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The effect of magnetic nanoparticles on the acoustic properties of tissue-mimicking agar-gel phantoms

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ABSTRACT

In ultrasonic hyperthermia, ultrasound-induced heating is achieved by the absorption of wave energy and its conversion into heat. The effectiveness of ultrasounds can be improved by using sonosensitisers that greatly attenuate ultrasonic waves and then dissipate the acquired energy in the form of heat. One possible candidate for such a sonosensitiser are superparamagnetic iron oxide nanoparticles. Here, we used magnetic nanoparticles embedded in a tissue-mimicking agar-gel matrix. Such tissue-mimicking phantoms possess acoustic properties similar to those of real tissues, and are used as a tool for performance testing and optimisation of medical ultrasound systems. In this work, we studied the effect of magnetic nanoparticles on the acoustic properties of agar-gel phantoms, including the attenuation of ultrasonic waves.

1. Introduction

Ultrasound has been used in medical diagnostic systems and in a variety of therapeutic applications [1,2]. It has been used, among other things, to affect cancer cells (sonodynamic therapy). The therapeutic effect of ultrasound irradiation can be achieved by local hyperthermia, thermal ablation, and cavitation processes [3,4]. In ablation procedures or high-intensity focused ultrasound (HIFU) hyperthermia, the mechanical energy of ultrasonic waves converts to thermal energy as the wave propagates through the tissue. Ultrasound-induced heating is achieved by the absorption of wave energy and its conversion into heat. The challenge is to utilize the energy of an ultrasound beam effectively, i.e., to heat up and damage cancer cells, while keeping the peripheral healthy tissues untouched. Compared with other ways of treatment such as radiofrequency (RF) waves or microwaves [5], the ultrasound method has the advantages of deep penetration length, flexible operation, easy access, and low cost [6]. However, the applicability of ultrasound is generally limited by the damage done to healthy tissues and by the prolonged treatment time due to the relatively low heating or cavitation effect [6].

The effectiveness of ultrasound can be significantly improved by using sonosensitizers: nanoparticles that considerably increase the absorption and heat produced by ultrasound [4,7]. For example, nanoparticles can be used to enhance the HIFU thermal ablation of cancer tumours [4]. One possible candidate for such sonosensitiser are superparamagnetic iron oxide nanoparticles (SPION). The presence of magnetite nanoparticles in the material enhances the effectiveness of ultrasonic hyperthermia, leading to increased temperature. Magnetic nanoparticles can also be used for magnetic hyperthermia: they heat the sample when exposed to an alternating magnetic field. Thus, magnetic hyperthermia and ultrasonic hyperthermia may work synergistically to produce a more efficient treatment [8]. It is easy to study the characterisation of the ultrasonic hyperthermia process using tissue-mimicking phantoms with known acoustic properties. Over the last decade, tissue-mimicking phantoms have been routinely used as a powerful tool for performance testing in elastography [9], magnetic resonance imaging [10], and ultrasonic imaging and hyperthermia studies [11–13]. The advantage of using phantoms with tissue-mimicking material is that idealised tissue models can be constructed with well-defined acoustic properties, dimensions and internal features [11]. In addition, such test sections, which can be made similar to those of human tissue, can be reused repeatedly without affecting acoustic and thermal properties [4]. The phantoms, if well characterised, allow for a comparison of experimental results with theoretical predictions.

The gel form of agar has been widely used as a phantom of human tissue because its acoustic characteristics are similar to those of the human tissues [14]. Gel with agar concentrations lower than 4% has a porosity similar to that of soft tissue such as the brain, while gel with greater agar concentrations has a microstructure similar to hard tissue [15]. In this work, we prepared phantoms with an agar concentration of between 3% and 10% by weight. We studied the acoustic properties of the pure agar-gel phantoms and how they changed after the addition of

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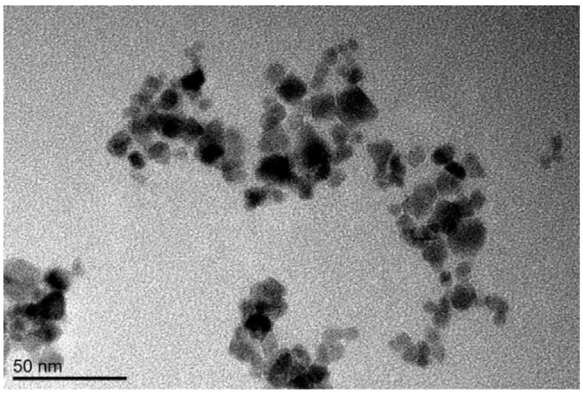

Fig. 1. TEM micrograph of synthesised Fe_3O_4 nanoparticles.

magnetic nanoparticles.

