● *Original Contribution*

AN MRI TISSUE EQUIVALENT LESION PHANTOM USING A NOVEL POLYSACCHARIDE MATERIAL

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A new polysaccharide material, TX-150, and method is described which will potentially allow formation of stable, multi-compartment MRI phantoms constructed without intervening septa. TX-150 can be made into water based gels which are nominally tissue equivalent. Although contiguous regions of different water content are not possible, as water diffusion will occur until equilibrium is reached, TX-150 gel T_1 and T_2 values can be adjusted independently, while maintaining a constant water composition, by appropriate additives. Unlike paramagnetic ions and chelates, metal phthalocyanines have been found to bind tightly to TX-150, thus, permitting formation of stable contiguous regions of differing T_1 relaxation properties. Phantom T_2 values can be effectively modified with 2-2-diphenyl-1 picrylhydrazyl, which has little affect on gel T_1 values, to form septumless lesion phantoms of varying T_1 and T_2.

Keywords: MRI phantoms; TX-150; Lesion phantoms; Observer performance studies.

INTRODUCTION

Phantoms used to study magnetic resonance imaging (MRI) systems without use of a human subject have been, to date, limited to water solutions doped with paramagnetic agents or organic liquids, and gels contained within discrete compartments, separated by intervening septa.[1,2] Gels require intervening septa due to migration of matrix components, destroying the specific T_1/T_2 values of individual elements. As septa produce image discontinuities, these phantoms have been, heretofore, restricted to the measurement of standard geometric parameters or relaxation times. These phantoms do not provide a means of optimizing image contrast for the identification of anatomic structures and pathological conditions, and preclude observer performance studies.

Three classes of materials have been suggested for use in MRI phantoms: (i) multicomponent paramagnetic ion solutions; (ii) organic liquids and semisolids; and (iii) modified hydrated polysaccharide gels. We describe a potential MRI tissue-equivalent system based on TX-150, a novel member of the third group, which will allow formation of stable, multicompartment MRI phantoms, constructed without intervening septa.

Polysaccharides—high molecular weight complexes of simple sugar monomers or sugar derivatives—are structural elements of tissue cell walls, coat intercellular spaces and connective tissue and, thus, are naturally related to tissue.[3] The presence of one to six C-OH groups per monomer unit provides ample sites for hydrogen bonding in hydrated gels. Such bonding yields a simple mechanism for altering water proton T_1 and T_2 relaxation properties. TX-150 (proprietary material from Oil Center Research, Lafayette, LA) has an advantage over other polysaccharides proposed for MRI tissue equivalents,[4] (e.g., animal gelatin or agar[5-7]), in that hydrated gels are made by mixing TX-150 solute with water (and T_1 and T_2 modifiers)

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at reduced temperatures of 5°C to 15°C, without free radical initiators. Regions of varying T_1 and T_2 properties can be cast separately and contiguously without disrupting boundary interfaces, as the gel setting time is short (2 min to 1 hr). It is therefore possible to develop septum-less lesion phantoms for observer performance studies in MRI.

MATERIALS AND METHODS

Sample Preparation

Simple TX-150/water gels were prepared with distilled water and a polysaccharide content ranging from 3% to 21%. Another group was prepared with de-gassed water to examine paramagnetic oxygen effects on gel T_1 and T_2 values (MRI phantoms will require de-gassed solutions to prevent bubble formation). As stabilization of hydrated TX-150 gels requires the addition of a bacteriostat, a third group of samples containing 1-2% by weight of propyl paraben was prepared, to assess the influence of this material on relaxation parameters and its long term stabilization effect. (Oil Center Research studies had previously established, propyl paraben as an effective stabilizing preservative.)

Spectrometry samples were prepared using the following standardized procedure: (i) preweighing all components: TX-150 powder, gelling solution, water and paramagnetic metal complex solution, T_2 modifier (insoluble organic free radical), and preservative (propyl paraben); (ii) mixing components together until semi-solid; (iii) transferring the pliable gel to an NMR tube using a syringe; (iv) after labeling, sealing the sample against water loss with a low melting point paraffin-polymer wax.

