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Ultrasound nanobubbles and their applications as theranostic agents in cancer therapy: a review

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ABSTRACT

Cancer is known as a dangerous disease at cellular and molecular level of organism which necessitates its detection and treatment in early stages. With the development of nanomedicine, the fabrication of structures/materials at the range of 1 to 100 nm offers good advantage to clinical applications. Among nanostructure, nanobubbles (NBs) have received great attention to overcomes to the limitations of low sensitivity and specificity of diagnostics and therapeutics. In addition, NBs have high potential for encapsulating and attaching therapeutic agents. Therefore, they can be used as a novel nanostructure in clinical applications. The purpose of this review is to focus on the ultrasound NBs and their applications as theranostic agents for cancer therapy.

Keywords:*nanobubbles, theranostic agents, cancer therapy.*

1. INTRODUCTION

Cancer is known as a dangerous disease at cellular and molecular level of organism which necessitates the advanced treatments. Irradiation and surgical methods are the early forms which are used against this dangerous disease whereas all cancers are not curable with these methods due to its metastasis nature, incompletely removing cancerous cells and the drug resistance [1-6]. The resistance of the cancerous cells to chemotherapy is proposed because of mechanisms such as the activation of alternative signaling pathways, the expression of drug efflux pumps (ABC super-family), the evasion of cell apoptosis and the increase in DNA repair mechanisms [7]. Conventional therapy for cancer is focused on the reduction of tumor mass through surgery by anti-cancer drugs. These anti-cancer drugs have the limitations such as poor half -life, non-specific biodistribution. Contrast agents and radiolabelled molecules show similar non-specific distribution pattern as well [8].

With the development of nanomedicine, the fabrication of structures/materials at the range of 1 to 100 nm offers potential advantages to clinical applications [9-19]. In cancer therapy, nanostructured materials can circulate in the blood vessels and interact with cancerous tissue/cell [20]. Therefore, it is suggested that these nanomaterials such as polymeric/lipid nanoparticles (NPs) can act as a delivery system by either encapsulating or attaching therapeutic agents[21]. Depending on the type of delivery system, the release of therapeutic agents from these nanostructures can be controlled by either through stimulation of local environment (such as pH, temperature) or diffusion of fluids into the polymer/lipid matrix [22-27]. Surface and geometry properties of nanomaterials also determine the release of therapeutic agents and interactions of nanostructured materials with cancerous cells [28].Various reports indicate that polymeric based theranostic [29-33], lipid based theranostic [34-38], inorganic based theranostic [39-43] and hybrid based theranostic[44-48] systems have high potential for clinical applications. The ultimate goal of these systems is the increase in both the diagnostic and therapeutic functions by probing agents. In comparison with nanoparticles and nanodroplets that have solid and liquid core, respectively, NBs has a gas core. This NB system is gas carriers in aqueous solution, with a shell layer containing polymers, phospholipids, or possible molecules of therapeutic agent encapsulating the gas. The application of ultrasound energy on the NB system offers an optimum theranostic function for cancer therapy without a need for the encapsulation of contrast agent. Totally, nanodroplets form via a lipidic or polymeric shell with liquid core whereas a gas core exist in nanobubbles instead of liquid core. The presence of gas in the solution results in the formation of micorobubbles and nanobubbles[49]. By applying ultrasound, liquid of nanodroplets in core can be evaporated and changed to gas phase which leads to convertion of nanodroplets to nanobubbles.This review focuses on the theranostic applications of ultrasound NBs for cancer therapy with the diagnostic and therapeutic functions.

2. NANOBUBBLES

NBs are either created by heterogeneous nucleation (within two interphases (solid/liquid/gas) [50] or prepared homogeneously under atmospheric conditions in the presence of gas [51]and may be also generated by the coalescence of vacancies in the diameter less than 1μm [52]. Experimental studies report that NBs majorly form on hydrophobic solid surface which can alter interfacial properties such as lubrication surface forces and adsorption [53] and stabilize the colloidal particles

[54]. These NBs are experimentally produced by pressure release[55] heating [56] solvent-exchange [57-59] and water electrolysis [60-62]. It was proposed that interfacial NBs results from supersaturation of gas at any interface[63, 64] whilst another study suggest that supersaturation is not required for bubbles nucleation[65]. Despite the broad studies on NBs, the mechanisms of the whole principles including nucleation, formation, and stability of NBs are not well known yet.

