ULTRASOUND GUIDED MICROBUBBLE TECHNOLOGY GUIDING THE FUTURE OF DRUG DELIVERY

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ABSTRACT

Current research supports ultrasound being a future method for treatment using micro bubble technology. A lipid shell coats the micro bubble to give it stability in the human vascular system and allows for gradual reabsorption with no harm to the patient. Micro bubbles work by excitation; the bubbles expand and contract rapidly when exposed to the pressure changes exerted by ultrasound waves, and thus resonates with the ultrasound. The increased resonance causes the bubbles to be several thousand times more reflective then regular tissue and this enhances grey-scale and Doppler imaging. The size of micro bubbles allows unopposed passage through the capillaries. Although micro bubbles were originally developed to enhance diagnostic testing, they can also be used as vectors for pharmaceutical and genetic materials. Properly designed Microbubble avoids extravasation to normal tissues and recognition by reticulo-endothelial system cells, which prolongs their circulation time after systemic injection. This allows their use in targeting cancerous or inflamed tissues. Passive targeting is based on enhanced permeability of defective microvasculature that allows extravasation of drug-loaded nanoparticles through large interendothelial gaps. In addition to enhanced vascular permeability, tumours demonstrate poor lymphatic drainage, this positive effect provides for a long retention of the extravagated particles in tumour tissue. Potent tumour accumulation of the nanoparticles requires sufficient particle residence time in circulation, for which it is commonly coated with polyethylene oxide chains.

Keywords: Ultrasound Therapy, Micro bubbles, Ligand Binding, Micro vessels, Pharmaceutical delivery.

INTRODUCTION

The property of micro bubble permits minimally invasive administration of pharmaceutical agents. Unlike conventional pharmaceutical therapies, ultrasound guided therapy eliminates drug effects on the body by guiding the medication to specifically targeted locations in the system. By guiding the pharmaceuticals to a specific location within body, the drug concentration can be increased at its site of action minimizing its dosing time, interval and side effects. The size of Micro bubble allows unopposed passage through the capillaries. Ultrasound mediated destruction of micro bubbles has become a promising tool for site specific drug and gene delivery. One of the most important properties of drug loaded micro bubble is their destructibility by ultrasound. They can be visualized through diagnostic ultrasound and destroyed precisely on the target site, thus releasing their therapeutic load. Microbubble in combination with ultrasound can transiently enhance permeability of several biological barriers, such as the blood-brain barrier, small blood vessels or cell membranes and thereby facilitate the delivery of bioactive substances into tissues and cells.

BRIEF REVIEW

Ultrasound contrast agents are examples of micro imaging devices that already are in medical use. They consist of micrometer-sized bubbles made of a lipid shell with a core containing a stabilizing gas:-

- Well-suited for delivery of biologically active gases such as nitric oxide.
- They may be coated with several molecules on the external surface enabling attachment of ligand to the surface.
- To further improve their diagnostic and therapeutic features, they should be able to target the tissue by chemical binding or affinity.
- When injected in the bloodstream, if they can be loaded with drugs, local release and local non-invasive therapy will be possible.

Micro bubbles subjected to the ultrasound of their resonance frequency oscillate depending on the wave energy. With gradually increasing peak negative acoustic pressure, micro bubble initially perform stable linear and then non-linear oscillations. When reaching a certain intensity limit, Micro bubbles can be fragmented or "burst" and release the payload in their near vicinity. The half-life, oscillation behaviour and fragmentation of micro bubbles in the ultrasound field depend on the physico-chemical properties of the shell, diameter, drug-loading, etc. On their turn, these factors are decisive for the magnitude of non-thermal mechanistic in situ effects of cavitations and accordingly for the permeabilization of biological structures. For example, micro bubbles with robust shells made of protein or polymeric material are rather weak oscillators and are mostly fragmented by "sonic cracking", when the gas explosively escapes the shell causing intense physical effects in the surrounding tissue. On the other hand, micro bubbles with soft shell such as phospholipids monolayer follow a different pattern of destruction. During oscillation the flexible membrane expands and reseals again, accompanied by gradually shedding out of submicron lipid aggregates in the order of liposome to micelles. The mechanistic effect of soft-shelled micro bubble on capillaries and cells is therefore considered more moderate and safe. Depending on their diameter and ultrasound parameters, they may undergo one-step collapse fragmentation producing a set of smaller fragments, or continuously pinch off small shell fragments and eventually shed out a large fragment, containing the main fraction of shell material. It is influenced not only by the type of phospholipids, but even more by the physico-chemical properties and amount of the drug loaded to micro bubbles