2. Materials and methods

2.1. Magnetic nanoparticles

Magnetite nanoparticles were prepared through chemical coprecipitation using ferric and ferrous salts in an alkali medium [16]. Freshly prepared Fe_3O_4 nanoparticles were coated with a surfactant sodium oleate ($C_{17}H_{33}COONa$) bilayer to prevent the agglomeration of the particles. The stabilised magnetic particles were dispersed in water. The volume concentration of magnetic materials in suspension was 70 mg/ml. The morphology of the synthesised magnetic nanoparticles was observed using transmission electron microscopy (TEM: Fig. 1).

After adding the surfactant layers, the nanoparticle size increased. The mean core-shell nanoparticle diameter $\langle x \rangle$ is called the hydrodynamic diameter. The hydrodynamic size distribution of nanoparticles in the suspension was determined by dynamic light scattering (DLS) and differential centrifugal sedimentation (DCS). The particle size measurements by DLS were carried out using a Malvern Zetasizer NanoZS. DCS determines particle size by measuring the time required for colloidal particles to settle in a density gradient in a disc centrifuge. The DC24000 UHR disc centrifuge (CPS Instruments, Inc.) was used to perform sedimentation-based size distribution measurements. Fig. 2 shows the results of volume weighted particle size distribution as measured by the DCS and DLS methods. In order to determine the mean particle hydrodynamic sizes, a log-normal distribution was fitted to the experimental data. The values of the mean hydrodynamic diameter are 64.9 nm and 83.7 nm obtained from the DCS and DLS, respectively.

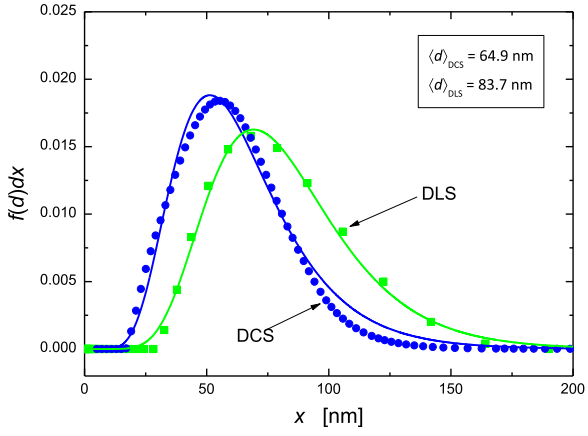

Fig. 2. Volume weighted hydrodynamic size distributions of nanoparticles measured by DLS and DCS. Solid lines were obtained by fitting the lognormal distributions to the experimental data.

2.2. Agar tissue-mimicking phantom

Phantoms are composed of tissue-mimicking materials, with a simple homogeneous internal structure. Agar forms a thermoreversible gel in an aqueous solution, and the gel remains stable over a wide temperature range [17]. Two types of agar phantom samples were prepared for the measurements: pure agar-gel without any added scattering material, and agar-gel with Fe_3O_4 nanoparticles. Agar powder was dissolved in hot distilled water. During the production process of the gel, magnetic nanoparticle scatterers – covered with layers of surfactant that prevent its agglomeration – were added. All the components were neatly mixed together. It can therefore be assumed that a nearly homogenous distribution of magnetic nanoparticles in the prepared samples was obtained.

