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REVIEW PAPER

A study on the possibility of drug delivery approach through ultrasonic sensitive nanocarriers

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ABSTRACT

Physical drug delivery through smart nanocarrier and external stimulus could lead to significant improvements of drug potency as well as noticeable decrease in unwanted side effects. Currently, many external energy sources such as light, magnetic fields, ultrasound, ..., are under investigation as external stimulus for physical drug delivery. The purpose of this paper is to review most recent developments of triggered release of drugs and biomolecules under external ultrasound exposure. A special attention has also been paid to the metal nanostructures for ultrasound mediated drug delivery and also, other nanostructures were also considered. We briefly introduced ultrasound regulation and safety consideration. Further it is concluded that the use of nanostructures for delivery of active biomolecules in combination with ultrasound as a stimulus to trigger drug release from the nanocarriers and increased drug penetration has gained much attention for effective drug delivery and overcoming difficulties of multi-drug resistance of cancer.

Keywords: *Drug Nanocarriers, External Trigger Release, High Intensity Focused Ultrasound, Ultrasound, Ultrasound Safety*

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INTRODUCTION

Utilization of ultrasound as a safe, simple, and cost effective technique in the fields of diagnostics and therapy, has attained prominence among other modalities. For several decades it has played a significant role in the realm of imaging (high-frequency and low-intensity of wave) for gynecologists, urologists, oncologists, obstetricians, cardiologists and so on, as well as in the treatment of muscle or tendon injuries(low frequency and high intensity of sound wave) for physiotherapists [1].

Delivery of sufficient amounts of therapeutic drugs into target cells or tissues is often a hurdle in medicine [2]. Ultrasound energy was introduced as an external tool to stimulate drug release from nanocarriers to increase the drug efficacy in the region of the disease while decreasing undesired side effects [3]. Recent studies have shown that therapeutic ultrasound can enhance the effects of thrombolytic agents, transdermal drug-delivery, anti-cancer drugs, and gene therapy [4]. It also has been reported that the delivery of antibiotics and anti-inflammatory drugs into the eye has increased with ultrasound [5].

Ultrasound is an extremely useful stimulus modality in drug-delivery because of its non-invasive technique using an external source. It is effective in attaining location specificity,

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minimizing the systemic side effects of the drug, and increasing drug uptake. It has been used for drug release from carriers such as liposomes, micelles, and microbubbles, thus improving the therapeutic effects of the drug [6]. Each of these carriers has its own cons and pros [7]. Hence, synergic application of different types of drug carriers and ultrasonic waves opens new approaches for effective drug delivery.

Three different approaches for ultrasound application in drug delivery are introduced in this paper. First, a localized and non-invasive method of delivering drugs, and macromolecules, into the skin through, ultrasound exposure is considered the first strategy and is called sonophoresis [8]. Ultrasound also can be used to facilitate nanoparticle transport from skin layers. Paliwal et al. studied the heterogeneity of transdermal transport through sonophoresis using quantum dots (QDs, 20 nm in diameter) as tracer nanoparticles. These nanoparticles were shown to penetrate into the viable layers of the skin [9]. Second, ultrasound can change the permeability or absorption of the drug into cells. Yang et al. performed sonoporation of liver tumor cells to uptake Fe3O4 nanoparticles [10]. The last and most important strategy is to apply ultrasound to change the chemical nature of drug carriers to achieve external stimulus release [11]. This technique could be very helpful for increasing efficacy and decreasing the toxic side effects of chemotherapy tumor treatment. This manuscript focuses on the application of ultrasound in stimulus release of drugs from nanocarriers.

Ultrasound regulation

Mechanical waves like sound can pass through the medium by moving the molecules. The sound is easily passed through water or soft tissue but it has difficulty penetrating bone or cavities. Sound with the frequency higher than 20 kHz was called ultrasound. The intensity of ultrasound beam is defined as power carried per cross-section area of the beam (Watts/cm2) [12], which is an important factor for ultrasound medical application.

