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Abstract. Medical imaging is an effective technique used to detect and prevent disease in cancer research. To optimize medical imaging, a calibration medium or phantom with tissue-mimicking properties is required. Although the feasibility of various polymer gel materials has previously been studied, the stability of the gels' properties has not been investigated. In this study, we fabricated carrageenan-based polymer gel to examine the stability of its properties such as density, conductivity, permittivity, elastic modulus, and T_1 and T_2 relaxation times over six weeks. We fabricated eight samples with different carrageenan and agar concentrations and found that the density, elastic modulus, and compressive strength fluctuated with no specific pattern. The elastic modulus in sample 4 with 3 wt. % carrageenan and 1.5 wt. % agar fluctuated from 0.51 to 0.64 MPa in five weeks. The T_1 and T_2 relaxation times also varied by 23% to 29%. We believe that the fluctuation of these properties is related to the change in water content of the sample due to cycles of water expulsion and absorption in their containers. The fluctuation of the properties should be minimized to achieve accurate calibration over the shelf life of the phantom and to serve as the standard for quality assurance. Furthermore, a full liver phantom with spherical lesion particles was fabricated to demonstrate the potential for phantom production. © 2014 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: [10.1117/1.JMI.1.3.035502](https://doi.org/10.1117/1.JMI.1.3.035502)]

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1 Introduction

Medical imaging is investigated intensively in the healthcare industry, both for clinical and research purposes. It is used to prevent and to detect diseases early, identify optimal treatment, for surgical intervention, and for monitoring the response to treatment. Among medical imaging modalities, magnetic resonance imaging (MRI) is recognized as the most advanced medical modality for detailed three-dimensional (3-D) visualization of the internal structures and soft tissues of the body. Unlike other imaging methods such as X-ray and computed tomography, MRI does not utilize ionizing radiation and thus eliminates the harmful side effects associated with the prolonged exposure of a patient to radiation. Physicians can use MRI to detect and evaluate lesions, multiple sclerosis, tumors, and strokes within soft tissues.

MRI technology has improved over the last few decades to enhance the image quality and to provide various diagnostic techniques and assist image-guided therapy. In order to ensure the accurate diagnosis, MRI requires systematic calibration of the equipment regularly with a phantom that simulates the values of human tissue. An imaging phantom is a calibration medium that is scanned or imaged to evaluate, analyze, and tune the performance of various imaging devices. A phantom used for evaluating an imaging device should respond in a manner similar to those of human soft tissue in the specific imaging mode.

Currently, a normal human patient is used for imaging calibration, but the process is time consuming, costly, and often does not provide consistent values that set the standard for calibration. Therefore, a phantom that behaves similarly to human soft tissue functions as a replacement. The optimal characteristics of MRI phantoms used for such purposes are as follows: (1) relaxation times equivalent to those of human tissues, (2) dielectric properties equivalent to those of human tissues, (3) the relaxation times and dielectric properties should be homogeneous throughout the phantom, (4) mechanical properties suitable for fabrication of a human torso without the need for reinforcement, (5) can be used to form shapes of human organs, (6) ease of handling, and (7) stability of physical and imaging properties over an extended period.¹

Over the last few decades, several studies have been conducted on water-based polymer gels with paramagnetic ions as potential materials for MRI phantoms. Paramagnetic ions (i.e., CuSO_4 , NiCl_2 , MnCl_2 , and GdCl_3) are known to improve the visibility of internal body structures in MRI by altering the T_1 and T_2 relaxation times. The T_1 and T_2 relaxation times represent the rate at which the longitudinal and transverse components of the magnetization vector of human tissue return to thermodynamic equilibrium. Some polymer gels that have been investigated include agarose,^{2–4} agar,^{5,6} polyvinyl alcohol,⁷ gelatin,⁸ and polysaccharide gels TX-150⁹ and TX-151.¹⁰ These studies have demonstrated that each material has potential for

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phantom application, but this is limited due to fragility and storage conditions.