Different parameters are considered to obtain a stable system for NBs. These parameters include the molecular interaction between the gas core and surrounding fluids (Laplace pressure), the components of each bubble system as the dispersed phase which interact with the components of the surrounding fluids (continuous phase). Gas diffusion between two bubbles is related to Ostwald ripening due to the surface tension effect which generates a pressure for the gas dissolution and affects the stability and preparation of a NB[66]. The stability of NBs depends not only on the composition of surfactant and polymers at the interface but also the size and a low density gas in its core which are then stabilized by coating materials such as, lipid and synthetic polymer (Fig. 1). This property of low density reflects its importance in medical applications such as thrombosis treatment and site-specific delivery.

NBs filled with octafluoropropane within the size range of 450-700 nm exhibited a dose response echo enhancement for medical imaging both *in vivo*[67] and *in vitro*[68]. NBs containing perfluoropentane stabilized by co-polymers can be used as a drug delivery enhancer [69] and increase the half-life of NBs. Tumor imaging with a system of NBs enhance medical diagnostics due to its unique and strong backscattering effects when exposed to ultrasound [69, 70].

3. ULTRASOUND EFFECTS ON NANOBUBBLES

Ultrasound is a frequency of mechanical vibrations or pressure waves which are equal or above that of human hear (20 kHz) due to its compressional and rarefactional pressure fluctuations. In evaluating tumor, MBs can be used as ultrasound contrast agents for perfusion [71], diagnosis [72, 73] and treatment response[74-76]. These contrast agents are comprised of a polymer/lipid shell and gas filled bubbles which provide contrast due to its distinctive quality in the acoustic impedance between the gas core and the surrounding fluids. Ultrasound MBs have been extensively studied and gained the increased attentions in its pharmaceutical applications due to high ability to form acoustically induced pores in membrane layer for enhanced cellular uptake of drugs [77, 78]. However, the size range of MBs (1–10 μm) limits its clinical application because they cannot penetrate into tumor tissue through a leaky tumor vasculature due to large dimensions. Nanoscale bubble system within the range of (1– 500 nm) can accumulate at the tumor endothelium [79, 80] and deliver diagnostic and therapeutic agents (drug/gene) for the theranostic assessment.

During the past decades, ultrasound has been employed for the tumor treatment using NBs to enhance both imaging of body's tissues/organs and the delivery of drugs to echogenic tissues (multiple interface tissues) and hypoechoic (no internal interface). Acoustic pressure act on MBs when exposed to an ultrasonic field which results in the variation in bubble radius due to the bubble's stiffness and inertia. The bubble behaves as an oscillator with stiffness provided by the gas within the bubble and inertia of the surrounding fluid. The fluid which surrounds the bubbles provides the inertia and moves with the bubble wall. The compression of the gas also provides a force that resists its compression. Generally, the delivery of drugs to organs and tissues are affected by two main ultrasound effects including the cavitation and sonoporation effects. The cavitation effect results in the reduction of bubble size, whilst the sonoporation effect leads to uptake of the reduced bubble.

3.1. Cavitation Effect. In unresectable tumor, radiofrequency (RF) ablation is an invasive procedure in treating tumor diseases [81-83]. However; RF ablation have limitations on the size and location of the tumor (lesion) which produces variable results due to the flow of blood and act as heat sink to the tumor vessels [84, 85]. Pluronic is an effective thermosensitizer to increase the efficacy of RF ablation on MBs. Pluronic as an amhiphilic surfactant has the ability to decrease the size of MBs without reducing the echogenicity [69, 86] as shown in Fig. 2.

An echogenic effect on MBs can create small enough NBs to passively extravasate through the gaps in the tumor-associated endothelium [87, 88]. Cavitation effects and radiation force are the main driving forces behind improved extravasation and convection of drugs via the reduction of its carrier (delivery device) when exposed to ultrasound as a result of pressure wave passing through the media [89].

As shown in Fig 3, cavitation can become stable (non-inertial) if acoustic pressure amplitude would be above a threshold level, lead to the growth and subsequently explosion of the NBs. High temperature and highly reactive radicals may occur during the explosion of the bubbles. In addition, cavitation can be transient (inertial) if the resulting oscillation which creates a circulating shear flow of bubble at the surrounding fluid would be proportional to the amplitude[78, 90-92].