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ULTRASOUND GUIDED MICRO VESSEL RUPTURE

By selectively exciting the Micro bubbles with high pressure ultrasound, transient cavitation occurs. When this occurs in vessels and capillaries, rupture of bubble causes perforation in wall (Figure 1). The small rupture site is enough to allow transfer of relatively larger molecules, such as genetically modified erythrocytes & proteins, into the surrounding tissue. The effectiveness of extravasations of foreign molecules is determined by factors like tissue resistance; rupture site geometry, pressure gradient across the site and local forces. Shell construction & acoustic pressure also contributes many of these factors and allow the operator to selectively determine how well the particle will disperse.

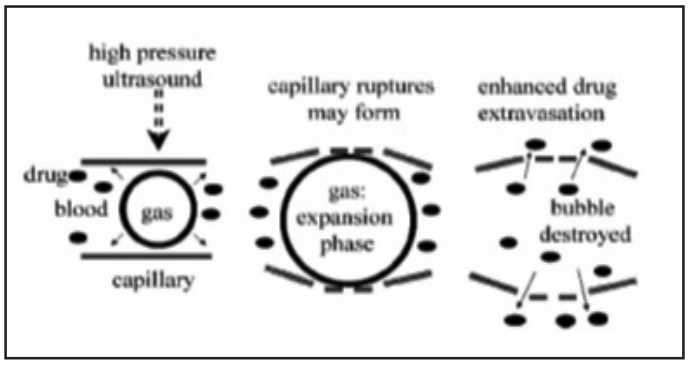

FIGURE 1: High pressure ultrasound causes the micro bubbles to burst. The energy released on bursting causes the capillary walls to rupture allowing extravasation of drugs

Although still in the in vivo stages of testing, Ultrasound Guided Micro vessel Rupture appears to be a very effective and safe method for delivering genetic material and pharmaceuticals across the endothelial lining. By using genetically modified Red Blood Cells as a drug-delivery vehicle, the body does not recognize foreign entities and rejection does not occur. With further research, several of the most complex pathogens may be able to be controlled with a simple and quick ultrasound.

LIGAND MEDIATED ULTRASOUND GUIDED MICRO BUBBLES

Ligand is molecules that bind to a specific site on protein. By attaching ligand to the shell of micro bubble, the ability for a specific bubble to selectively bind to certain tissues is established. Antibodies are currently the choice as ligand for research. To selectively treat only specific tissue, such as thrombus or plaque, a tissue specific method is developed. There have been several experimental models of antibody attachment.

Direct attachment

The antibody attaches directly to the micro bubble shell (Figure2). The direct bond does not provide enough attachment for reliable stability due to the positioning of antibodies on a sphere.

Antibody attachment

It uses an avidin-biotin pair improving stability (Figure 3). Avidin-biotin is a non-covalent mechanism that increases the length of the antibodies to allow more bonds to increase stability. Although this creates a stronger bond, introduction of foreign proteins (avidin-biotin) makes this method less desirable. The last mechanism for antibody attachment uses a flexible polymer spacer arm (Figure 4).

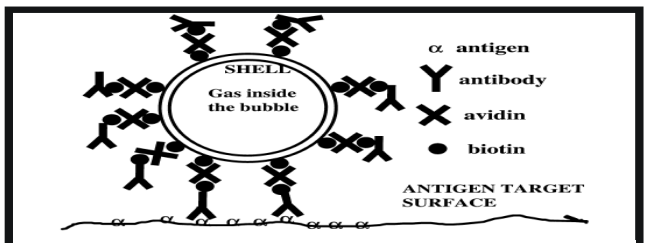

FIGURE 3: AVIDIN-BIOTIN ATTACHMENT OF ANTIBODIES TO THE SHELL OF THE MICRO BUBBLE.

