MDDT SUMMARY OF EVIDENCE AND BASIS OF QUALIFICATION DECISION FOR
A TISSUE MIMICKING MATERIAL (TMM) FOR PRECLINICAL ACOUSTIC PERFORMANCE CHARACTERIZATION OF HIGH INTENSITY THERAPEUTIC ULTRASOUND (HITU) DEVICES

BACKGROUND

MDDT NAME*:* A TISSUE MIMICKING MATERIAL (TMM) FOR PRECLINICAL ACOUSTIC PERFORMANCE CHARACTERIZATION OF HIGH INTENSITY THERAPEUTIC ULTRASOUND (HITU) DEVICES

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TOOL DESCRIPTION AND PRINCIPLE OF OPERATION

This Nonclinical Assessment Model provides the formulation and characteristics of a hydrogel-based tissue mimicking material (TMM) for the preclinical acoustic characterization of high intensity therapeutic ultrasound (HITU) devices. The substrate is a high temperature hydrogel matrix (gellan gum) combined with different sized aluminum oxide particles and other chemicals. Attenuation coefficient, speed of sound, acoustical impedance, thermal conductivity and thermal diffusivity, are characterized as a function of temperature from 20 ºC to 70 ºC. The backscatter coefficient and nonlinearity parameter, B/A, is characterized at room temperature. The attenuation coefficient displays a linear frequency dependence, mirroring the behavior of most human soft tissues at 37ºC. Potential applications of this TMM include characterization and visualization of acoustic fields during bench testing. TMM cannot replicate the complexity or the thermal response of soft tissues and thus should not be used for these purposes in lieu of ex vivo or in vivo tissue studies.

QUALIFIED CONTEXT OF USE

This tissue mimicking material (TMM) serves as a nonclinical assessment model for use in the first stage of preclinical development and evaluation of ultrasound medical devices. A standardized generic recipe is provided for a TMM having acoustical properties in the range of non-fatty soft tissues. The TMM is formulated to assist in the design evaluation phase of high intensity therapeutic ultrasound (HITU) Class II or Class III devices operating at clinically-relevant parameters.

The TMM is intended as a standard material that can be used for acoustic performance evaluation during HITU bench testing. The TMM has been acoustically characterized over the frequency range from 1.0 MHz to 8 MHz and used at absolute temperatures ranging from 20 ºC to 90 ºC. However, the TMM's thermal response has not been verified against tissue measurements. Therefore, the TMM should not be used to infer thermal response in ex vivo or in vivo tissues. The TMM is intended for single-session use (within 3 days of manufacture). Continued use of the TMM after the detection of cavitation or boiling is not recommended. If cavitation cannot be monitored, it is recommended that the mechanical index (MI) not exceed 4.5.

SUMMARY OF EVIDENCE TO SUPPORT QUALIFICATION

The TMM is a nontoxic high temperature hydrogel matrix dispersed with different-sized aluminum oxide particles and other chemicals. The phantom elastic matrix is gellan gum, an agar-like, nontoxic, polysaccharide gelling powder produced from the bacterium *Pseudomonas elodea*. Hydrogels solidified with gellan gum have higher temperature stability (melting point >100ºC), stronger mechanical strength, and better transparency than traditional agar or gelatin-based phantoms. To mimic acoustic property of non-fatty soft tissues, several other chemicals are added to the gellan gum matrix. Different sized aluminum oxide particles (<1µm, 1-2µm, 10-40µm) are used for ultrasound absorption and scattering. Isopropanol (1-propanol) is added to set the acoustic velocity. Calcium chloride dehydrate enhances the mechanical strength and potassium sorbate acts as a preservative. Table I below summarizes the range of measured TMM physical properties at 20ºC in comparison with that of generic soft tissues available in the literature (Duck 1990, ICRU-61 1998). Even though reported soft tissue properties vary in a certain range due to biological heterogeneity, the measured phantom physical characteristics are within the clinically relevant range of reported non-fatty soft tissue values. The constituents (Table II) and manufacturing protocol for producing 500 ml of TMM is described below.

