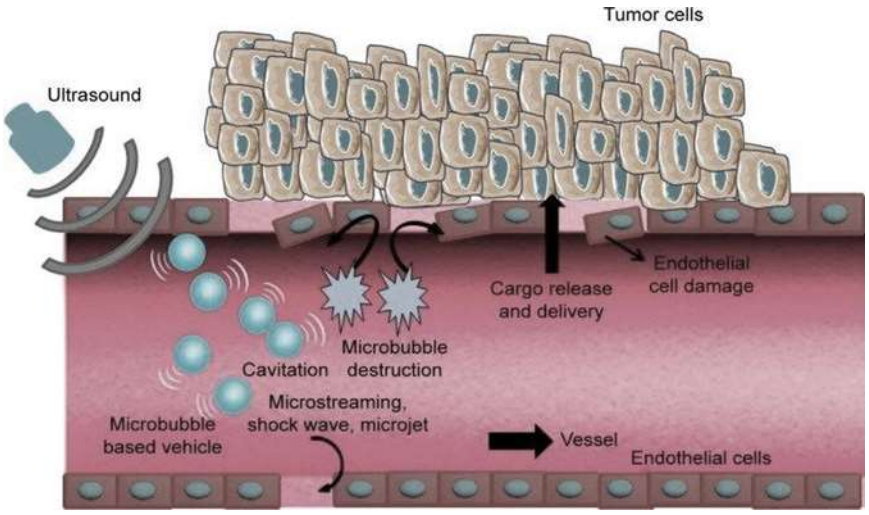

Fig.1. Demonstrates how cancer immunotherapy uses ultrasound-mediated microbubble destruction (UMMD).

The following advantages come with using a microbubble for drug delivery:

i. Because the microbubble delivers the drug close to its target, a lower dosage of the treatment is required than with traditional procedures.

ii. Because the drug is released near its target and at a low dosage, there is also a decrease in adverse effects, especially for antineoplastic drugs.

iii. By attaching various ligands, they can be used for tailored drug delivery.

FUS MBs, or focused ultrasound with microbubbles, can support an effective medication delivery method. Because of its restricted pressure field, the microbubble's oscillation and destruction are limited in medication delivery. To get around the drawbacks of FUS-MB DDSs, unfocused ultrasound with microbubbles and a movable acoustic lens can adjust and strengthen the pressure field for microbubble destruction. Cavitation, or the creation of microbubbles and their subsequent implosion in a fluidic environment, is a phenomena caused by pressure changes in tissue brought on by US waves.

Certain acoustic phenomena, such as microstreaming, shockwaves, and microjet forms, are produced by this mechanism. Transient cellular openings or disruption of intercellular connections can result from one or more of these sonic events, which increases the permeability and extravasation of the therapeutic chemicals into the targeted area.Microbubbles are a key element in enhancing the effects of US. The adoption of MBs in numerous medical specialties has been made possible by their adaptability.

In a number of medical specialties, such as oncology, neurology, cardiology, and gene therapy, US-mediated drug delivery has enormous promise. US improves the delivery of drugs to tumors in oncology, increasing their therapeutic benefit while reducing side effects. The US provides novel approaches to delivering medicinal drugs across the blood-brain barrier in neurology. Similar to this, US-mediated medication delivery has demonstrated potential in cardiology for boosting tissue healing by focusing on ischemic heart areas. Despite the wide range of potential uses, it is crucial to solve the inherent difficulties associated with this novel approach.

In the realm of US mediated drug delivery, a variety of methods and strategies have been investigated; however, MBs are given special attention in this study. Their important contribution to the field's development is what motivates this attention. MBs are now important drugs in targeted therapy rather than only experimental tools. The turning points and developments that have influenced MB-based drug delivery, emphasizing why it is a particularly promising and extensively studied strategy.

