Microbubbles As a Boon for Novel Delivery System

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Abstract— Microbubbles designate air or gas filled microspheres suspended in a liquid carrier phase which generally results from the introduction of air or gas. The liquid phase contains surfactants to control the surface properties as well as stability of the bubble. Microbubbles have an average size less than that of RBC's i.e. they are capable of penetrating even into the smallest blood capillaries & releasing drugs or genes, incorporated on their surface, under the action of ultrasound. Microbubbles in general have a wide variety of applications. However in the biomedical field these are primarily used as diagnostic agents in combination with ultrasound for molecular imaging of various organs and even tumors. These are also proposed for drug and gene delivery to targeted regions in combination with various ligands. Most of the physicians today prefer imaging with ultrasound in combination with microbubbles compared to other diagnostic techniques for low cost and rapidity.

Index Terms— Micro bubbles, diagnostic agents, ultrasound, drug delivery, gene delivery, ligands.

I. INTRODUCTION

Micro bubbles are also small spherical bubbles comprising of gas, they remain distinct from each other or separate from each other i.e. do not agglomerate, also they have their size range in micrometers usually 1-100 μm. There has been a lot of research on micro bubbles in recent years. Micro bubbles are miniature gas bubbles of less than 50 microns diameter in water. The micro bubbles, which mostly contain oxygen or air, can remain suspended in the water for an extended period. Gradually, the gas within the micro bubbles dissolves into the water and the bubbles disappear.

In the medical field micro bubbles have been used as diagnostic aids to scan the various organs of body and recently they are being proposed to be used as drug or gene carriers and also for treatment in cancer therapy. Microbubbles have been used in a variety of fields , these have been used to improve the fermentation of soil, used to increase the hydroponic plant growth, have been to used to increase the aquaculture productivity, these have been also used to improve the quality of water, used in sewage treatment . Bio medically micro bubbles are defined as small spherical gas bubbles made up of phospholipids or biodegradable polymers, that are approximately the size of RBC's and are used as diagnostic aids, as drug and gene carriers in combination with ultrasound.

II. ADVANTAGE

1. Ultrasound imaging allows real-time evaluations of blood flow.
2. Ultrasonic molecular imaging is safer than molecular imaging modalities, such as radionuclide imaging, because it does not involve radiation.
3. Alternative molecular imaging modalities, such as MRI, PET, and SPECT are very costly. Ultrasound, on the other hand, is very cost-efficient and widely available.
4. Targeting strategies for micro bubbles are versatile and modular. Targeting a new area only

entails conjugating a new ligand.

5. Targeting ligands can be immunogenic, since current targeting ligands used in preclinical experiments are derived from animal culture

III. DISADVANTAGES

1. Contrast-enhanced ultrasound suffers from the following disadvantages:
2. Microbubbles don't last very long in circulation. They have low circulation residence times because they either get taken up by immune system cells or get taken up by the liver or spleen, even when they are coated with PEG.
3. Ultrasound produces more heat as the frequency increases, so ultrasonic frequency must be carefully monitored.
4. Microbubbles burst at low ultrasound frequencies and at high mechanical indices, which is the measure of the acoustic power output of the ultrasound imaging system. Increasing MI increases image quality, but there are tradeoffs with microbubble.

IV. PROPERTIES OF MICROBUBBLES:

The ideal properties of microbubbles can be divided into two classes,

1) Functional Properties
2) Structural Properties

V. COMPONENTS OF MICROBUBBLES

Microbubbles basically comprise of three phases

1) Inner most Gas Phase
2) Shell Material Enclosing the Gas Phase
3) Outermost Liquid or Aqueous Phase

In addition to this the formulation may also comprise of various other components.