The change in fluidity can also control the resonant response of NBs to the ultrasound irradiation, leads to increment of bubble echogenicity [25]. Interestingly, nanodroplets (NDs) are nanocarriers which are able to be vaporized and changed to micro-nano scale gas bubble through the application of ultrasound. The particle volume increases upon transition, resulting in decrease in droplet shell and favor the release of the therapeutic agent[87, 93]. Different reports suggest that the droplet to bubble transition causes the release of the therapeutic agent and enhances intracellular uptake.

3.2. Sonoporation. The sonoporation effect is a process in which ultrasound is used to alter the permeability of the cell plasma membrane and provide a very specific and high concentration of drugs at the site of interest while minimizing the overall exposure of the drug to other part of the body [94, 95]. Depending on the

type of tissue surface, an asymmetrical collapse occurs near the surface which eject a liquid at sonic speed towards the surface and then pierce the tissue surface[91]. The collapsing bubbles can create transient holes in cell membrane and large molecules such as nucleotide can be entered into the cells [94, 96]. Generally, this mechanism has been demonstrated by experiments [91, 97, 98] and proven by theoretical explanation [99]. The collapsing bubble is not only dependent on the physical properties of the bubble but also the higher intensity and lower frequency of the ultrasound which affects its cavitation process [100-102].

There are four main processes on the sonoporation of NBs for the enhanced delivery of therapeutic agent under the influence of ultrasound. Firstly, the effect of lowering cavitation threshold which creates shears stress and increases the permeability of the membrane layer. This effect sets the fluids around NBs in motion by creating shock waves for the destruction of NBs along the endothelia cell. The increment in permeability of the membrane is probably due to membrane transient holes [103]. Secondly, the generation of reactive oxygen species (ROS) such as hydrogen or hydroxyl radicals and hydrogen peroxide decrease the threshold of cavitation and results in the production free radicals which are related to cell apoptosis and may enhance the permeability of therapeutic agent to the endothelial cells [104, 105]. Thirdly, the high pressure of ultrasound which causes the increment in tissues temperature and alters membrane bilayer fluidity [106]. Lastly, the membrane transport mechanisms, endocytosis/phagocytosis and exchange or the fusion such as the phospholipid coated NBs with the phospholipid layer of a cell membrane which can also cause the delivery of therapeutic agent into the cytoplasm as shown schematically in Fig. 4.

4. APPLICATIONS OF ULTRASOUND NANOBUBBLES TO CANCER THERAPY

Ultrasound induced cavitation on the bubbles causes volume change to bubble and large shear stresses which can alter the bilayer structure by creating transient holes for the penetration of the therapeutic agent or producing large-scale disruption of the entire NBs, leading to instant release of the drug loaded[107].

In cancer theranostics, the ability in the detection and treatment of disease selectively at cellular level requires to the use of probe agents such as the luminescent and fluorescent probes [108-110], liposomes, micelles, and polymers [111-113], NPs [108, 110, 114] and plasmonic gold NPs [115, 116]. These systematic probes provide cell theranostics depending on the tune ability of each theranostic function (therapy, diagnosis and guidance). In delivery applications of ultrasound NBs, therapeutic agent can be incorporated into or onto NBs by different ways such as association with the bubble's membrane, binding to ligands which are embedded in the membrane and construct multiple layers of NBs.

4.1. Oxygen Loaded Nanobubbles. Hypoxia (acute mild, ischemic and chronic) is known to be a critical issue in the treatment of tumor tissues [117] including burns, diabetes and wounds due to the low level of oxygen in access for the tissues. The principle of laplace pressure on MBs and NBs has developed the delivery of therapeutic gases such as oxygen loaded microbubbles (OLMBs), oxygen-loaded nanobubbles (OLNBs), echogenic liposomes and nanosponges for the treatment of oxygen deficiency. Recent research deals with the formulation of oxygen bubble at the nanometer range by either coating the bubble with dextran or chitosan. Chitosan coated MBs act as an efficient oxygen delivery system without any sign of toxicity for human blood and Human JEG-3 choriocarcinoma cells [118]. Fan et al investigated the disrtibution of NBs in the gastric cancer xenograft. The results demonstrated that the NBs were distributed through tumor blood vessels into the intercellular tissue spaces under the influence of ultrasound which can used for extravascular imaging of tumors [119]. As demonstrated by oxymetry and revealed by photoacoustic imaging, in vitro OLNDs filled with decafluoropentane gas are known to be more effective than ordinary PFP gas in releasing oxygen to hypoxic environment[120, 121]. OLND with the shell made of chitosan or dextran and 2H,3H-decafluoropentane (DFP) as core oxygen gas that is either in liquid formulations or in a gel formulation (enabling decrease in gas diffusion) displays good oxygen carrying capacity both in vivo and in vitro. The results suggests that ultrasound activation can be an efficient treatment of hypoxia without any toxicity [122]. These same techniques were carried out on OLNDs with dextran shell and core fluorocarbon gas. The results also demonstrate an efficient in-vitro release by ultrasound on human keratinocytes with no sign of toxicity[120].