Ultrasound with high frequencies (2-18 MHz) is commonly used for different diagnostic application [13] (Fig 1).Ultrasound imaging is based on scattered waves resulting from different tissue density that will occur in low intensities [14]. But, focusing the beam in a small area at higher intensities, will transfer high energy input could provide therapeutic benefit [15]. With ultrasonic exposure, the quantity of the energy is absorbed by tissue, resulting in local heating. Besides intensity, the absorbed energy is depending on many other factors like tissue density and ultrasound frequency [16]. Because of high-intensity, therapeutic ultrasound has considerable non-thermal and thermal effects.

The absorption of high-frequency ultrasound (LFU) can generate thermal effects. Non-thermal effects are generated by low-frequency ultrasound (LFU) (Fig1) and are linked to principals of cavitation, standing waves, acoustic streaming, and microstreaming [17].

Ultrasound cavitation is one of major mechanism for producing heat and pressure in microenvironments.

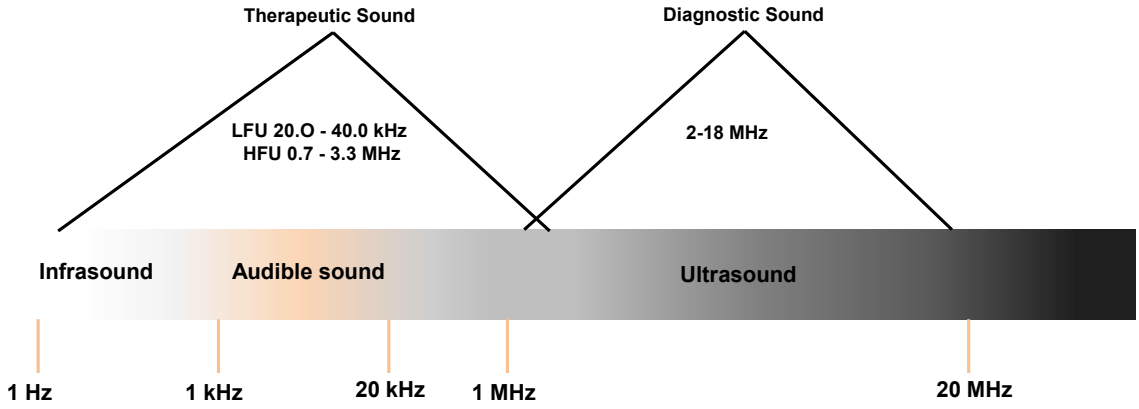

Fig 1. Sound has both therapeutic and diagnostic applications. Therapeutic ultrasound could be divided into two ranges. High-frequency ultrasound (HFU, 0.7 – 3.3 MHz) and low-frequency ultrasound (LFU 20 – 40 kHz)

Ultrasound cavitation is the production of cavities inside the ultrasound irradiated liquids because of microbubbles presence in liquid [18]. Two types of cavitation are known: none-inertial (stable) and inertial. Formation of each type depends on frequency, intensity, and size of bubbles [19].

Passing the pressure wave (ultrasound) through medium causes wide range of bubbles to oscillate, and those with resonance frequency close to the frequency of applied ultrasound, show higher oscillation. If contraction of bubbles size at high-pressure and expanding at low-pressure shows a stable mood (Fig 2-a), the cavitation called non-inertial. In this mood of cavitation, circulating flows around the bubble, called microstreaming, with shear stress and velocity proportional to the amplitude of cavitation will occur (Fig 2-b). Microstreaming shear force can rupture cell membrane or drug containing vesicle [3].

Circulating flows around the bubble can enhance the drugs and molecule transport by high velocity [20]. By increasing the intensity of the ultrasound waves, the bubbles will oscillate in the greater range of contraction and expansion leading to a point which inward moving of the liquid wall attains adequate inertia resisting backward movement.

