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Preliminary communication

Carbohydrate contrast agents for nuclear magnetic resonance imaging (m.r.i.): enhancement of water relaxation by ferromagnetic particles

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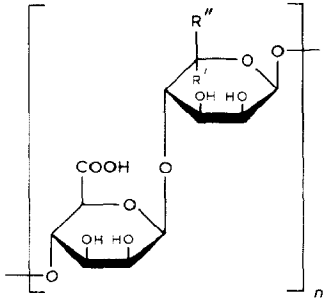
Carbohydrate derivatives can be used variously[1–4] to create substances which have defined structures and properties that may be useful in clinical diagnosis. This work was prompted by the facts that (*1*) polysaccharides can be used to fabricate particles the diameter of which range from several millimetres to sub-microns and thereby provide hydrophilic environments for a variety of incorporated materials[4–9], and (*2*) ferromagnetic materials have a more substantial effect on the spin–spin relaxation rate (R_2 value) of water than on the spin–lattice relaxation rate (R_1 value)[10–13]. We now describe the formation of large calcium alginate and fine dextran particles which incorporate various quantities of ferromagnetism without compromising their integrity and report on their n.m.r. properties.

The techniques used to form the particles depended on the final sizes required. Ferrite was mixed severally with 1, 2, and 3% solutions of sodium alginate (**1**) in 0.15M saline. Each mixture was added, dropwise by syringe, into aqueous



1 R′ = H, R″ = COOH
or R′ = COOH, R″ = H

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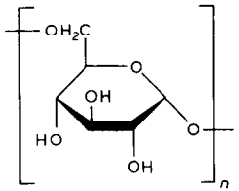

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1.5% calcium chloride. A vacuum was used to aid the detachment of the drops which gelled immediately on contact with the chloride solution.

Fresh aqueous 35% dextran (**2**) was stirred with cottonseed oil, corn oil, or rapeseed oil to give a coarse pre-emulsion that was homogenized (Ultra-Turrax), then poured slowly into a stirred solution of Tween in acetone. The resulting precipitated spheres were collected and washed by centrifugation, resuspended in Tween–acetone, centrifuged, and then dried at room temperature[14]. An aqueous solution containing 1.51 g of $FeCl_3 \cdot 6\ H_2O$ and 0.64 g of $FeCl_2 \cdot 4\ H_2O$ was then mixed with the dextran particles before being placed under vacuum. Cold aqueous 7.5% ammonia was added, the vacuum was released, and the temperature was raised. The mixture was recooled, and the magnetic particles were separated by centrifugation and then washed several times with water to remove excess of ammonia and ammonium chloride[15].

N.m.r. images were obtained from a single row of close-packed beads in a glass vial. The imaging and relaxation measurements involved an imaging spectrometer based on an Oxford Instruments 31-cm, horizontal-bore magnet coupled to an Oxford Research Systems Biospec II console operating at 85 MHz (21°). The inversion–recovery sequence[16–18], with phase cycling and a 180° composite pulse[19], and the spin-echo sequence[17,18,20], with phase cycling, were used to determine the rates of spin–lattice (R_1) and spin–spin (R_2) relaxation, respectively. The images were obtained using a spin-echo imaging sequence[21].

At 85 MHz, the normal R_1 and R_2 values of water were 0.36 s^{-1}. Aqueous 1, 2, and 3% solutions of **1** had R_1 values of 0.4, 0.44, and 0.5 s^{-1}, respectively. Spheres, 1 mm in diameter and prepared from 1% solutions of **1**, gave an R_1 value of 1.3 s^{-1} and a line-width of 200 Hz. A 24% suspension of these spheres in 2% carboxymethylcellulose (CMC) gel caused the R_1 value to decrease to 0.5 s^{-1} and the line-width to 100 Hz. In contrast, identical spheres containing 5% of ferrite caused the R_1 value of the water to increase slightly to 5 s^{-1}, the R_2 value to 770 s^{-1}, and the line-width to 1000 Hz. When suspended in the 2% CMC gel, the same spheres produced an R_1 value of 0.7 s^{-1}, an R_2 value of 50 s^{-1}, and a line-width of 1650 Hz. Thus, the 1-mm diameter spheres containing 5% of ferrite enhanced the R_2 relaxation rate of water 2140-fold (*cf.* 130-fold enhancement for the R_1 value).

The addition of various concentrations of magnetic dextran particles increased both the relaxation rates, although the R_2 values were increased more significantly. For example, a solution containing 10 μg/mL gave an R_1 value of 1.8 s^{-1}, but an R_2 value of 92.6 s^{-1}, a 260-fold enhancement in the R_2 value of water. The data in Tables I and II show that both the relaxation rates were linearly depen-

TABLE I

VARIATION IN THE SPIN–LATTICE RELAXATION RATES AND LINE-WIDTHS OF SAMPLES OF DEXTRAN MAGNETITE

Conc. of Fe (mg/mL)	T_1 *(s)*	*Half line-width (Hz)*	R_1 (s^{-1})
0.001	2.15	50	0.5
0.005	0.95	95	1.1
0.01	0.56	110	1.8
0.05	0.19	135	5.1
0.1	0.093	200	10.7
0.5	0.023	750	43.1
1.0	0.011	1500	87.7
4.0	0.003	6450	370.4