Table I

Physical Properties (20^oC)	**TMM**	Soft tissue
Acoustic Attenuation, dB/cm	**0.64 $f^{0.95}$ ± 10% (2-8MHz)**	(0.5-1.0) $f^{(0.9\text{-}1.44)}$
Speed of sound, m/s	**1579±17**	1510 ~ 1590
Nonlinear Parameter B/A	**8.2±1.3**	7.5 – 9.7
Acoustic Impedance, kg m^{-2} s^{-1}	**1.62±0.2**	1.6-1.7
Backscatter Coefficient, $cm^{-1}Sr^{-1}$	**2.2 e^{-4} @3.5 MHz**	2.0 e^{-3} @3.5 MHz
Thermal Diffusivity, mm^2s^{-1}	**0.11±0.005**	0.10 ~ 0.15
Thermal Conductivity, Wm^{-1} K^{-1}	**0.56±0.013**	0.47 ~ 0.57
Density, g/cm^3	**1.027±0.019**	1.0 ~ 1.07

Table II

Constituents for the TMM	**% (w/v)**	**Function**
Gellan Gum (CG-LA, CP Kelco Div., A Huber Co., Atlanta, Georgia)	1.5	High temperature hydrogel matrix
Degassed water (O_2 content <3 ppm)	100 (v/v)	Hydrogel substrate
Calcium Chloride (4160, Fisher Scientific, Pittsburgh, PA)	0.4	Mechanical strength
Potassium Sorbate (A12844, Alfa Aesar, Ward Hill, MA)	0.1	Preservative
1-Propanol (S93101, Fisher Scientific, Pittsburgh, PA)	12 (v/v)	Speed of sound
Aluminum oxide (<1 µm, 1-2 µm, 10-40 µm) (AL600, AL601, and AL602, Atlantic Equipment Engineers, Bergenfield, NJ)	0.45 each	Acoustic attenuation

Manufacturing Protocol for the TMM

1. Weigh all the constituents in Table II precisely to within a 0.1g tolerance.
2. Add calcium chloride (2g) and potassium sorbate (0.5g) to a beaker with 100 ml of degassed water (< 3 ppm), along with a magnetic stir bar. This solution is mixed on an electric stir plate under 27 in. Hg vacuum in a bell jar. This mixture is allowed to mix and degas for the duration of the TMM construction process.
3. Mix the aluminum oxide powder (a total of 6.75g for three size range) and 1-propanol (60 mL) into 400 ml of degassed water using a magnetic stir bar. This solution is mixed on a separate electrical stir plate while under 27 in. Hg vacuum in a bell jar for 1hr.
4. After 1 hr, add the gellan gum powder (7.5g) slowly to the aluminum oxide solution (step 3) by sprinkling it from a spoon as close to the surface of the liquid as possible. This solution is further mixed and degassed under 27 in. Hg vacuum for another 1 hr.
5. Start heating the above gellan gum solution and keep stirring. At the same time, heat the calcium chloride solution (step 2) to 80°C on another hot plate.
6. Heat the gellan gum solution to boiling for 2-3 minutes until no apparent clumps.
7. Turn off the heat and continue stirring the gellan gum on the plate as the solution cools to 80°C, then add the heated calcium chloride solution. Gently stir and cool the final milky solution on the stir plate.
8. At 70°C, pour the gel solution into the designated phantom holder. Tap the side wall of the holder to allow any trapped large air bubble flow to the top surface.
9. This gel solution will start to solidify around 60°C and will form a solid TMM in 3-4 hr for a total volume of 500 ml. Multiple 500mL phantom batches can be made and poured into molding apparatus sequentially for special or extended ultrasound beam study.