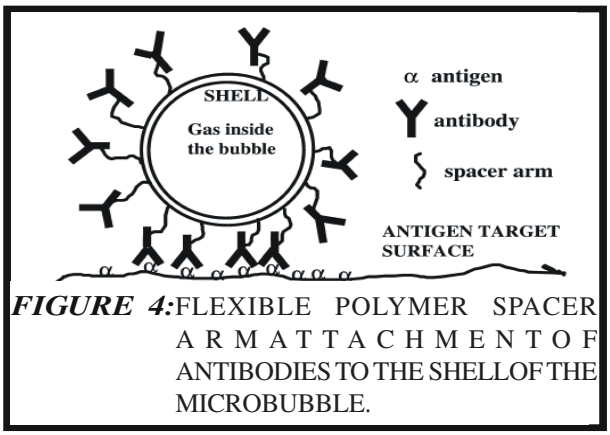

FIGURE 4: FLEXIBLE POLYMER SPACER ARM ATTACHMENT OF ANTIBODIES TO THE SHELL OF THE MICROBUBBLE.

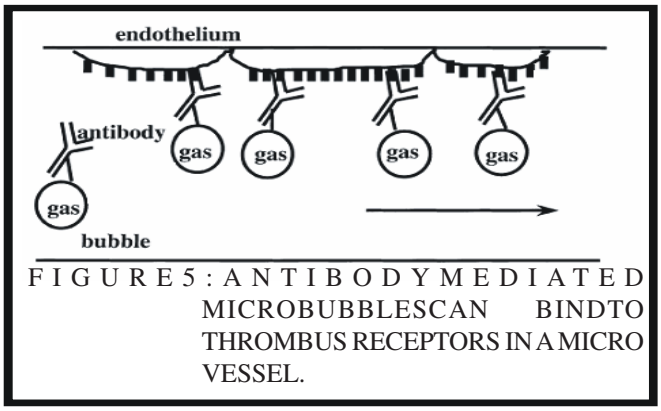

FIGURE 5: ANTIBODY MEDIATED MICROBUBBLES CAN BIND TO THROMBUS RECEPTORS IN A MICRO VESSEL.

Ligand mediated technology has several uses, both diagnostic and therapeutic. Ligand technology had been taken to the next step by entrapping pharmaceutical agents within the bubbles. Once the bubbles have had time to circulate and bond to their antigen, a high pressure ultrasound pulse ruptures the bubble, thus releasing medication to the effected site. In conjunction with pharmaceutical agents, ligand mediated micro bubbles may, in the future, become an accelerated treatment for thrombus, gene therapy, and drug delivery.

FUTURE SCOPE

The medical world is experiencing a change in the way disease is viewed and treated. By harnessing technology such as Ultrasound Guided Micro vessel Rupture and Ligand Mediated Ultrasound Guided Micro bubbles, lengthy and painful medical procedures such as chemotherapy may no longer be needed. Diseases that are currently rampant in the world have the potential to be as easy to cure as a simple ultrasound examination. The types of research that is currently being conducted accounts for different types of diseases, some of which utilizes current technology to develop a pathogen specific ultrasound guided micro bubble technique. Even though therapeutic micro bubble technology is several years away from public use, future of ultrasound appears to be both diagnostic and therapeutic. Microbubbles manifest ecogenic properties in biological tissues which creates better contrast in ultrasound images. Even more importantly, only bubbles undergo inertial cavitations, which concentrates ultrasound energy and substantially enhances ultrasound-mediated drug delivery. Although drug delivery from micelles, liposome etc may be ultrasonically enhanced even without Micro bubbles, their presence dramatically increases intracellular uptake of drugs. A novel ultrasound-mediated chemotherapy is based on systemic injection of drug-loaded nanoemulsions that convert into Micro bubbles in situ.

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