Similar to the materials stated above, carrageenan-based gel has been previously studied for its viability as an MRI phantom material.¹ The results demonstrated that by varying the concentrations of the carrageenan and the modifier, the values of T_1 and T_2 could be modified to match those of a human tissue. However, there has been no study to investigate the mechanical stability of the material, except a brief report on the fungal growth over time. Because carrageenan gels have high water content, their properties may fluctuate with time due to continuous cycles of water expulsion and absorption. The stability of the material properties of a phantom, such as the density, elastic modulus, and T_1 and T_2 relaxation times, is essential for its commercialization owing to the required long shelf life. If the properties of a phantom vary with time, it would produce false results when used to calibrate an MRI system.

Therefore, the motivation of this study is to study the change in the properties of a carrageenan-based gel phantom by investigating its stability over a 6-week period. A carrageenan-based liver phantom was fabricated by copolymerization of carrageenan, and agar and Gd-DTPA were used as T_1 and T_2 modifiers. To investigate the effects of the polymer and modifier on structural integrity and relaxation times, eight samples with different concentrations of the polymer and modifier were fabricated and characterized. The sample densities and chemical, dielectric, mechanical, and imaging properties were determined and compared with those of human tissue. The properties of each sample were measured and analyzed to assess their property stability for MRI phantom application.

2 Experimental Setup

2.1 Experimental Materials

Polymers with two gelling agents, namely carrageenan and agar, were used for the study. Commercial-grade type 1 carrageenan (Sigma Life Science) was used as a gelling agent, whereas agar (BioShop) was used as both a gelling agent and T_2 modifier. Gd-DTPA Omniscan gadodiamide injection ISP 287 mg/ml (0.5 mmol/ml) (GE Healthcare) was used as the T_1 modifier. NaN_3 was employed as an antiseptic to prevent deterioration of the polymer gel over a prolonged period.

Table 1 Contents of carrageenan, agar, GdCl_3 , and water in the polymer gel samples.

Sample	Carrageenan (g)	Agar (g)	GdCl_3 (μL)	H_2O (mL)
1	3.0	0.0	1.7	97
2	3.0	0.5	1.7	96.5
3	3.0	1.0	1.7	96
4	3.0	1.5	1.7	95.5
5	2.5	1.5	1.7	96
6	2.0	1.5	1.7	96.5
7	1.5	1.5	1.7	97
8	1.0	1.5	1.7	97.5

2.2 Fabrication of Polymer Gel

The polymer gel samples were fabricated in test tubes prior to characterization. Different degrees of crosslinking were achieved by using various amounts of the gelling agents. The 100 mL of deionized water was heated to boiling temperature in a 150 mL beaker. Eight different samples with various concentrations of carrageenan (1 to 3 wt. %) and agar (0 to 1.5 wt. %) were fabricated where each powder material was poured into the heated water. The solution was stirred to obtain a homogeneous dissolution of the powder. The 1.7 μL of Gd-DTPA was dropped into the solution. The compositions of the samples are given in Table 1. After prolonged mixing for ~ 30 min to ensure homogeneity, the gel mixture was poured into a 15 mL glass test tube and set at room temperature for 30 min to remove air bubbles and cool. Parafilm was used to seal the open end of the glass test tube to minimize water evaporation during storage. The samples were then stored in a refrigerator at 4°C to observe changes in their properties.

2.3 Characterization

The characterization of the polymer gel samples was divided into four categories, namely chemical properties, mechanical properties (density, elastic modulus, and toughness), dielectric properties (conductivity and permittivity), and imaging properties (T_1 and T_2 relaxation times). Three of each sample was tested to examine the repeatability for each characterization. Fourier transform infrared spectroscopy (FTIR) was performed with Bruker Alpha FT-IR spectroscope to analyze the spectrum of the polymer gel.

The density of each gel sample was determined by dividing the mass by the volume. The density of each gel was compared with that of a real human tissue, which is $1.03 \times 10^{-3} \text{ g/mm}^3$.¹¹ The compressive modulus was measured using an Instron compression-testing machine with a 500 N load cell in accordance with ASTM standards.¹² A cylindrical disk was cut from the mold with a size of 16 mm diameter and 10 mm height. The disk samples were placed on the compression testing plate and a 500 N load cell was slowly lowered until it made contact with the sample. The contact between the sample and the plate was ensured by slowly moving the plate down until the Instron detected the load. The compression test, which was conducted after calibration, was done at a rate of 1 mm/min.