DISCUSSION OF THE EVIDENCE STRENGTH TO SUPPORT QUALIFICATION

Results from several studies support the use of the TMM for assessing HITU transducer acoustic performance. Some of the submitted data was directly acquired to support MDDT qualification, however most supporting work was leveraged from published studies regarding the TMM. Possible advantages/disadvantages of the TMM were additionally provided as evidence to support qualification of the TMM for preclinical acoustic performance characterization of HITU devices.

Sound Speed and Attenuation

Attenuation and speed of sound are critical for determining the acoustic wave focusing. To this end, frequency and temperature-dependent (20~70°C) ultrasound attenuation and sound speed of the TMM phantom were measured using an ultrasonic time delay spectrometry (TDS) system in a temperature-regulated water bath. The TMM speed of sound displays an increasing trend with temperature, where the mean sound speed rises from 1579 m/s at 20°C to 1602 m/s at 40°C to 1647 at 70°C. The acoustic impedance of the TMM is $1.62 \times 10^6 \pm 200$ kg m^{-2} s^{-1} at room temperature (20°C), as determined by multiplying the speed of sound with density (1.03±0.02 g/cm^3).

Acoustic attenuation as a function of frequency was characterized through a power law ($\alpha = a \cdot f^{b}$) regression (R > 0.95) to yield the coefficient *a* and exponent *b*. The mean attenuation was found to be $0.64f^{0.95}$ dB/cm at 20°C room temperature (King et al., 2011), which is approximately linear with frequency (2-8 MHz) and is within the reported soft tissue range (Table I). At fixed frequencies, attenuation was observed to drop with increasing temperature, corresponding to a steady temperature-dependent decrease in coefficient *b*. This trend is consistent with the data reported in the literature for tissue at sub-coagulation thresholds (Duck 1990, ICRU-61 1998). A closer exam of these attenuation results (1-8 MHz) was further reported recently (Maruvada et al., 2018).

To assess attenuation stability after high temperature exposure, a TMM sample was heated to 90°C in a water bath for 15 min then cooled to room temperature. Attenuation values were unaffected by this heating-then-cooling process. Temporal attenuation stability was also evaluated by acquiring attenuation data on the day of production, then 5 days and 10 days later. With the TMM stored at 20°C in a 10% 1-propanol water solution, the frequency-dependent attenuation was found to be stable over a 10-day period.

Backscatter Coefficient

Ultrasound backscatter coefficient ($cm^{-1}Sr^{-1}$) was measured using a broadband pulse-echo reference phantom technique (King et al., 2011). Conventional B-scan images of TMM samples were obtained using a 5.3 MHz linear ultrasound imaging array (Siemens Medical Solutions, Malvern, PA). In the range of 3.2 MHz to 6.0 MHz at room temperature, the TMM displayed a frequency-dependent backscatter coefficient ranging from approximately 0.2×10^{-3} $cm^{-1}Sr^{-1}$ at 3.2 MHz to 0.7×10^{-3} $cm^{-1}Sr^{-1}$ at 6 MHz. The average exponent of frequency dependence was measured to be 3.6 ± 0.2, which agrees with the theoretical quartic relationship for Rayleigh scatters, when the scatter diameter is much smaller than the acoustic wavelength.

Nonlinearity Parameter B/A

Nonlinear behavior of the material was assessed using a finite amplitude insert-substitution (FAIS) method with simplified modification (King et al., 2011) that eliminates the need to aquire absolute pressure amplitude measurements as well as to correct for diffraction effects. The TMM nonlinearity parameter B/A was found to be 8.2±1.3. This value is comparable to reported B/A of 6 – 9 in soft tissues (ICRU-61 1998).

Thermal Properties

Thermal conductivity, κ, and diffusivity, *D*, were quantified with a thermal property analyzer (KD-2, Decagon Devices Inc, Pullman, WA) from 20 °C to 70 °C. This temperature range was selected to match the range typically encountered in ultrasound thermal therapy. Both parameters were found to increase slightly as a function of temperature (~16% for conductivity and 14% for diffusivity) in concordant with general observations for soft tissues (Duck 1990, ICRU-61 1998).