Therefore, the compression will continue to force the bubble to a very small size and collapse with creation high pressure and temperature at the site of the collapse. This is known as inertial cavitation (Fig 2-c) [21]. The outcome of this type of cavitation is high shear stress for the induction of shock waves and free radical as a result of high temperature, which both can disturb biological and non-biological nanostructures. In addition, occurring inertial cavitation near a solid surface will induce an asymmetric collapse of the bubble, leading to a jet of flow at sonic speed toward the surfaces such as vessel wall, cell membrane or drug-containing vesicles and pierce their surfaces (Fig 2-d). Even non-inertial cavitation can damage the structures like cell since the shear stress around the bubble can rupture the cell membrane or vessel wall, thus the cell permeation or extravasation could be achieved [22, 23]. According to the study by Ampfel and Holland the onset of collapse cavitation can be predicted for the single acoustic cycle, developed to a parameter called mechanical index (MI), which measures the probability of collapse. With MI in the range of 0.3 and 0.4 collapse cavitation occurs, while biological effects start to show at 0.7 and with MI > 1 detrimental cell effects appears; besides, for multitude acoustic cycle this threshold

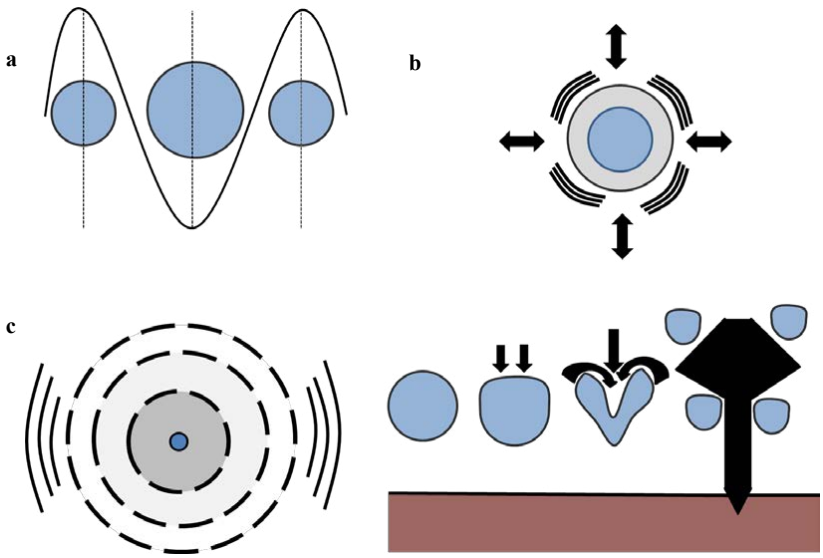

Fig 2. Schematic representation of various bubbles interaction with the ultrasonic wave. Ultrasonic sine wave causes expansion at low-pressure and contraction at high-pressure of the bubbles sizes (a). Change in bubble size lead to circulating flows around the bubble which is called microstreaming and it is the result of stable cavitation (b), In inertial cavitation, pressure wave (ultrasound) could lead the bubble collapse and cause shock wave (c) Formation of a liquid microjet will occur during inertial cavitation near an extended surface (d)

will decrease.

Generally the probability of collapse cavitation increase with low frequencies and higher densities [24].In the absence of cavitation two diffusion mechanisms for drug transport are introduced. Oscillation of the liquid could augment the diffusion and transport of molecule. Convection flow as a result of ultrasound momentum was considered as the second mechanism induces overall transport of molecules.

Probably, convection flow seems to have no effects in vivo, due to excitants of the circulatory system and lack of adequate liquid environment in most of the tissues.

High Intensity Focused Ultrasound (HIFU)

The HIFU beam is focused in several cubic millimeters of an area. In this focused area, the ultrasound is very intense but in other areas is very weak. Among the physical stimuli that have been introduced for controlling drug release from nanocarriers, HIFU has advantages such as powerful special and temporal control over the exposure area, and deep body penetration in a noninvasive and nonionizing way [25]. Since HIFU applications operate around 0.8-3.5 MHz [15], thermal effects are more dominant in compared to cavitation effects with high-frequency ultrasound. Therefore, thermosensitive nanocarriers would be applicable for this stimulus.