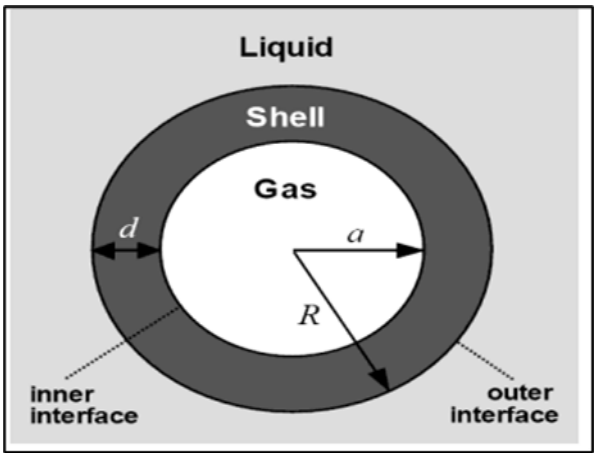


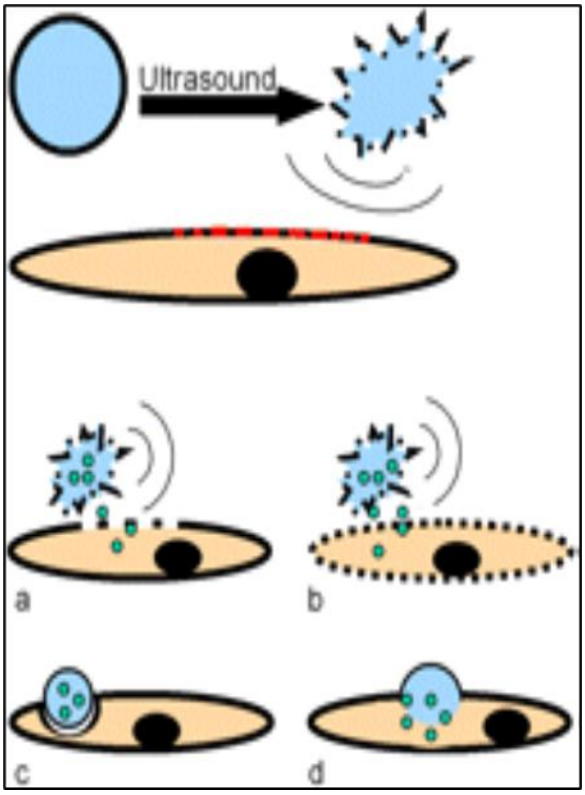
FIG. 3: Components of Microbubbles

HOW MICRO BUBBLES WORKS

METHODS TO PREPARE MICROBUBBLES:

The various methods that can be used for the preparation of these microbubbles include:

1) Cross Linking Polymerization
2) Emulsion Solvent Evaporation
3) Atomization & Reconstitution
4) Sonication
5) BIOMEDICAL APPLICATIONS
6) 1) DIAGNOSTIC AIDS:
7) Micro bubbles are elastic and compressible, these undergo compression and rarefaction thereby creating an acoustic impedance mismatch between biological tissues and fluids as these are efficient reflectors of ultrasound, hence used as contrast agents
8) These are used as diagnostic aids for:
9) 1) Organ Edge Delineation
10) 2) Blood Volume and Perfusion
11) 3) Inflammation
12) 4) Cancer
13) 5) Liver
14) 6) Also used to scan the tumors arising in the body.
15) 7) Used for imaging the gall bladder stone.
16) 2) DRUG DELIVERY:



Two factors which are taken into account for drug delivery are:

1) Incorporation of drug into these micro bubbles

2) Drug release from these micro bubbles

The following figure shows drug delivery via the micro bubbles

a. Drug delivery by cavitation

b. Drug release by cavitation as well as increasing the permeability of cell membrane

c. Phagocytosis of the microbubble by cell membrane

d. Fusion of microbubble with the cell membrane

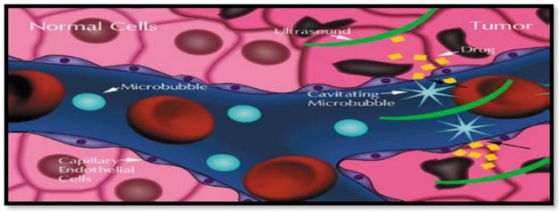


FIG.5 : Drug Release From Microbubbles By Cavitation

3) GENE DELIVERY:

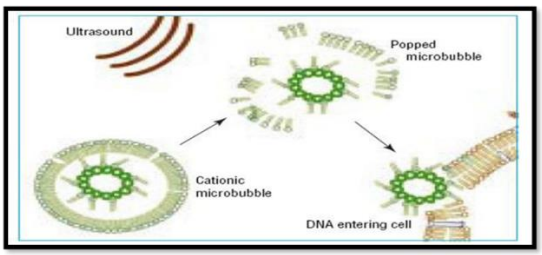


Fig: 6 Ultrasound Scan Of Liver Using Levovist Micro bubbles

CONCLUSION

1. The application of micro bubble with ultrasound which gives a synergistic effect for drug/DNA delivery is currently in its infancy.
2. The use of targeted micro bubbles is a great step forward and has created various challenging therapeutic options, not only in cardiovascular disease but also in treatment of inflammatory and malignant diseases
3. Micro bubbles have rapidly evolved from a diagnostic adjuvant to a possible therapeutic agent. In the coming years, this promising technique needs further development to make it available for clinical applications.

FUTURE PERSPECTIVES

1. The use of micro bubbles as a tool for drug delivery enhancement has an enormous clinical potential, especially in oncology and vascular applications.
2. Whereas free drugs often possess harmful side effects, their encapsulation in micro bubbles and subsequent local release, deposition, and potentiation in the target tissue by ultrasound triggering will help improve the therapeutic index, lower the incidence of adverse events, and achieve successful therapy.
3. Microbubbles combined with ultrasound offer a possibility to optimize the action of the currently approved drugs and drug delivery systems by improving their pharmacokinetics and delivery to the target

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