The dielectric properties of materials, such as conductivity (σ) and permittivity (ϵ), vary with the frequency. For example, the permittivity of liver decreases and the conductivity increases with increasing frequency. The dielectric properties of the polymer gel samples were measured using a dielectric Win DETA 5.64 (Novocontrol Technologies). The samples were cut with flat surfaces and placed between two gold plates to obtain accurate results. The gold plates were placed in the dielectric equipment and secured by tightening the sample mounting screw. The dielectric properties were measured using a frequency range of 1.0×10^{-1} to $3.0 \times 10^5 \text{ Hz}$.¹³

2.4 MRI Scan

An MRI technician at Sunnybrook Hospital assisted in acquiring the imaging properties of the polymer gel samples. We examined the stability of the properties over 6 weeks and assessed the viability of the polymer gels as MRI phantom materials. The prepared samples contained in glass test tubes were arranged on

a Styrofoam tube rack. The T_1 and T_2 relaxation times of the samples were obtained using a GE 3 Tesla MRI system with a 32-channel head coil. The sample in the container was placed inside the head coil of the MRI and aligned with the guideline. Inversion recovery was applied for T_1 and Spin echo for T_2 sequence. To measure the T_1 relaxation time, repetition time (TR) values of 2400, 1700, 1000, 500, 300, 150, 90, and 50 ms were used. The T_2 relaxation time was measured using echo time (TE) values of 10, 20, 30, 50, 75, 100, 150, 200, and 300 ms and TR of 2500 ms. The image resolution is 256×256 over a 16 cm field of view with a pixel size of 0.625 mm and 5 mm slice thickness. After the MRI images of the polymer samples had been obtained, a MATLAB algorithm was used to analyze the T_1 and T_2 values for every pixel of an image and store them in a large matrix form. For this particular experiment, a nonlinear least squares fit equation was used to fit the test data to a high-order polynomial. Equations (1) and (2) below were used to obtain the T_1 and T_2 signal values for the calculation:

$$S = M_0 \left[1 - \exp\left(-\frac{T_R}{T_1}\right) \right], \quad (1)$$

$$S = M_0 \exp\left(-\frac{T_E}{T_2}\right), \quad (2)$$

where S is the signal intensity, M_0 is the initial magnetization, T_R is the repetition time, T_E is the echo time, T_1 is the longitudinal relaxation time, and T_2 is the transverse relaxation time.¹⁴ A set of eight samples with different concentrations was stored in a low-temperature refrigerator for 6 weeks and then tested under MRI to examine the stability of the T_1 and T_2 values of the polymer gels over time. The signal to noise ratio (SNR) was calculated, which ranged between 435 and 850.

2.5 Polymer Gel Liver Phantom with Lesion Particles

Following the fabrication of polymer gel, a 1 L volume liver phantom was constructed with embedded lesions as illustrated in Fig. 1.

First, spherical lesion particles with various sizes between diameters of 1 to 10 mm were prefabricated with different

agar and carrageenan concentrations. The molten polymer gel solution was extracted with a 10-mL syringe and dropped in chilled oil. The chilled oil is composed of olive and castor oils to obtain high viscosity in order for polymer gel particles to slowly sink to the bottom. While the particles sink to the bottom of the oil beaker, they retain their spherical shape. Depending on the force exerted on the syringe, the size of the lesion particles can be varied. The size of the spherical inclusion was measured after fabrication. Then, 1 L of polymer gel solution was prepared to mimic the liver tissue. A small amount of NaN_3 was added as an antiseptic material to enhance the quality of the phantom and to avoid fungus formation over time. A layer of polymer gel was poured into a plastic container with dimensions of $10 \times 10 \times 10 \text{ cm}^3$, which was then placed in a vacuum chamber to remove air bubbles and into the freezer to quickly solidify. When the solution solidifies, prefabricated lesions with different sizes were spread on top of the polymer gel layer. Another layer of molten gel was slowly poured to avoid melting or disrupt the location of the lesions. Once four layers of polymer gel were stacked with lesion particles, a final layer was poured on top to cover the phantom. The phantom was stored in the refrigerator until it was imaged under MRI.

3 Results and Discussion

3.1 Chemical Properties (FTIR)

The compositions of the carrageenan gel samples were examined by FTIR as shown in Fig. 2. The samples exhibited similar IR peaks such as a strong broad band peak between 3150 and 3350 cm^{-1} , which corresponded to the O—H stretch, and a peak at 1640 cm^{-1} , which indicated the C=O stretch bond. The broad peaks indicated high water contents of the samples. The height of the peak increased with increasing water content.