The samples were made by varying the weight concentration of the agar from 3% to 10% (w/v). The weight concentration of the magnetic particles was constant: 8 mg/ml. Each prepared tissue-mimicking material is macroscopically uniform. The phantoms should possess acoustic properties similar to those of the tissue. Due to the limited stability of the agar material (over time it begins to dry up and deform) and the fact that agar phantoms with low concentration are very soft and prone to mechanical damage, we only used fresh agar samples for the measurements, prepared the day before the experiments.

2.3. Acoustic measurements

The ultrasonic insertion technique [18] is used to measure the acoustic properties of agar-gel. This technique is a relative measurement method of the transmission of longitudinal ultrasonic waves through gel embedded in an aqueous environment [18]. The experimental setup for the measurements of the velocity and attenuation of an ultrasonic wave is presented in Fig. 3. The transducer operated in pulse-echo mode and was driven by Optel Pulser/Receiver Card 01/100, which provided a unipolar spike pulse with an amplitude of 360 V and fall time better than 20 ns. The received signal was sampled at a rate of 100 MS/s and recorded. The ultrasonic velocities in the samples were determined from the temporal shift (Δt) between the pulse transit times with and without samples (Fig. 4a). The velocity of an ultrasonic wave can be calculated as:

$$c = \left(\frac{1}{c_0} - \frac{\Delta t}{2l} \right)^{-1} \tag{1}$$

where c_0 – is the acoustic velocity in water and l – the thickness of the gel sample.

The attenuation was determined by applying the same experimental configuration and measuring the amplitude of the signal for two samples with different thicknesses. The attenuation was calculated as:

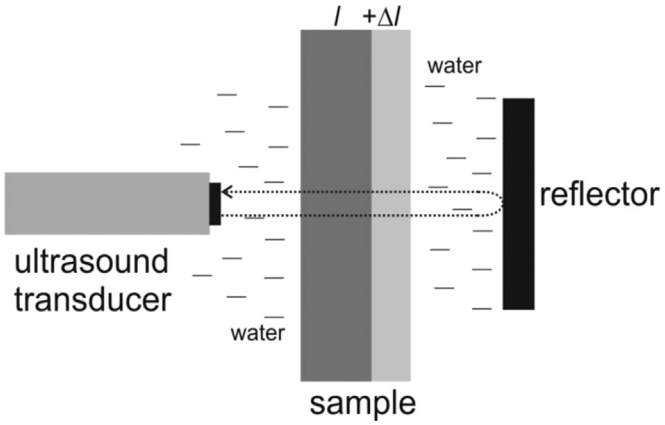

Fig. 3. Experimental setup for the velocity and attenuation of the ultrasonic wave measurements.

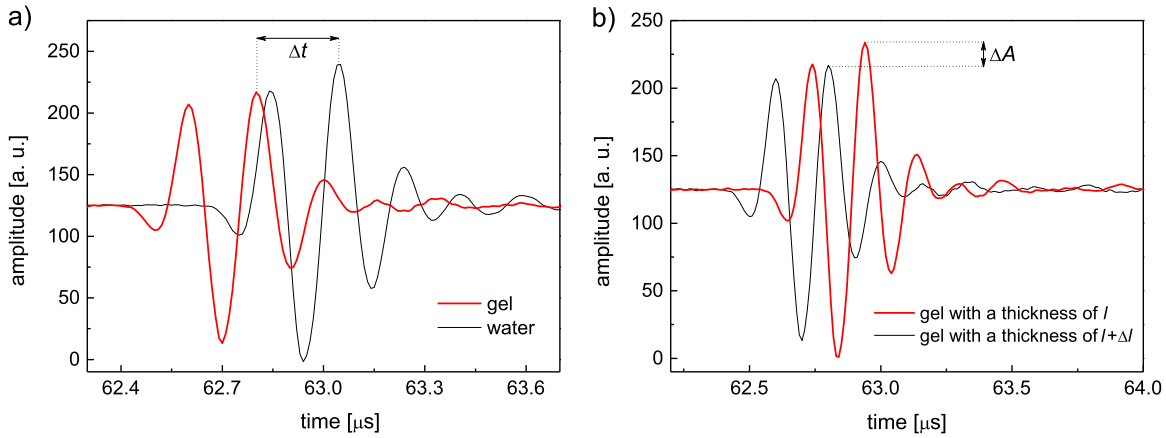

Fig. 4. Time-domain detected signals: (a) ultrasonic pulses with and without the agar samples; (b) measured pulses for two samples with different thicknesses.