Energy quantities carried in the HIFU beam are much higher than those of a standard diagnostic ultrasound beam [15]. Therefore, HIFU has been applied for ablation of solid tumors [26]. Another application of HIFU is stimulus drug delivery. Dromi et al. indicating HIFU induced drug delivery in animal models. They used magnetic-loaded nanocarriers for stimulus release under MRI-controlled high intensity focused ultrasound [27].

Is ultrasound safe?

Investigating the risks of the biological effects of ultrasound in medicine and biology conducting annually by the symposium of World federation for ultrasound in medicine and biology (WFUMB) and the results are released and suggestions are offered. To date, on the basis of epidemiological findings, no definite relationship between diagnostic ultrasound and destructive effects has been found [28]. However, for new medical applications for higher intensities of ultrasound, such as ultrasound assisted drug delivery, new concerns have been raised. Ultrasound exposure has led to two different effects on the human body: thermal and non-thermal.

Thermal effects

Generally, the transferred energy of ultrasound can induce heat in the environment. Tissues with a higher absorbent coefficient (bone) show more temperature increase compared to lower absorbent tissues [29]. In the diagnostic realm, this increase is about 1.5 0C, which is not significant. Increase in the temperature of the tissue is in direct relation to the time of exposure, and the intensity and frequency of the waves. Increasing the time of irradiation can increase the temperature up to 2^0C, resulting in some abnormality in the animal fetus. A parameter named the time of threshold (TT) introduces the threshold of tissue tolerance on the basis of exposure duration [30]. This time-dependent temperature effect can be reduced by the optimum time duration of the exposure.

Non-thermal effects

Among the non-thermal effects, cavitation can play an important role in terms of its energy transfer. Eddies flow around the bubbles, sonic jet flow after bubble collapse, and free radical are the matters need to be considered for the probable harmful impact on the cells and biological environment. This phenomenon of cavitation is important when low frequencies and high intensities of ultrasound are applied [31].

The sonic effect of ultrasound is another non-thermal effect. Cutting power of sonic flow can induce tissue damage. This effect is important when a tissue shows different sonic impedance from surrounding tissues.

So far, most conducted research evaluating the safety of these waves has been done on the skin and its underlying tissues [32]. Many of these studies are on the basis of the histological change of the animal skin. For instance, several separated histological studies on rat, rabbit and porcine skin revealed no effect after ultrasound application [33-36). By applying ultrasound with low intensity (48kHz, 0.5 W/cm2), a comparison between human and rat skin via electronic microscope indicated that rat skin is more sensitive and stratum corneum of rat skin was completely eroded; However, only the keratinocytes around the follicles in the human skin were disturbed and is thought to be as a consequence of cavitation

effects [37]. In another comparative study between mouse and human by low-intensity ultrasound (≤2.5 W/cm2), no histological changed occurred in human skin [38].

The treatment of solid tumors with HIFU was investigated by developing noninvasive, image-guided, in situ tumor ablation with focused ultrasound energy [39]. Because of high levels of shear force and inertial cavitation of HIFU, there is concern that maybe ultrasound exposure could lead to dissemination of cancer cells and subsequent metastasis. The Oosterhof report on Fisher-Copenhagen rat models does not show a significant difference in metastases growth of ultrasound exposed and unexposed samples [40]. However, ~30% increase of lung metastatic growth in mice treated with pulsed-HIFU was reported by Hancock et al [41]. Recent clinical reports indicated local pain, skin toxicity, and transient fevers of applying high-intensity ultrasound on cancer patients [26].

On the basis of mentioned studies, the possible adverse effects of ultrasound are directly related to functional parameters, including intensity, frequency, exposure time, the distance between probe and tissue, and type of tissue. Investigating these parameters and their impacts on the safety should completely be considered in every new bio and medical application of ultrasound.

Ultrasound responsive drug carriers

Microbubbles

Gas-filled bubbles are named microbubbles with the size range of 1 to 8 µm and have been in use for imaging purpose for several decades. However, its emergence in drug and gene delivery has opened a new rout of application for this microsphere. As a contrast agent, they produce acoustic backscatter waves with different acoustic impedance to the surrounding medium. [42]. Gases like perfluorocarbon or sulforhexafloride with low solubility in blood and low diffusion coefficient was preferred and with different coating materials including denatured albumin, lipid or surfactant layers, poly-butyl-cyanoacrylate a shell around the microbubbles, the lifespan and stability of the microbubble was improved [43].