Although ultrasound incentive encourages drug transdermal penetration, it still needs to be improved because the majority of ultrasound energy is squandered in deeper biotissues and only a small percentage is applied to the drug delivery patch. An appropriate percentage of ultrasonic energy can be converted into electric energy thanks to the piezoelectric soft structure and microsized air pockets. To improve drug transdermal delivery, the enhanced drug flow and the complementary ultrasonic pressure and electric field work together.The size of the small air pockets, the chemical makeup of the drug molecules, and the strength of the ultrasonic motivation all affect how well the medicine is delivered. The patch's temperature stays within a safe range during delivery, and the slight temperature increase causes the thermochromic patch's color to change, which is a sign of successful ultrasound–patch matching.

Animal tests on a model delivery patch for pain relief show that the drug blood concentrations are 100% higher than when delivered solely by ultrasound and even more significantly improved when compared to static delivery without external motivations or only electric-field-motivated delivery.

Applications:

- Gene transfer:

Utilizing these microbubbles as instruments for gene transfer is their most promising usage. These microbubbles' key characteristics that make them effective for gene transfer are as follows:

• The gene associated to the microbubble is transported to its destination without being broken down by the different enzymes.

• Microbubbles are metabolically inert.

• When injected into the body, they do not trigger an immune reaction.

- Biomedical applications: Because microbubbles are elastic and compressible, they are utilized as contrast agents because they effectively reflect ultrasound and provide an acoustic impendance mismatch between fluids and biological tissues through compression and refraction.

Diagnostic tools:

  - liver imaging
  - cancer imaging
  - blood volume and perfusion
  - organ edge delineation
  - Inflammation
  - used to image gall bladder stones
  - scan malignancies that develop in the bod

- The Microbubble Drug Delivery System's Therapeutic Applications:
  - For medical ultrasound imaging, encapsulated gas microbubbles are frequently utilized as ultrasonic contrast agents.
  - Drug administration is another therapeutic purpose for encapsulated ultrasonic microbubbles. Microbubbles, which are extensively utilized in the cardiovascular system as well as for the diagnosis and therapy of tumors, have recently had targeting ligands affixed to their surface.
- Vascular thrombosis, which may be the primary cause of death overall, is responsible for the majority of occurrences of myocardial infarction and ischemic stroke. Blood flow must be promptly restored in order to improve the outcome of a heart attack or stroke. Sonothrombolysis, a largely non-invasive technique that disintegrates blood clots and restores blood flow, can be performed with microbubbles and ultrasound.together for sonothrombolysis, a generally non-invasive procedure that breaks up blood clots and restores blood flow.
- Ultrasound is mostly utilized for diagnostic purposes, but it can also be employed to influence cellular activity and the release or administration of anticancer medications.
- Ultrasound-mediated nano drug delivery for cancer treatment.:

Therapeutic ultrasound (TUS) has demonstrated promise as a treatment for cancer and as a way to trigger the release of specific drugs from nanocarrier systems.

- Ultrasound-activated microbubbles as a new intracellular medication delivery method for UTI: UTI is one of the most prevalent infectious infections in the world and causes significant financial and medical problems.During an acute UTI, uropathogenic bacteria enter the urothelial wall and create latent intracellular reservoirs. For this, microbubble medication delivery was shown to be the most effective. The bladder model's epical surface was buffered with the microbubble suspension before being subjected to ultrasound for 20 seconds at 1.1 MHz, 2.5 MPa, and 5500 cycles with a 20 ms pulse length.
- Microbubbles Delivery of Insulin Genes to the Pancreas: When rats exhibit a drop in blood sugar, insulin genes are transferred to the pancreas using the ultrasound-targeted micro bubble destruction (UTMD) technique. The bloodstream receives tiny gas-filled bubbles coated in DNA that codes for the insulin gene. The Islets of Langerhans, a pancreatic organ that contains the beta cells that produce insulin, is the next target of the ultrasonic beams. When the microbubbles in the surrounding blood vessels burst, the insulin gene is released. Additionally, the

penetration of the ultrasonic beams allowed DNA to flow through the beta cell membranes. Without having any effect on the pancreas, it decreases blood sugar.