TABLE II

VARIATION IN THE SPIN–SPIN RELAXATION RATES AND LINE-WIDTHS OF SAMPLES OF DEXTRAN MAGNETITE

Conc. of Fe (mg/mL)	T_2 *(s)*	*Half line-width (Hz)*	R_2 (s^{-1})
0.001	0.12	40	8.7
0.005	0.02	80	50.5
0.01	0.011	95	92.6
0.05	0.003	140	294.1
0.1	0.002	240	555.6

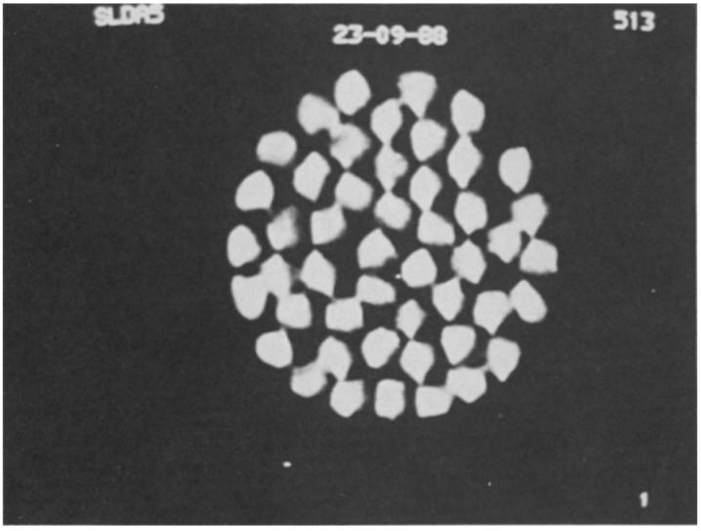

Fig. 1. N.m.r. image of dry calcium alginate spheres.

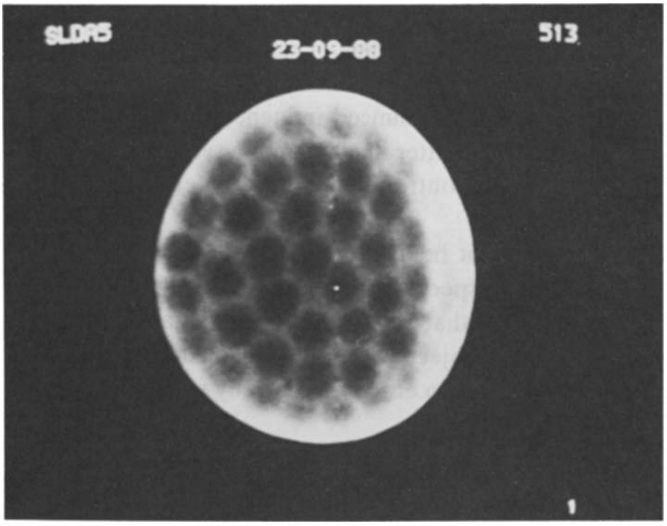

Fig. 2. N.m.r. image of calcium alginate spheres in 0.1mM gadolinium chloride solution.

dent on the concentration of iron (magnetite) present, as were the line-widths.

The use of these materials as contrast media for magnetic resonance imaging (m.r.i.) for clinical diagnosis depends on the relationship between the R_1 and R_2 values induced and the timing intervals. Fig. 1 shows an image of dry calcium alginate spheres derived from a 1% solution of **1**, Fig. 2 is an image of the same spheres in 0.1mM gadolinium chloride, and Fig. 3 is an image of the same spheres

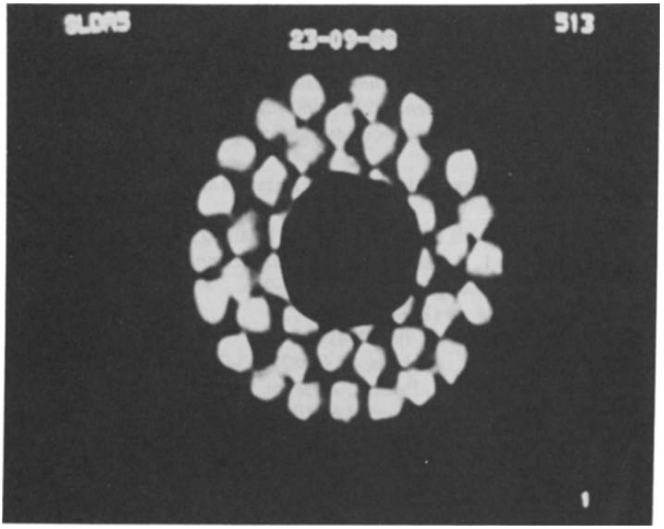

Fig. 3. N.m.r. image of dry calcium alginate spheres surrounding one central sphere containing 5% of ferrite.

surrounding one central sphere containing 5% of ferrite, which demonstrates destruction of the image by ferromagnetic materials.

Thus, polysaccharides can provide a facile means for controlling the amount of incorporated magnetism and have a pronounced influence on the R_2 value of water. Given the prior use of particulate matter in mammalian systems, these materials offer prospects for the delivery of controlled amounts of ferromagnetism to specific regions in humans.

The magnetization delivered might help to increase the specificity of m.r.i. by acting as an image-contrast agent especially in the gastro-intestinal tract. For some examinations, it is advantageous that the beads remain intact during their passage through the entire tract. This objective can be achieved by cross-linking within the beads and providing them with an enteric coat, or by utilising particulate matter fabricated from other polysaccharides.

Alternatively, m.r.i. might allow quantitation of the distribution of these particles in humans and thereby enhance understanding of their use as drug delivery vehicles.

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