Liposomes

In theory liposomes and micelles are not acoustically activated in an ultrasound field; however, some studies show that even carefully prepared liposomes contain some gases inside which has the ability to activate in response to ultrasound, and their payload will release upon cavitation effect [44]. Raman spectroscopy showed that permeation of liposomes can increases in ultrasound field [45]. Dye loaded liposomes stopped dye leakage when the ultrasound field terminates. This can be considered as a sign of a positive effect of ultrasound on a liposomal carrier for control drug delivery [46].

Stabilizing microbubbles by phospholipids results in the liposomal structure named echogenic liposome [47], which has shown its efficiency in ultrasound-mediated application. In synthesizing echogenic liposome, three structures are possible. The possibilities are 1) the liposome with the entrapped air in their lipophilic portion between two phospholipid layers. 2) Monolayered air vesicles in the hydrophilic core. And 3) a third state obtained by binding the liposome to the microbubbles by various binding strategy, like the avidin-biotin bond (Fig 3) [48, 49]. The two first states are considered as nanobubbles. The sensitivity of these nanobubbles to ultrasound field can be adjusted by liposomal composition, type of encapsulated gases and ultrasound condition [50]. Microbubbles with phospholipid coverage have shown the tolerance of contracting and expanding in more than 10 times of their initial surface area [48].

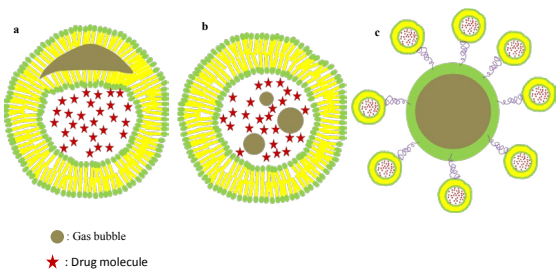

Fig 3. Different schematic views of bubbles that have been stabilized by liposomal drugs formulation (a). The nanobubble is surrounded by liposomal structures by different binding techniques. (b) An example of nanobubble loaded within the hydrophobic phospholipid bilayer of the liposomal structure. (c) Stabilized bubbles that have been loaded in the hydrophilic container created by a liposomal structure

Polymer sphere and micelles

The feasibility of co-administration drug-containing polymeric micelles, which are activated by ultrasound, was studied by several researchers and the outcome was promising. There are three

required characteristics needed for the mentioned purpose: 1) sufficient drug loading, 2) retention of the drug after intravenous administration and 3) release or internalization of the drug upon applying ultrasound field. Among polymeric micelles, the pluronic family with maneuverable phase state has shown the potential to be responsive to ultrasound field and release some drug after insonation [51]. The phase state in different temperature of Pluronic micelles is depend on block length ratio and molecular weight of each part of triblock copolymers (poly (ethylene oxide) (PEO) – poly (propylene oxide) – poly (ethylene oxide) (PEO)) [52]. Also very small micelles (5 and 20 nm), could be formulated at physiological temperatures which is appropriate size for cancer drug deluivery [53].

Metallic nanoparticles

Metallic nanoparticles are very good energy absorbent. Metal nanoparticles under NIR laser [54-56], X-ray [57, 58] or electric field exposure [59, 60] and magnetic nanoparticle under magnetic field exposure [61] have been applied for stimulus release application.

Metal nanoparticles are typically made by a chemical or biological method [62-65]. But many metal nanoparticles were also synthesized based on sonochemistry [66-68]. Applying high-intensity ultrasound to perform a chemical reaction was called sonochemistry [69]. Physical phenomenon responsible for the chemical reaction is cavitation. Collapse of cavitation bubbles made by high intensity sonic wave, result in tremendously high pressures and temperatures in a focused area. This phenomenon is lead to reduction of metal ions into small metal nanoparticles [67]. But high-intensity ultrasound exposure on synthesized nanoparticle may cause aggregation of Zn, Cr, Ni, and Mo nanoparticles [70]. In case of the gold nanoparticle, this kind of aggregating was not reported in different frequencies [71]. Recently even direct formation of gold particles from bulk gold in a surfactant solution using ultrasound was reported by Watt et al [72]. Similar to sonochemistry high intensity of temperature and pressure that generated by cavitation break down the bulk gold into small nanoparticles.