T_1 Modification

Solutions of paramagnetic ions, chelate complexes and soluble phthalocyanine sulfonate dyes were considered for use as T_1 modifying agents. Preliminary diffusion experiments had suggested that, of the three, only phthalocyanine dyes appeared to have the potential for spatial localization—a necessity for multicompartment, septumless phantoms. The specific binding mechanism of phthalocyanine dyes to TX-150 is electrostatic binding on the organic substrate. Phthalocyanine tetrasulfonates of copper and nickel were used to make hydrating solutions ranging in concentrations from (10–40) g/L of water. In addition, a soluble phthalocyanine salt of iron was prepared by sulfonation of iron phthalocyanine with concentrated sulfuric acid at 100°C. A neutral sodium salt was obtained with sodium bicarbonate followed by repeated selective crystallization. The brown crystallate of unknown

stoichiometry, $FePcSu_x:Na_x$ was used to prepare solutions ranging in concentration from (0.2–5 g)/L of water. These phthalocyanine complexes were then used to fabricate samples having a fixed TX-150 composition, but variable metal content. The choice of 8% TX-150 allowed for a wide range of variability in sample T_1, while producing a gel suitable for casting into a phantom matrix.

T_2 Modification

Selective T_2 modification is possible in water gels through the addition of materials which increase the proton spin-spin coupling interaction of water. Stable, water-insoluble free-radicals offer significant T_2 modification potential. A representative compound, 2-2-diphenyl-1 picrylhydrazyl was used to fabricate hydrated TX-150 gels as previously described. Free radical concentration varied from 0.5% to 2.5% by weight. Particulate size ranged from 0–90 microns, as graphite of 0–90 micron particulate size has been used effectively in animal hide gels as a T_2 modifier.[6] A constant concentration of 10% TX-150 by weight was used for the TX-150 component.

Spectrometry

Measurements of sample T_1 values were obtained using a NMR pulsed spectrometer (Bruker Model 322) operating at 20.9 MHz, equivalent to a 0.5 T magnetic field. A 180°–t–90° inversion recovery pulse sequence was employed to generate sample free induction decay (FID) signals. A nonlinear least-squares analysis was then performed on the digitized signal amplitudes for 30 delay times, t, fitting the data to the functional form

$$S(t) = S_o(1 - 2\exp(-t/T_1)) \ . \tag{1}$$

A single relaxation component was extracted for all newly prepared samples. After a three-week period, a second, very short (30–50 msec) component was required to fit unpreserved samples for testing temporal stability limits.

Measurement of T_2 relaxation times was performed on a 0.5 Tesla Magnetic Resonance Imager (Technicare Teslacon™) in imaging mode using pixel signal amplitudes from a modified spin echo (90°–t–180°) pulse sequence. To reduce field inhomogeneity effects, sample measurements were made in a fixed reproducible geometry within the imager head coil. Sample inhomogeneities were minimized by software control of the active sample signal volume: 1.5 cm × 1 cm × 1 cm. Four signal averages were accumulated, and a repetition time, TR, equal to 5 times the sample T_1 was used to ensure complete magnetization re-

covery. A least-squares exponential fit was applied to the 20 time, t, signal amplitudes, fitting the data to the functional form

$$S(t) = S_o \exp(-t/T_2) \ . \qquad (2)$$

A single T_2 component was extracted for all newly prepared samples.

Image Uniformity and Spatial Confinement

Homogeneously prepared TX-150 gels, unlike solutions, exhibit MRI imaging artifacts attributable to mechanically incorporated gas bubbles or insoluble solids. Four factors were examined for influence on image uniformity: TX-150 concentration and modifier particulate size; gelling solution temperature and gelling retardants:

1. Particulate size: (a) unsieved; and (b) 0–90 micron
2. TX-150 Composition: 3%–20%
3. Solution temperature: 5°C–15°C
4. Retardants: >10% NaCl; 10% EtOh; and 1%–3% propyl paraben.