- Targeted immunotherapy microbubbles :

- Monoclonal antibody immunotherapy aims to induce cell death by targeting specific antigens, sequences, or epitopes expressed at the disease target region.
- Immunological check point inhibitor therapy: These monoclonal antibodies (mAbs) work by preventing immunological check point receptors from functioning, hence activating T cells.
- Adoptive cell immunotherapy involves intravenous injection of resident T lymphocytes in vitro to target tumor antigens and initiate anticancer activity.
- cytokine delivery throughout the body to boost immunity. In order to elicit an immune response, vaccine immunotherapy entails delivering certain antigens or protein fragments.
- Microbubble as a technique for local medication delivery in endodontic treatment
- One practical method for enhancing root canal disinfection is microbubble infusion. Therefore, it might be regarded as a new method for a local drug delivery system .
- In order to elicit an immune response, vaccine immunotherapy entails delivering certain antigens or protein fragments.

- Animal-Based Research on Micro Bubble Cancer Therapy:

To determine how the inside environment impacts the efficacy of the micro bubble drug delivery devices, numerous research teams employ test animals, typically mice. This is carried out in order to determine the various Micro bubble technologies' effectiveness and possible hazards. Malignant cells of some kind are injected into the mice, and they are then let to proliferate until they reach the required size or volume. To assess the efficacy of the 10-Hydroxycamptothecin-loaded micro bubbles, researchers from Chongqing Medical University deliberately injected test participants with tumorous cancer cells in the dorsal flank region.

Challenges of microbubble drug delivery system:

- Short half life:

The brief half-life of microbubbles in circulation restricts the duration of treatment.

- Large size: Because microbubbles are only 1–10 micrometers in size, it is challenging for them to pass through epithelial cells and get to the target region.
- Microbubbles are caught in the lungs following intravenous infusions when gas shifts take place.This restricts their application to tumor endothelium and cardiovascular targets.
- Filtered by liver and spleen: These organs may be at risk for toxicity as a result of their filtering.
- Low ultrasonic frequencies and high mechanical indices (MI) are the two conditions under which microbubbles explode.
- Microvasculature ruptures: Hemolysis and local microvasculature ruptures can result from microbubble destruction.

May result in small negative events:

- Dizziness, erythematous rash, itching, nausea, and vomiting are among its symptoms

Future perspectives:

- With continuous research aimed at enhancing their effectiveness and mitigating their drawbacks, microbubble drug delivery systems appear to have a bright future.
- Microbubbles are essential for improving precision and focused medicine administration.
- Theranostics innovations present opportunities for individualized care.
- Treatment for cancer:

Ultrasound is used to burst the microbubbles,the drugs are released directly into the tumour.This targeted release of drugs can improve tumor response.

- The microbubbles are ruptured by ultrasound, allowing the medications to enter the tumor directly.The tumor response may be enhanced by this focused medication release.

- Microbubbles can be utilized to deliver inhibitors of bone resorption and compounds that target bone in osteoporosis.
- Microbubbles can be utilized to treat acute illnesses such urinary tract infections and brain infections.

Atherosclerosis: Genes, cholesterol-lowering medications, and anti-inflammatory substances can be delivered to atherosclerotic plaques using microbubbles.

- Myocardial infarction :Microbubbles can be used to transport stem cells,growth factors or other regenerative agents to damaged heart tissue.

Conclusion:

This review focuses on microbubble formulations intended for drug and cell delivery. Intravascular microbubbles can improve drug absorption into tissues when combined with targeted ultrasound therapy. It is feasible to attach medicinal molecules to microbubbles for release in ultrasound-activated organs and tissues. Microbubble drug delivery system effectively exploits ultrasound waves, aiming to augment extravasation and efficacy of therapeuticcompounds. Ultrasound mediated drug delivery presents an attractive alternative to traditional drug delivery system. In ultrasound based therapeutic drug delivery, use of microbubbles is of greater importanceultrasound based therapeutic drug delivery, use of microbubbles is of greater importance.Because of their high encapsulation effectiveness, targeted drug release, enhanced biocompatibility, and prolonged blood circulation, microbubbles have demonstrated significant potential in nanomedicine.They are safer, non-invasive, and better suited for concentrating on specific body parts.In fluid dynamics, chemistry, medicine, and other fields, bubbles are produced using microbubble generators.Microbubble-based drug delivery improves penetration without posing a risk of systemic toxicity..

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