Gold nanoparticles show a great capability for ultrasound mediated drug delivery, not only because of biocompatibility and versatile surface modification but also higher density in comparison to other nanoparticles that lead to higher penetration in tissue-mimicking material under ultrasound exposures [73, 74]. Like liposomes anisotropic gold nanocones could be loaded by small bubbles by drying and redispersing in water. These cone shaped gold nanoparticle were capable of ultrasound-mediated drug delivery [75].

The sensitivity of the polymeric microcapsules assembled was significantly increased if different metallic nanoparticles were loaded in the carriers [76-78]. In all of these experiments, carriers which decorated by metallic nanoparticles released the payload by stimulus ultrasound much better than the simple organic carriers. The carriers' sensitivity to ultrasonic power depends on stiffness and elasticity of the shell's structure and can be tuned to actuate at safe medical power intensities. Actually with this technique Pavlov et. al achieved stimulus release of protein from gold nanoparticles decorated polymeric capsule in low power ultrasound [1–3 W and 850 kHz] that close to appropriate medical uses ultrasound [79]. Similar to polymeric microcapsules liposomes as also could be decorated by gold nanoparticles [80, 81] but these nanostructure are not applied for ultrasound drug delivery until now.

Combination of drug carrying vehicle and ultrasound for drug delivery

Microbubbles

Ultrasonic wave can push the microbubbles in a specific direction according to its propagation, and enhance the aggregation of the bubble on the desired site in vessels [82]. So microbubbles enhance extravasations and cell permeability due to the several mechanisms. Firstly shear stress of microjets and microstreaming creates transient non-lethal hole on cell membrane or lining endothelial cells on vessels wall through which drug and gene can penetrate [83], secondly intracellular reactive oxygen species may contribute to cell permeability without lethal effects [84], thirdly phospholipids layer of cell membrane fluidity increases due to the high local temperature and molecular diffusion from cell membrane increases; therefore, drug and gene delivery can be improved utilizing these phenomena [85]. In this regard, either can microbubbles be co-administrated with drug and gene or preloaded with them, then targeted to the site of interest. Intracellular deliveries of fluorescently labeled particle have been demonstrated after insonation

of microbubbles [86].

Microbubble gene delivery to the cardiovascular tissue has attained remarkable notice. Utilizing reporter genes, Bekeredjian et al studied the deliverance of reporter genes to heart. in this study luciferase transgene marker was delivered to the left ventricle of a rat with commercial and custom microbubbles and the validity of targeted delivery was proved by expression of the gene in the heart with slight expression in liver and pancreas; in addition, no effects were observed in brain, muscles, and lung [87].

Tumors as sites of genetic variation can also be good targets for microbubble gene delivery. Atsuko et al induced tumor regression by applying Herpes simplex thymidine kinase gene in combination with nanobubbles and trans-dermally ultrasonic field [88].

Liposomes

Investigating the release of doxorubicin from Doxil (liposomal nanoparticles) in the presence of ultrasound, different release pattern in different frequency was observed. Exposing the Doxil in Salin and Human-sourced plasma in 20 KHz for 30 min led to release of 85% and 61% respectively; however, in 1MHz, low release (5%) from liposomes in Human-sourced plasma was reported [45]. To overcome blood-brain barrier (BBB) for drug delivery purpose, the combination of liposome-encapsulated doxorubicin, microbubble, and ultrasound, resulted in higher drug concentration in brain tissue with linear relation to microbubble concentration [89]. The echogenic liposomes with 15% calcein as a model drug was investigated for drug release and reasonable structural maintenance and release was observed upon applying ultrasound field [90]. Echogenic liposomes containing hydrophilic drug are a better candidate for control drug delivery since the hydrophobic drug is rather a resistance to release from liposomes by the ultrasound and remains in lipid fragment of disrupted liposomes [23]. Generally believed that the mechanism of release seems to involve cavitation events that either pierce a hole in or shear open the liposomes [91].