Samples were prepared in 150–200 gm quantities, while systematically varying parameters. The solidified gels were imaged on a 0.5 T MRI system using a multislice, spin-echo technique, with TE = 30 and TR = 1000, with 128 phase-encoding steps, displayed in a 256 square image matrix (standard Teslacon software). Eight 0.4-cm-thick slices per sample were reconstructed and the number of image artifacts in excess of 1 mm diameter was determined empirically and correlated with sample parameters.

The degree of spatial confinement of modifying agents was evaluated using a two-compartment concentric cylinder phantom. The outer cylinder was cast by pouring an 8%–10% TX-150 water gel in a container with a removable 1.4-cm center cylinder. After the outer cylinder had solidified, the inner cylinder was formed with a gel of the same TX-150 proportion (8%–10%), but with differing solution identity: Cu2+ and Mn2+; DTPA chelates of Fe, Cr, and Gd; and copper phthalocyanine sulfonate. Multislice images of the phantom were acquired on the 0.5 T MRI system at varying time intervals. The inner cylinder diameter was determined for each slice using regions of interest (ROIs) to quantitatively determine the interface position between inner and outer cylinder. Signal intensity variations past the boundary of the inner cylinder were evaluated with ROIs over 42 days to assess component diffusion, and any distortion in definition of the inner cylinder. Diffusion was estimated from the

Table 1. T_1 and T_2 values for TX-150 phantom mixed with varying amounts of water

Percent (%) TX-150 by weight	T_1 without degassed water (msec)	T_1 with degassed water (msec)	T_2 (msec)
3	—	2211 (37)[a]	—
6	1397	1410 (33)	287
8	—	1248 (41)	—
9	1048	1078 (22)	170
12	825	811 (30)	108
15	735	709 (41)	76
18	652	586 (30)	57
21	—	—	44

[a]Values in parentheses are standard deviation for multiple measurements.

results, by noting changes in the inner cylinder diameter over time.

RESULTS AND DISCUSSION

At 0.5 T (20.9 MHz) the T_1 and T_2 values for normal human tissue (excluding lipids) ranges from 400–700 msec and 50–150 msec, respectively.[8] The T_1 and T_2 values obtained from the TX-150 samples are listed in Table 1. Examination of Table 1 indicates that TX-150 can be readily made into water based gels which are nominally tissue equivalent. The presence or absence of O_2 does not markedly effect the relaxation parameters under the conditions of this experiment. This is important, as MRI imaging gels require degassed solutions to eliminate matrix bubbles. Figure 1 illustrates an alternative way of presenting the data,
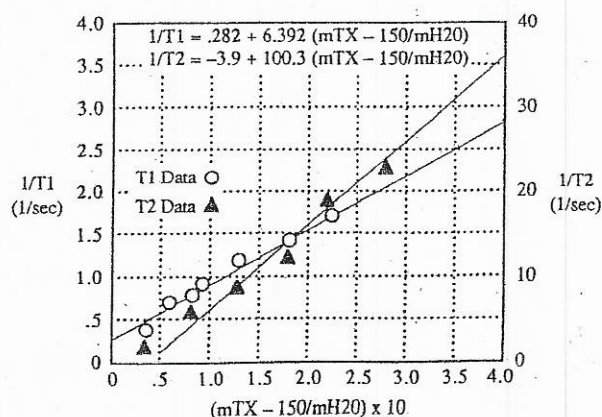

Fig. 1. Relaxation rates, $1/T_1$ and $1/T_2$, for TX-150/water gels vs. ratio of TX-150 to water.