3.2 Mechanical Properties: Density, Elastic Modulus, and Compressive Stress

The changes in the density of the gel samples with different agar and carrageenan concentrations were observed over 6 weeks to establish the density-time relationship. Samples subjected to density measurements were cut into a cylindrical disk shape and brought to room temperature for 30 min. Then, the volume and the mass of each sample were measured to calculate the density. As shown in Fig. 3, there was no distinct pattern in the density

Fig. 1 (a) Spherical lesion particle placement and (b) a fabricated phantom with embedded lesion particles.

Fig. 2 FTIR graph of carrageenan-based polymer gel.

change. However, the density fluctuation was more pronounced in samples with higher water content and lower gelling agent concentrations. This change occurs when water vapor is saturated and expelled to the wall of glass container or when the water droplets accumulate on the wall of glass container and condense back to gel mass. The air temperature and humidity of the refrigerator are kept constant to minimize the water-release

cycle. Thus, samples with higher water content will be subject to more dynamic density change. The densities of samples 7 and 8, which respectively contained 1.5 and 1.0 g of carrageenan together with 1.5 g of agar, exhibited greater fluctuations. The average fluctuation of sample 7 was 17.7%, whereas that of sample 8 was 10.3%. To make the densities of the samples similar to that of human tissue, which is 1.03 g/cm³, the agar and

Fig. 3 Density changes in the carrageenan-based gel samples.

Fig. 4 Changes in elastic modulus of eight polymer gel samples over 6 weeks: (a) samples with various agar concentrations (0.0 to 1.5 wt. %); (b) samples with various carrageenan concentrations (1.0 to 3.0 wt. %).

carrageenan concentrations can be varied as shown in Fig. 3, where the densities of the different samples can be observed to match that of human tissue at different times.

The mechanical properties, namely the elastic modulus and compressive strength, were measured to determine the compressive force that the gel samples could withstand while retaining their shape. The cylindrical disk was cut from the sample in a similar method as the density measurements and the elastic modulus was measured every Monday afternoon over 6 weeks. Changes were observed in all the samples, although the amount of change varied. As shown in Fig. 4, the modulus of samples with different agar concentrations fluctuated more dramatically than those of samples with different carrageenan concentrations. For example, the modulus of sample 4 initially increased by 25% from 0.51 to 0.64 MPa but dropped back to 0.45 MPa after 3 weeks. The modulus continuously changes over time and the fluctuation of the modulus values may be due to inconsistency in the water content. Although the samples were completely sealed with Parafilm and the container cap, they continually release and absorbed water vapor within the glass container. Thus, the rigidity of each sample could change. Similar trends of inconsistency in the modulus were observed in samples with different concentrations. It can be seen from Fig. 4 that the samples with lower concentrations of carrageenan, which acted as a gelling agent, had lower modulus values of about 0.1 to 0.4 MPa. The elastic modulus of normal

liver tissue reported in the literatures ranges between 6.4 and 60 kPa.¹⁵ Comparing the modulus values of liver tissue, the elastic modulus obtained from carrageenan samples range between 0.13 and 0.66 MPa. The result values are two orders of magnitude higher than that of normal human liver tissue. Considering the wide range of modulus values that can be achieved by varying the carrageenan and agar contents, polymer gel can be tailored to match the modulus of human liver tissue.

Similarly, the compressive stress at the maximum load of the samples determined by the Instron compression test machine shows variations. As can be seen from Fig. 5, the compressive stresses were highest for sample 1 (0.181 MPa) and lowest for sample 8 (151 kPa). This was predictable considering that sample 1 had the highest carrageenan concentration, whereas sample 8 had the lowest. Furthermore, the compressive strength fluctuated over time. In the case of sample 1, the strength initially increased by 42% from 0.128 to 0.181 MPa, and then reduced to 0.171 MPa after 6 weeks. The percent change in the compressive strength was highest for samples 1 and 8 (42% and 53%, respectively), which had the highest water content.