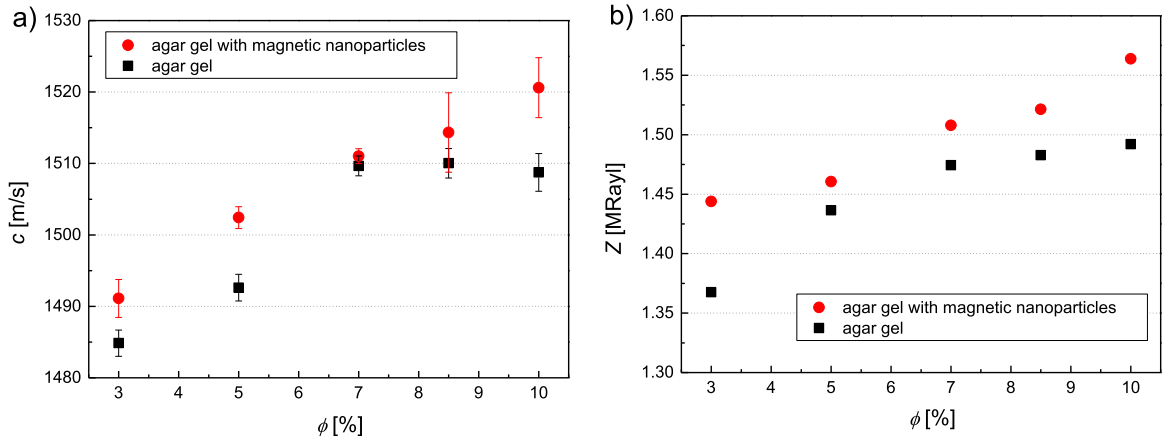

Fig. 5. Longitudinal ultrasonic wave velocity (a) and acoustic impedance (b) for different concentrations of pure agar-gel samples (squares) and agar-gel samples with magnetic nanoparticles (circles).

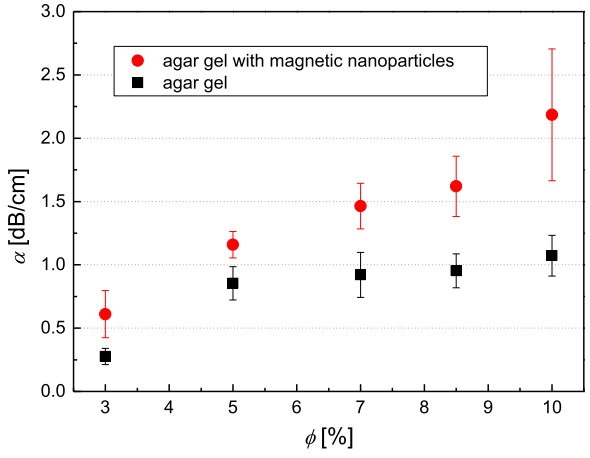

Fig. 6. Ultrasonic wave attenuation for different concentrations of pure agar-gel samples (squares) and agar-gel samples with magnetic nanoparticles (circles).

$$\alpha = \frac{1}{2\Delta l} \ln\left(\frac{A_1}{A_2}\right), \tag{2}$$

where A_1 and A_2 are the amplitudes of the ultrasound pulses propagating in the samples with lengths l and $l + \Delta l$, respectively (Fig. 4b).

3. Experimental results

Ultrasonic wave velocity is a significant source of information about the physical and chemical properties of materials. Fig. 5a presents the propagation velocity c of the ultrasonic wave in pure agar gel samples and in-agar samples with magnetic nanoparticles for different concentrations of agar from 3% to 10%. It can be seen that agar concentration has a clear impact on ultrasonic velocity. The velocity increases because of the increase in the number of junction zones with the agar concentration. The junction zones that connect the different polymer chains in the agar-gels have a structure that is thought to be very rigid [19]. Young's elastic modulus is roughly proportional to the square of the gel concentration [20].