Table 2. Paramagnetic phthalocyanine effect on hydrated TX-150 gel T_1 relaxation at 0.5 T (20.9 MHz) and 20°C[a]

Concentration (g/kg H$_2$O)	CuPcSu$_4$: Na$_4$ T_1 (msec)	NiPcSu$_4$: Na$_4$ T_1 (msec)	FePcSu$_x$: Na$_4$[b] T_1 (msec)
0	1248	1248	1248
0.2	—	—	1071
1.0	—	—	1024
5.0	—	1042	909
10.0	—	1031	—
20.0	—	996	—
29.5	929	—	—
30.0	—	913	—
39.5	823	—	—

[a]8% TX-150 and 92% distilled water.
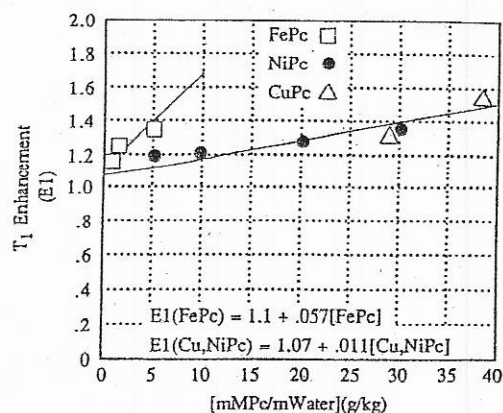[b]Stoichiometry of iron phthalocyanine sulfate unknown.

Fig. 2. T_1 relaxation rate modification for various concentrations [mMPc(g)/mwater (kg)] of Cu (triangles), Ni (circles), and Fe (squares) phthalocyanine sulfonates in 8% TX-150/water gels.

$$E1(FePc) = 1.1 + .057[FePc]$$
$$E1(Cu,NiPc) = 1.07 + .011[Cu,NiPc]$$

namely as relaxation rates. The straight lines are linear-least squares fits to the combined tabular data.

Unfortunately, contiguous regions of different water content are not possible with TX-150 gels, as water diffusion will occur until equilibrium is reached, yielding a single matrix T_1 and T_2 value. Examination of Tables 2 and 3 (graphed in Figs. 2 and 3), however, indicates that gel T_1 and T_2 values can be adjusted independently, while maintaining a constant water composition, by appropriate additives. Figure 2 compares the effectiveness of the metal phthalocyanines in reducing proton relaxation time T_1 relative to a fixed TX-150/water composition (8% TX-150 by weight). On a gram for gram basis, soluble iron phthalocyanine is 3–4 times more effective than copper or nickel for altering proton T_1 relaxation. Gel T_2 (Fig. 3: triangles) can be varied essentially independently, with 2-2-diphenyl-1 picrylhydrazyl, which has only a slight affect on gel T_1 (circles), as can be noted in Fig. 3 and Table 3. For phantom construction, the slight effect

on T_1 with the T_2 modifiers should be considered if precise dependence on T_1 values is important in the phantom experiment undertaken.

TX-150 will undergo bacterial degradation (visually undetectable but apparent as a short lived component in the pulse sequence data). Fortunately, propyl paraben—an effective bacteriostat—provides stability without significantly altering gel relaxation characteristics, as illustrated in Table 4. Serendipitously, it also improves matrix homogeneity. Examination of the diffusion phantom profiles indicated that both paramagnetic ions and chelates rapidly diffuse throughout TX-150 gels. Complete loss of inner cylinder definition was estimated at less than one day for ions and less than one
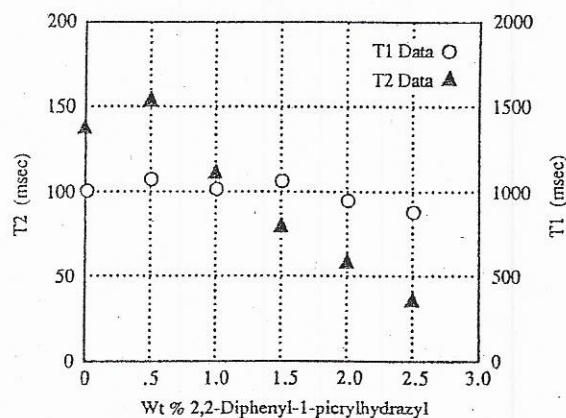
Table 3. 2,2-Diphenyl-1-picrylhydrazyl (2,2-D-1-Ph) effect on hydrated TX-150 gel T_1 (and T_1) relaxation at 0.5 T (20.9 MHz) and 20°C[a]

Weight (%) 2,2-D-1-Ph	T_1 (msec)	T_2 (msec)
0	1008 (30)[b]	140
0.5	1073 (36)	156
1.0	1021 (23)	106
1.5	1076 (10)	75
2.0	765 (21)	60
2.5	959 (55)	41

[a]10% TX-150 and 90% distilled water.
[b]Values in parentheses are standard deviation for multiple measurements.