3.3 Dielectric Properties: Permittivity and Conductivity

The dielectric properties, namely conductivity (σ) and permittivity (ϵ), of soft human tissue have wide ranges of values

Fig. 5 Compressive strength of eight-polymer gel samples over 6 weeks.

Fig. 6 (a) Permittivity and (b) conductivity of sample 4 over 6 weeks.

and vary with the test frequency range. The dielectric properties of the samples need to be similar to those of human tissue because the homogeneity of the magnetic field depends on the wavelengths of the tissue and air. The wavelength of an RF field in air is about 468 cm^{-1} but is much higher in human tissue. If the wavelength of the RF field was different from that in human tissue, it would create constructive or destructive interference of the transmitted field, resulting in regional brightening or signal loss.¹³ Thus, to achieve optimal calibration, the dielectric properties of polymer gels should mimic those of human tissue. The dielectric properties of the polymer gel samples were measured using a dielectric Win DETA 5.64 (Novocontrol Technologies) and a frequency range of 1.0×10^{-2} to $3.0 \times 10^5 \text{ Hz}$. Normally, the dielectric test of human tissue is conducted using frequencies between 915 MHz and 2.45 GHz,¹³ which is beyond the range of the machine. However, the results of the present test showed that the conductivity increased and the permittivity decreased with increasing frequency. As shown in Fig. 6, the conductivities and permittivity of sample 4 exhibited no significant change over 6 weeks.

3.4 Imaging Properties: T_1 and T_2 Relaxation Times

The T_1 and T_2 relaxation times of the samples were determined using a GE 3.0 Tesla head MRI system to investigate their

variation with time. The T_1 and T_2 maps of the samples are shown in Fig. 7.

Figure 8 compares the effects of the agar, carrageenan, and Gd-DPTA concentrations on the relaxation times. Theoretically, carrageenan should not have any effect on the relaxation times because it was used as a gelling agent. Agar, which was used as a T_2 modifier, was expected to decrease the T_2 values with increasing concentration. Gd-DPTA, which was used as a T_1 modifier, was expected to suppress the T_1 values of the samples. The T_1 and T_2 values varied among the samples, which corresponded to different carrageenan and agar concentrations. For sample 5, the T_1 values ranged between 186.56 and 232.41 ms and the T_2 values between 72.43 and 88.77 ms. As was expected, with agar acting as a T_2 modifier, the T_2 values for samples 1 and 4 were different. The T_2 values for samples 6, 7, and 8 were similar, whereas that for sample 5 was much lower at 78 ms. Since the GdCl_3 concentration remained the same, the value of T_1 was expected to be consistent for each sample; however, it varied among the different samples. The foregoing indicates that variation of the agar and carrageenan concentrations can be used to further modify T_1 and T_2 . Therefore, further study on the effect of the concentrations of the components on the T_1 and T_2 values should be pursued to achieve polymer gels that mimic the T_1 and T_2 values of human tissue and lesion particles with reference to the values in Table 2.¹⁶⁻²⁰

Fig. 7 T_1 and T_2 maps of polymer gel samples at week 3 generated by MATLAB algorithm.

Fig. 8 T_1 and T_2 relaxation times of polymer gel samples after 5 weeks.

Several studies conducted on other polymer gel phantoms revealed that there were no significant changes in the T_1 and T_2 relaxation times when the phantoms were stored in tightly sealed containers.²¹ Thus, it is necessary to conduct a further time sensitivity study on T_1 and T_2 using more reliable storage systems.

The T_1 and T_2 relaxation times of sample 2 over 6 weeks are shown in Fig. 9. T_1 changed by 29% from 204.27 to 286.8 ms over 3 weeks. However, T_2 changed by 23% from 91.09 to 119.04 ms in first 2 weeks. These changes should be considered since the inconsistency of the relaxation time values over the phantom's lifetime might result in inaccurate calibration of MRI.

Table 2 T_1 and T_2 relaxation times of human tissues at 3T.

Tissue	T_1 (ms)	T_2 (ms)
Liver	812 ± 64	42 ± 3
Skeletal muscle	1412 ± 13	50 ± 4
Heart	1471 ± 31	47 ± 11
Kidney	1194 ± 27	56 ± 4
Cartilage 0°	1168 ± 18	27 ± 3
Cartilage 55°	1156 ± 10	43 ± 2
White matter	1084 ± 45	69 ± 3
Gray matter	1820 ± 114	99 ± 7
Optic nerve	1083 ± 39	78 ± 5
Spinal cord	993 ± 47	78 ± 2
Blood	1932 ± 85	275 ± 50

Fig. 9 T_1 and T_2 relaxation times of sample 2 over 6 weeks.