From the ultrasound velocity c and density ρ of the agar phantoms, the acoustic impedance $Z=c\rho$ and elastic modulus $E=c^2\rho$ were estimated. The densities of the phantoms were determined from the measurements of the mass and volume of the sample. Fig. 5b presents the acoustic impedance of the agar-based gel obtained from ultrasound measurements. The effect of magnetic nanoparticles on the acoustic

Table 1
Main acoustic properties for pure agar gel and agar gel with magnetic nanoparticles with the concentration of 8 mg/ml. In both samples the concentration of agar was 8.5%.

	Pure agar-gel	Agar-gel with magnetic nanoparticles
Ultrasound velocity c [m/s]	1510.0	1514.3
Ultrasound attenuation α [dB/cm]	0.95	1.62
Density ρ [kg/m^3]	981.9	1004.7
Acoustic impedance Z [MRayl]	1.48	1.52
Elastic modulus E [GPa]	2.24	2.30

impedance of tissue-mimicking agar-gel phantoms is clearly visible. The values of the impedance increased after the addition of nanoparticles. As for the stiffness of agar-gel phantoms, the compressive elastic moduli increase with agar-gel concentration and the presence of nanoparticles in the sample. The values of the elastic modulus (measured by the ultrasonic technique) in the samples with 7% concentration of agar are E=2.23 GPa without nanoparticles and E=2.28 GPa after the addition of sonosensitisers. Thus, the stiffness of agar-gel phantoms can be controlled by both the agar and nanoparticle concentration.

The results of the measurement of acoustic attenuation as a function of agar weight concentration for pure agar-gel and agar-gel with magnetic nanoparticles are presented in Fig. 6. The attenuation coefficient for both types of phantoms increases when the agar concentration increases. This can be explained by the process associated with the interactions in the junction zones or aggregates. These interactions are apparently dominated by entropy and volume changes. The number of aggregated junction zones increases with agar concentration [19]. The attenuation also increased after the Fe_3O_4 particles were added. This is reasonable considering the frictional and scattering nature of the attenuation processes. The particles possibly swing in the gels under the influence of the acoustic field, just like in viscous liquid suspensions [21]. Nanoparticles induce some additional attenuation of ultrasonic waves, characteristic of particulate media. This effect depends, in part, on the contrast between the physical properties (viscosity, density, thermal properties, and compressibility) of both the suspended particles and the continuous phase, and also on the concentration of solid particles, wavelengths of compressive waves and, in certain cases, on a thermal wave that gives rise to heat flow between the material phases [22]. The acoustic properties can be controlled by adding scattering materials – magnetic nanoparticles – because they affect the attenuation of sound. This fact is very important in hyperthermia studies. The obtained results should be useful for modelling ultrasound propagation and heating in human tissues. The heating achieved via the sonosensitising properties of nanoparticles has been observed and explained by the strong scattering and absorption of ultrasound radiation in the region near the nanoparticles [23]. During the experiments, it was observed that the agar samples immersed in water over long periods of time started to swell (due to the absorption of water). As a result, measurements over time were more difficult, and differences in the results occurred more often. This may be (one of) the important causes of experimental error in the obtained results.

Table 1 summarises the obtained values of the acoustic velocity, attenuation, density, impedance, and elastic modulus in agar-gel of concentration 8.5%, both with and without magnetic nanoparticles. The prepared tissue-mimicking materials have properties within the range of human tissues [11,14].

4. Conclusions

Biological systems can be simulated well by using agar-based gels. Tissue-mimicking phantoms made of agar are good reference materials for examinations of both ultrasonic and magnetic hyperthermia.

Ultrasonic wave properties in the agar-gels together with magnetic nanoparticles have been experimentally studied. The effect of adding scattering material manifested itself as changes of ultrasonic wave parameters. We found that the attenuation of ultrasonic waves in the agar-gel samples with magnetic nanoparticles is greater than that in the pure agar-gel sample. Therefore, magnetic nanoparticles can serve as sonosensitisers for acoustic wave-induced hyperthermia. The use of sonosensitisers is very beneficial as they increase the heat effect during ultrasonic hyperthermia.

Acknowledgments

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