Fig. 3. Behavior of T_2 (triangles) modifier, 2-2-diphenyl-1-picrylhydrazyl, in 10% TX-150/water gels. T_1 values (circles) indicate little effect of 2-2-diphenyl-1-picrylhydrazyl on T_1 relaxation values.

Table 4. Propyl parabene preservative effect on
T_1 relaxation for hydrated TX-150 gels at
0.5 T (20.9 MHz) and 20°C

Percent (%) TX-150 by weight	T_1 no preservative (msec)	T_1 1% p-parabene (msec)
6	1410 (33)[a]	1477
12	811 (30)	866
18	586 (30)	674

[a]Values in parentheses are standard deviation for multiple measurements.

□ – Best Casting Technique: 0-90μm TX-150, H_2O @ 10°C, 2% p-parabene
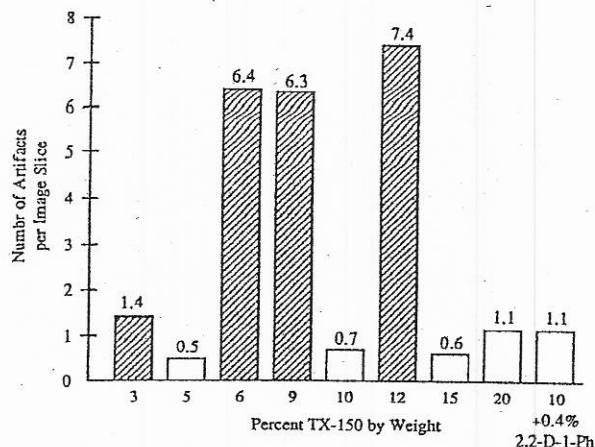▨ – Worst Casting Technique: H_2O @ 15°C, unsieved

Fig. 4. Image quality of hydrated TX-150 gels, comparing the average number of material artifacts (bubbles, etc.) for best/worst case casting technique, for 6 cm diameter uniformity phantom.

week for chelates. Table 5 shows average cylinder diameter for a 50 mM $CuPcSu_4:Na_4$ inner cylinder. Table 5 indicates that unlike paramagnetic ions and chelates, *metal phthalocyanines* bind tightly to TX-150, thus, *permitting formation of stable contiguous regions* of differing relaxation properties.

Figure 4 contrasts the best and worst uniformity achieved in the studies. Interestingly, propyl paraben, in addition to being a preservative, doubles as a retardant, increasing setting times by as much as a factor of 4, and thus, indirectly improving matrix homogeneity. The lack of image uniformity dependence on TX-150 concentration, while somewhat surprising, provides a greater latitude in gel composition. Further work will be necessary to lower the defects per slice to a negligible nuisance (<0.1).

CONCLUSION

Initial studies of TX-150 indicates, strongly, that this material can be used as a tissue-equivalent substance for use in MRI phantoms. When metal phthalocyanines are used as T_1 modifiers, stable phantoms with *contiguous regions* of differing relaxation properties can be fabricated for use in septum-

less MRI lesion phantoms. Observer performance studies would be possible using this new polysaccharide material.

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Table 5. Diameter of inner cylinder[a] of TX-150
contiguous phantom vs. days after fabrication

Day after fabrication	Inner cylinder average diameter (cm)
1	1.43 ± 0.02
11	1.42 ± 0.04
21	1.45 ± 0.02
42	1.41 ± 0.02

[a]50 mM $CuPcSu_4:Na_4$, 8% TX-150, with 1% propyl parabene.