4.2. Drugs Loaded Nanobubbles. Among methods which were applied for conjugating drugs to NBs using ultrasound in cancer therapy, a report[123] described the use of NBs combined with ultrasound to study the cytotoxic effect of two drugs (cisplatin and 5-FU) on four different cancer cells. Cell sensitivity to drugs loaded NBs effectively increased with ultrasound. In another study, NBs as contrast agents were prepared using Coumarin-6 as a model drug which is analyzed by a sigmoidal fitting of pharmacokinetics curve to study the nano-sized bubble's property for ultrasonic imaging and investigate the drug delivery potential to cells. The results demonstrated NBs function as an ultrasonic contrast agent in the liver region of mouse by presenting a contrast effect[124].

Theranostic model using a high sensitiveultrasound system can target imaging and triggered drug delivery base on applying aptamer-conjugated to NB techniques [125]. The results indicated that the aptamer provides exceptional binding affinity to tumor cells due to the different sizes of the bubbles in blood flow. In addition, the theranostic investigation was performed on three different groups of mice model by the system in which Doxorubicin and methoxypoly(polyethylene glycol) were conjugated to PLGA (Dox-PLGA-mPEG) [126]. The system was stable after filling with PFP as a result of the PEG shell in the form of NDs at a certain temperature. These NDs were transformed to NBs and the rate of doxorubicin release seems to be proportional to not only the temperature but also the pH and the ultrasound effect. In other work, methotrexate (MTX)-loaded NBs with PLGA shell were filled with PFC gas and active tumor-targeting monoclonal anti-HLAG antibodies were further conjugated onto the surface of NBs. The NBs systems exhibited both in vitr oand in vivo targeted efficiency towards the tumor tissues and enhanced ultrasound imaging. Further investigations shows that focused ultrasound can promote the release of MTX incorporated in the system[127]. Besides, the use of ultrasound

radiation (continuous or pulse) leads to an approach of a bimodal cancer treatment which can predict the metastatic cancer [128]. The treatment techniques were performed in vitro by exposing ultrasound with sorafenib loaded NBs. The results indicated that ultrasound ablation facilitate the drug delivery. Likewise, it was suggested that this combination might be a novel approach of treating liver cancer. Recently Extracorporeal Shock Waves (ESWs) have been proposed as a new tool to increase drug release from NBs with no side effect of heating. Like ultrasound, these ESWs produce cavitation focalizing with high precision in tissue depth. NBs filled with PFP stabilized by glycol chitosan shell were designed for the delivery of doxorubicin to anaplastic thyroid cancer cell lines to investigate the effect of ESWs on intracellular uptake of doxorubicin loaded NBs. The combined treatment of ESWs with the NBs demonstrated more cytotoxic effect than free doxorubicin, increased nuclear accumulation of doxorubicin, and enhanced intracellular uptake of drug-loaded NBs [129].

4.3. Nanobubbles as Gene Delivery System. A therapeutic procedure in gene therapy which involves the incorporation of new genetic material into host is often limited to inefficient cellular uptake due to its large size, hydrophilic properties, nuclease degradation in the blood and their negatively charged phosphate group. Therefore, viral and non-viral vector delivery has been developed to overcome these limitations. MBs and NBs provide a non-viral for the specific delivery of genetic material due to the activation of ultrasound mechanisms which may cause tissue damage as a result of ultrasound frequency.

Therapeutic ultrasound combined with NBs and MBs have been investigated for increasing gene transfection efficiency with low toxicity and organ specific delivery[130]. Studies exhibited that ultrasound is able to deliver genetic materials into the cell cytosol. These genetic materials can be incorporated into multilayer polymer, liposomes and NPs by either physical or chemical interactions onto the bubble surface during fabrication (as shown in Fig. 5) and most of the bubble encapsulating DNA demonstrated either high loading capacity or transfection efficiency[131-133].