The TMM gellan gum substrate without any additives are κ = 0.65 Wm^{-1} K^{-1} and D = 0.13 mm^2s^{-1} at 20 ºC. In comparison, for water the κ is 0.6 $Wm^{-1}K^{-1}$, and D = 0.14 mm^2 s^{-1} at 20 ºC (Kays and Crawford 1993). As noted earlier, the TMM should not be used to infer HITU thermal response in lieu of ex vivo or in vivo tissue studies.

Cavitation

Bubbles oscillating in the presence of a HITU wave can complicate the ultrasound field itself via either enhancement or shielding artifacts. Figure 1 presents real time ultrasound imaging associated with cavitation bubble formation and corresponding heating temperature traces under three repeated HITU TMM exposures (30s) at 0.825 MHz. During the first of the three repeated HITU exposures, temperature trace (6 MP-1) displayed an abrupt and dramatic rise around 26 s when the ultrasound B-mode image showed a funnel pattern (narrowest near the HITU focus) with strong hyper-echoic bright cavitation spot at HITU focus. This phenomenon is attributable to interference noise due to electrical saturation in the receiving electronics caused by large amplitude scattering of the HITU beam from the cavitation bubbles into the imaging transducer. The second HITU exposure (6 MPa-2) also showed a marked hyperechoic bright spot due to a cavitation cloud, as illustrated in the image at 36-50 s, which persists after the sonication has ended. This spot is indicative of bubble cloud formation, leading to the beam blockage and decreased heating as described above for distorted temperature trace. Hyperechoic regions are still detectable by B-mode imaging 1 minute after termination of exposure, indicating the slow diffusion process of the cavitation bubble cloud. This is the reason for waiting 20 min between consecutive exposures if cavitation (distorted temperature curve and hyperechoic imaging) occurred so that the bubble can dissipate before the next repeated HITU exposure (Maruvada et al., 2012). On the third exposure (6 MPa-3), however, no or insignificant bubble formation was observed on the B-mode imaging (no hyperechoic regions) and normal temperature curves and comparable (with previous two exposures) peak temperature rise were recorded.