Fig. 10 T_1 and T_2 maps of the phantom layer with lesion particles.

3.5 Polymer Gel Liver Phantom with Lesion Particles

A 1 L volume phantom is constructed layer by layer as described in Sec. 2.5. MR images were taken and T_1 and T_2 values have been measured for both phantom and lesions as shown in Fig. 10. We have successfully fabricated a phantom with embedded lesion particles located randomly between the layers. The T_1 and T_2 values of the lesions were obtained using MATLAB program, where T_1 values ranged between 411 and 766 ms and T_2 values were between 102 and 209 ms. Compared with the relaxation values of normal liver tissue and cyst in Table 2, the result values were closer to normal liver tissue. Relaxation time values of liver cyst and hemangioma can be obtained by changing the concentrations of carrageenan, agar, and Gd-DPTA of the lesion solution. Despite the success in the liver phantom with lesion particles, there are several obstacles raised during the imaging. Due to the stacked layers of polymer gel for lesion placement, bubbles form surrounding the lesion particles. After lesion particles are placed on the first layer, heated gel solution is poured on top of a solidified layer to create a second layer. During this process, the heated solution that is poured on first layer could melt and shift the location of the lesion particles, which results in air pocket formation and appears on the image as an artifact. Also, on the T_1 map, the edges of the lesions are blurry, which is hypothesized to be due to the diffusion of paramagnetic ions or poor SNR related to problems encountered during imaging.

4 Conclusions

With improvements in medical imaging technology, the need for the development of a phantom for calibration and training purposes has risen. Although few studies have been conducted on polymer-based phantom materials, the viability and durability of the phantoms are yet to be investigated. In this study,

carrageenan-based polymer gel samples were fabricated and their chemical, mechanical, dielectric, and imaging properties were examined to assess their similarity to those of human tissue. A 6-week stability test was also conducted on each property. The mechanical properties such as the density and elastic modulus fluctuated with time with no specific pattern, which was hypothesized to be due to the expulsion and absorption of water by the samples. The dielectric properties of the samples, namely the conductivity and permittivity, did not change with time. The imaging properties of the samples were also examined and the T_1 and T_2 relaxation times were observed over 6 weeks. Changes of about 23% to 29% were observed in T_1 and T_2 . For accurate calibration over the shelf life of a phantom, the fluctuation of its properties should be minimized. Although there is no direct effect of change in properties in terms of calibration accuracy and clinical relevance, it does have an indirect impact in its performance as a phantom. The shelf life of a phantom should be more than 6 months up to 3 years. If the physical, mechanical and imaging properties change significantly over a 6-week period, it can be projected to change with a wider range over a longer period during the shelf life of the phantom. Each property is not equally important, but mechanical and physical properties have more importance as they may change its shape or rigidity over time. The most significant property is the imaging property since it is related to calibration accuracy and clinical relevance. Since the phantom in this study tries to mimic the value of liver and its lesion particles to provide a standard value to compare to human tissue, it is important to retain stability. There is no standard guideline to define an acceptable degree of variation. However, since the T_1 and T_2 relaxation time values found in the literature^{16–20} have measurements with a mean standard deviation of 45 ms for T_1 and 4.4 ms for T_2 , the degree of variation in measurements should be within that range. The difference in relaxation time in sample 2 demonstrates the difference of 84 ms in T_1 and 28 ms in T_2 . This is a much larger fluctuation over time than the range of measurements of human tissue in 3T. Therefore, we can conclude that the change in the relaxation values is not within the acceptable range and thus, the carrageenan or agar gel does not perform as a stable material for phantom.

A carrageenan gel phantom with embedded lesion particles was fabricated and imaged under MRI to simulate human liver tissue. The T_1 and T_2 maps demonstrate the carrageenan gel phantom's potential to be used as MRI phantom and the lesion particles represent various T_1 and T_2 relaxation time values. However, there still are several challenges in the production procedure to reduce the air bubble generation and paramagnetic ion diffusion.

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