A report [134] discussed on the preparation and characterization of plasmid DNA-loaded chitosan NBs with a gas core of PFP which were formed with a mean diameter less than 300 nm with positive surface charge. In the study, chitosan was selected basically because of its low immunogenicity, biocompatibility and its low toxicity. The investigation of DNA release with either ultrasound combined NBs or NBs alone is observed to affects the experimental cell viability. In Addition, Yung et al [135] designed an approach to overcome to Multidrug resistance using a NPs-mediated gene silence of chemotherapeutic agents export proteins via RNA interference. For the increment of drug accumulation in drug resistance cell, DOX-PLGA/PEI/P-gp shRNA NBs were designed with an average size of 327 nm. The results exhibited that DOX-PLGA/PEI/P-gp shRNA NBs could increase cellular uptake of DOX into MCF-7 human breast cancer and enhance the cell proliferation suppression effect of DOX against MCF-7/ADR cells. The release profile of this NBs system demonstrated an efficient Dox release (> 80%) and suggested a pH-responsive release which could facilitate the DOX uptake to suppress the tumor cell proliferation against the receptors over-expressed on the tumor surface. In addition, the NBs efficiently enhance ultrasound imaging of the cancer cells. Ultrasound exposure also enhanced effectivelygene silencing effect of siRNA-NBs [136], and the co-delivery of siRNA-paclitaxel-NBs [137] which were formulated by the hetero-assembly of both liposomes and polymeric micelles caused more level of cancer cell apoptosis and an ideal delivery vector for tumor theranostics. Liposome bubbles with size range between 150-200 nm in combination with ultrasound enhanced tumor specific gene uptake as well [138]. Likewise, in the delivery of pDNA and siRNA by the application of ultrasound, pDNA-loaded bubble liposomes enhance transfection efficiency, membrane stability and ultrasound imaging effect in the hind limb ischemia mouse model. The results exhibited that pDNA loaded bubble reached to ischemic site and delivered bFGF-expressing pDNA by the use of ultrasound [139].

4.4. Targeted Nanobubbles. Target delivery can be achieved by either active or passive targeting to obtain a high amount cytotoxic agent in a specific organ using the modification of therapeutic agent conjugated to nano system. NBs in the same approach can also undergo surface modification to increase tumor selectivity and enhance tumor theranostic. Ligands and receptors can be incorporated to the surface of NBs for the specificity delivery of therapeutic agents [140]. In a study, Methotrexate (MTX)-loaded PLGA NBs filled with PFC gas is also synthesized by double emulsion evaporation method and subsequently an active tumor-targeting anticancer drug is conjugated onto the surface of the PLGA NBs. The system exhibited both *in vivo* and *in vitro* efficient targeted theranostic function [127]. In another research approach, the *in vivo* and *in vitro* experimental apparatus and rat model of VEGFR2-targeted NBs ultrasound contrast agent was investigated for the improvement of the contrast effect of ultrasound imaging due to the EPR effects at tumor vascular leaks [135]. The results demonstrated that the NBs had appropriate size, and exhibited a high contrast enhancement performance. Imaging results exhibited that the self-made targeted NBs have potential for tumor targeting. In addition, the limitations were observed on ultrasound imaging due to the low NBs concentration that reaches through tumor vessels. Herceptin molecules that were covalently attach to PEGylated phospholipid shell NBs indicated success in diagnostic and treatment responses. The NBs-Herceptin enhanced in-vivo and in-vitro ultrasound contrast in HER2 positive tumor and penetrated into the tumor tissue in vivo[141]. Herceptin molecules also demonstrated the same ultrasound effect when conjugated to only phospholipid shell NBs[142].