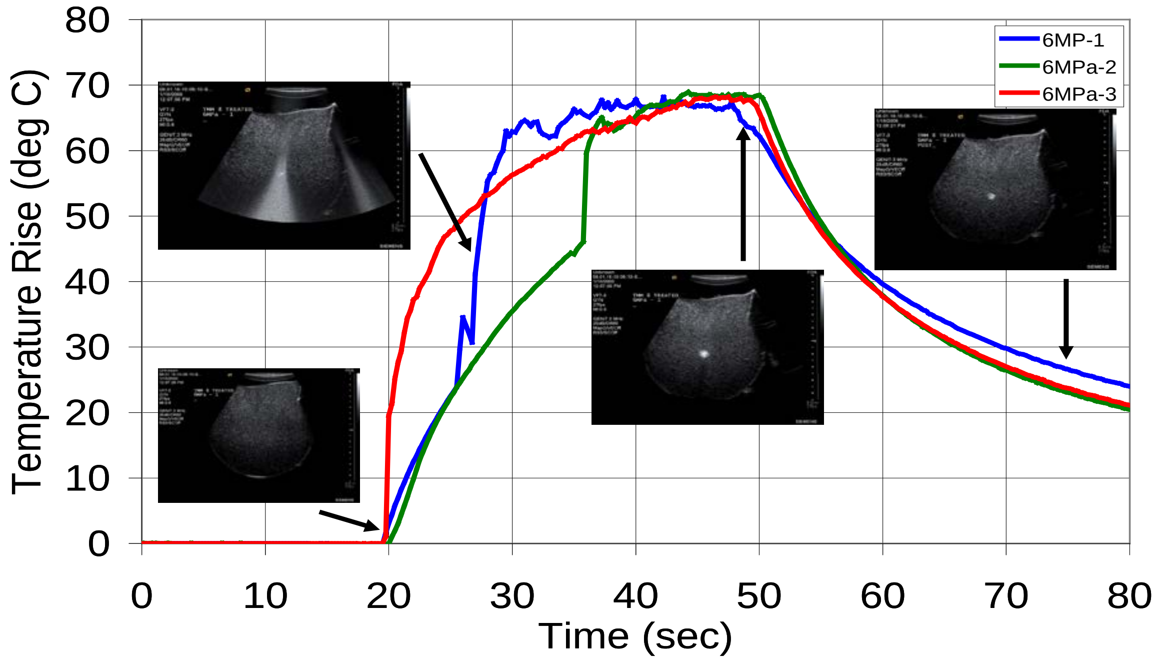

FIGURE 1. CAVITATION ARTIFACTS DURING HITU TMM TEMPERATURE MEASUREMENTS

ASSESSMENT OF ADVANTAGES/DISADVANTAGES OF QUALIFICATION

Assessments of Advantages of Using the MDDT:

- The TMM is a nontoxic hydrogel dispersed with different-sized aluminum oxide particles and additional chemicals. Acoustic properties of the TMM are similar to non-fatty soft tissues. The TMM (in a specific gel-thermocouple geometry) has been characterized over the frequency range from 1 MHz to 8 MHz and at absolute temperatures ranging from 20 ºC to 70 ºC. It helps characterize acoustic performance in the preclinical development and evaluation of high intensity therapeutic ultrasound (HITU) devices.
- Compared to traditional agar or gelatin gel substrates for HITU phantoms, gellan gum hydrogel possesses higher mechanical strength at the same gel concentration to withstand stronger radiation stress. Impurities in gellan gum contain no organic compounds making bacterial contamination less likely. Aside from the gellan gum gel matrix, chemical components in the TMM are low-cost and readily available.
- TMM-facilitated HITU bench testing provides supplementary engineering data that cannot be obtained in animal or human subjects. When combined with in vivo animal and clinical results, the bench testing data from TMM is expected to reduce overall device development burden and expedite regulatory review.

Assessments of Disadvantages of Using the MDDT:

- The TMM was developed to match literature values of soft tissue acoustic properties. The TMM cannot replicate the complexity or the thermal response of tissue thermal ablation and thus should not be used for these purposes in lieu of ex vivo or in vivo tissues. HITU-induced temperature rises in the TMM may differ from soft tissues. The shelf-life of the TMM has not been evaluated. Use of the phantom within 3 days of production is recommended. New TMM phantom can be manufactured in approximately 4 - 6 hours.

- Cavitation may occur at high acoustic pressure levels. Care should be taken to avoid cavitation, as it may cause artifacts during acoustic measurements. The presence of cavitation may be detected using passive or active detection techniques (Roy et al., 1990). Alternatively, cavitation artifacts may be identified in thermal data (Hynynen et al., 1983). Should cavitation occur, use of a new phantom is recommended. Continued use of the TMM after the detection of cavitation or boiling is not recommended. If cavitation cannot be monitored, it is recommended that the mechanical index (MI) not exceed 5.0.

Additional Factors for Assessing Advantages and Disadvantages of Using the MDDT:

- Phantom volume and dimensions should be large relative to the HITU focal volume and beam width to avoid potential reflection/interference from material boundaries. The TMM formulation was developed in 500 ml batches, which is sufficient to test mm-scale HITU focal volumes. For extended HITU beam requirements, multiple TMM batches can be combined. Formation of individual batches over 500 ml may require more sophisticated processing and cooling techniques to assure a homogeneous material.

CONCLUSION

Based on the experimental validation studies presented and the assessment of the advantages and disadvantages of the TMM, this tissue mimicking material (TMM) is qualified as a Nonclinical Assessment Model to characterize acoustic performance during preclinical bench evaluation of high intensity therapeutic ultrasound (HITU) devices.

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