Some gases play important biological role in the body and their delivery to the desired site for their therapeutic effects would be of great importance; however, most have short half-life in the body, for instance, nitric oxide with its important role in cardiovascular system has a half-life about 1.8 ms which needs to be enhanced by its encapsulation, which echogenic liposomes have improved its half-life to 8 hours. In vivo experiment showed that administration of nitric oxide loaded echogenic liposomes to balloon-injured carotid arteries resulted in 51±6% inhibition of intimal thickening relative to controls [92].

Polymer sphere and micelles

In a study by Marine et al, the intracellular uptake of Pluronic micelles loaded with DOX was investigated. Exposure to ultrasound enhanced the drug uptake by the nucleus of HL-60 cells and drug distribution altered from acidic compartment of cells to neutral compartment, showing non-endosomal pathway [93]. Zhang study indicated that ultrasound does not enhance extravasation of Dox-loaded polymeric micelles and preliminary passive accumulation of micelles in tumor site is required for drug effect enhancement. In this study, significant suppressive effect on tumor growth was observed when compared to molecularly dissolved DOX and this effect was dependent on time between ultrasound application and drug injection [94]. Husseini et al evaluated drug release from polymeric micelles in a different frequency ranging from 20 to 90 kHz and the result showed the enhancement of drug release was highest in 20 kHz in comparison to other frequencies, while for higher frequency in spite of higher power density the drug release dropped [95]. The effect of drug-loaded polymeric micelles on multidrug resistance cells, MDR, has found upon insonation. In a comparative study after applying DOX concentration of about 5 mg/ml only 15% of MDR cells were killed after 3h incubation following 72h culturing in drug-free medium while 5 mg/ml DOX in unimeric Pluronic solution killed 53% of MDR cells; however, the same drug concentration in unimeric Pluronic solution after 10 minutes insonation killed 66% of MDR cells after subsequent cell culturing [96]. The amount of DNA damage that DOX containing P150 micelles can induce with and without the ultrasound field was investigated by Munshi et al. the results indicated that in the absence of ultrasound, no significant DNA damage was observed when the cells were exposed to 10 mg/ml of DOX in the presence of 10 Wt% p105 after 9h incubation; however, applying US led to significant DNA damage and cell death [97].

Non-pluronic micelles have also been investigated for drug delivery in ultrasound field, for instance, Zeng and Pitt synthesized a micellar carrier from a block of polyethylene oxide (PEO), N-isopropyl acrylamide (NIPAAm), and a polylactate ester of hydroxyl-ethyl methacrylate (pENHL). Dox release upon 70 KHz ultrasound application was observed from these micelles [98].

Gas delivery was investigated by polymeric particles as well as liposomes. Oxygen was loaded in chitosan nanoparticles and oxygen delivery was enhanced by sonication in Cavalli et al report. The finding of the study might be useful in oxygen delivery to tumor site where hypoxia is the major hindrance in radiotherapy [99].

CONCLUSION

In the field of drug delivery, many studies have been conducting to bridge nanocarrier and ultrasound to each other and improve the therapeutic efficiency and declining side effects of many drugs. In this regard, liposomes, micelles, and micro/nanobubbles were the most area of research; however, the potential of this modality shows to be extensive, promising and many efforts has to be done in optimizing this technique and many questions waiting to be answered in terms of safety and feasibility.

By the advent of new and novel methods in the field of drug delivery, utilizing ultrasound has shown great promise to solve many problems. Developing new sound sensitive biomaterial for drug delivery application is essential. Materials such as metallic and oxide nanoparticles, polymeric nanoparticles (e.g, PLGA, PLA), ceramic nanoparticles (e.g, silica nanoparticles) might have the ability to enter this field.

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