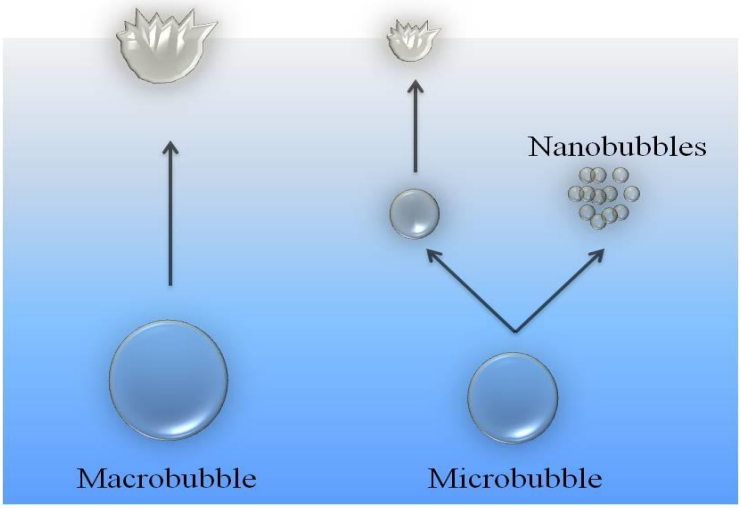

Figure 1. The stability differences among bubbles in fluids: Macrobubbles collapse rapidly, Microbubbles gradually decrease in size and may eventually collapse, Nanobubbles remain stable and do not burst out at once.

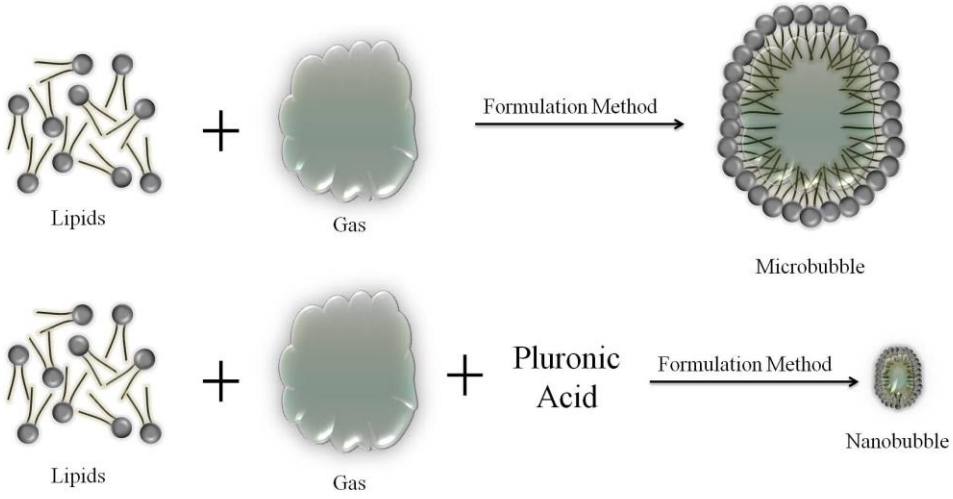

Figure 2. The pluronic effect on Microbubbles leads to the reduction of the bubble size.

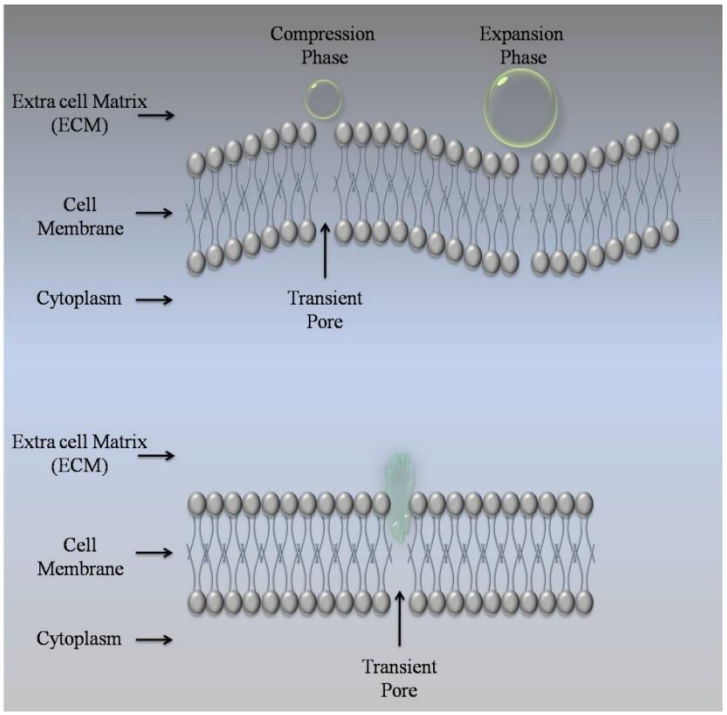

Figure 3. Non-inertia and inertia cavitations lead to the reduction of MBs and the formation of a transient pore on the cell membrane.

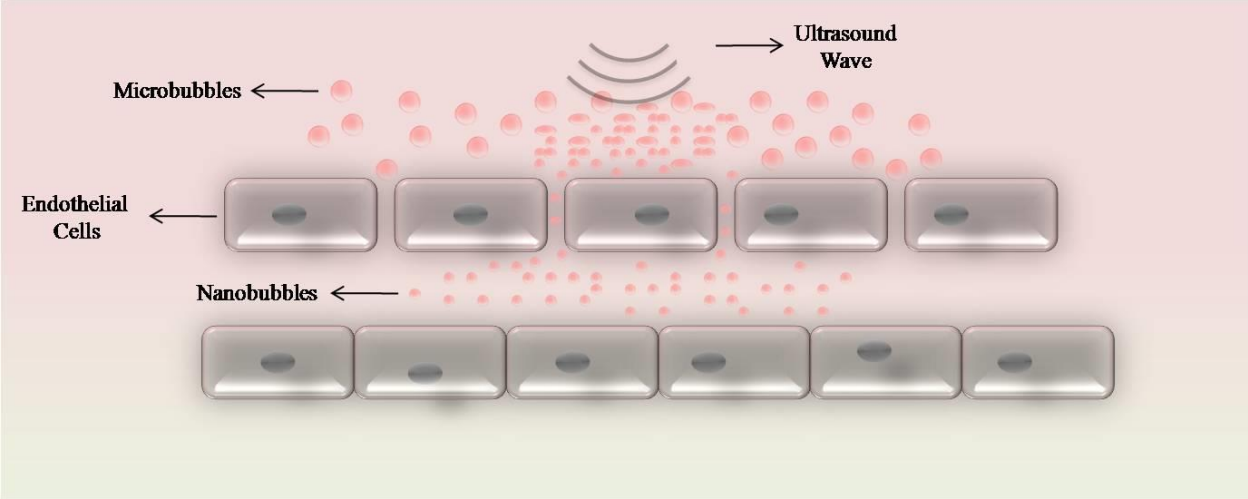

Figure 4. Schematic diagram shows the cavitational effect of microbubbles leading to enhanced uptake of nanobubbles.

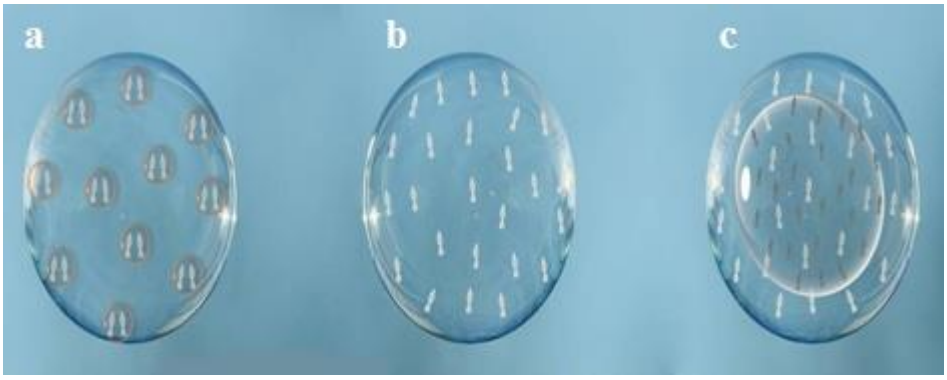

Figure 5. The schematic figure shows approach of incorporating genetic material onto NBs: (A) incorporating DNA into polyplexes, lipoplexes, liposomes or NPs (B) loading DNA to the external surface of a NBs through non covalent binding (C) incorporation into the shell of a multilayer polymer NBs.

4. CONCLUSIONS

NBs are proposed as potential nanovehicles for theranostic agents for the application in cancer therapy. Different parameters such as the molecular interaction between the gas core and surrounding fluids are considered to obtain a stable system for NBs. The stability of NBs depends on both the composition of surfactant and polymers at the interface and the size and a low density gas in its core. This property of low density reflects its importance in medical applications such as thrombosis treatment and site-specific delivery. However, the mechanisms guiding the whole principles of NBs are not well known yet.

Loading and conjugation of therapeutic agents can be also conjugated onto and within the NBs structure. In addition, receptor-based active targeting of NBs has a great potential to become an optimal delivery strategy. Generally, the outlook of nanobubbles in cancer therapy looks very promising. Despite rapid development in nanomedicine, there are still important challenges to provide more accurate data for the hazardsof biomedical applications of NBs and admittedly more work still needs to be done.

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