Description

This invention relates to particles of of a ferromagnetic material for the manufacture of an nmr contrast agent as defined below.

Nmr has found increasing use since the early 1970's as a medical diagnostic tool, in particular as an imaging technique. The technique provides high resolution and differentiation of soft tissue without the use of potentially harmful radiation. For several years radiologists believed that, with the high contrast achieved in nmr imaging in soft tissues without the use of contrast agents, the use of contrast agents would not be necessary.

However, it has recently been found that paramagnetic complexes can be used with advantage to achieve enhanced contrast in nmr imaging so extending the diagnostic utility of the technique.

The nuclei of many atoms have a property called spin which is associated with a small magnetic moment. In the absence of an external magnetic field the distribution of the orientations of the magnetic moments is random. In the presence of a static magnetic field the nuclear magnetic moments precess about the field direction and there will be a net alignment in the field.

As R. S. First describes in "Nmr in medicine in the 1980's" (1983), in nmr imaging a patient is placed in a static field and a short radio frequency pulse is applied via a coil surrounding the patient. The radio frequency or RF signal is selected for the specific nuclei (e.g. ^{1}H, ^{19}F) which are to be resonated. The RF pulse causes the magnetic moments of the nuclei to align with the new field and to precess in phase, and on termination of the pulse the moments return to the original distribution of alignments with respect to the static field and to a random distribution of precession phases giving off a nuclear magnetic resonance signal which can be picked up by a receiving coil. The nmr signal is generally from ^{1}H nuclei and represents a proton density map of the tissue being studied.

Two additional values can be determined when the RF pulse is turned off and the nuclear magnetic moments are relaxing or returning to equilibrium orientations and phases. These are T_1 and T_2, the spin-lattice and spin-spin relaxation times. T_1 represents a time characteristic of the return to equilibrium spin distribution, i.e. equilibrium alignment of the nuclear magnetic moments in the static field. T_2 on the other hand represents a time characteristic of the return to random precession phase distribution of the nuclear magnetic moments.

The nmr signal that is generated thus contains information on proton density, T_1 and T_2 and the images that are generated are generally the result of complex computer data reconstruction on the basis of that information.

The potential application of contrast agents in extending the diagnostic utility of nmr imaging is discussed by R.C. Brasch in Radiology 147 (1983) 781. Although numerous methods of enhancing nmr contrast are available, many, such as manipulation of tissue temperature, viscosity or hydration, are clearly not clinically feasible and the most advantageous prior art technique appears to be the use of paramagnetic contrast agents to reduce the spin-lattice relaxation time T_1.

A paramagnetic substance is one which contains one or more fundamental particles (electrons, protons or neutrons) with a spin whose effect is not cancelled out by another particle with like spin. These particles create a small magnetic field which can interact with neighbouring nuclear magnetic dipoles to cause a reorientation of the dipole, i.e. a change in nuclear spin and precession phase.

Since the magnetic field created by an electron is much greater than that created by a proton or a neutron, in practice only ions, molecules, radicals or complexes (e.g. those of EP-A-71564 and EP-A-95124) which are paramagnetic through containing one or more unpaired electrons are used as paramagnetic nmr contrast agents.

The contrast effect of paramagnetic ions and complexes (e.g. those of EP-A-71564 and EP-A-95124) is predominantly the result of reduction in T_1 (cf. DE-A-3129906). However, as discussed by R c Brasch in Radiology 147 (1983) 781, paramagnetic stable free radicals will also cause some reduction in T_2. Nevertheless the relative reduction of T_1 is greater than that of T_2.

The use of paramagnetic contrast agents in nmr imaging has been extensively investigated and solutions and colloidal dispersions of such agents have been proposed for oral and parenteral administration in conjunction with diagnostic imaging.

As yet, however, there have been no nmr contrast agents available for use in nmr imaging which are capable of selectively enhancing contrast between different tissue types in the T_2 image.

We have now surprisingly found that ferromagnetic particle dispersions can be used as contrast agents in nmr imaging, contrast being achieved by significant reduction in T_2 (accompanied by a generally lower relative reduction in T_1).

Ferromagnetic particles contain atoms which within volumes called domains have their magnetic

moments (resulting from their unpaired electrons) aligned. Ferromagnetism is thus a cooperative phenomenon unlike paramagnetism and can only exist in aggregations of atoms i.e. particles.

Ferromagnetic particles are capable of being magnetised, that is a particle containing a large number of atoms may generate a net magnetic field even in the absence of an external field. In paramagnetic particles having large numbers of atoms on the other hand, the magnetic dipoles of the individual paramagnetic atoms or molecules will randomise in the absence of an external field and thus no net field would be generated.

This ability to become magnetised and generate a relatively strong magnetic field is a major reason why the use of ferromagnetic particles as contrast agents in nmr imaging could have been considered to be contra-indicated, especially in in vivo diagnostic imaging.

Thus in nmr spectroscopy, from which technical field nmr imaging has developed, the presence of ferromagnetic particles is a well-known source of inaccuracy and it is not unusual to use a magnet to remove tiny ferromagnetic particles from samples to avoid the reduction in measured spectrum resolution and accuracy that results from the presence within the sample of the local field inhomogeneities that the particles cause.

Similarly, if the ferromagnetic particles become magnetised then they may be expected to cluster. Thus while paramagnetic contrast agents can achieve substantially uniform distribution of the paramagnetic centres whether in solution or in colloidal dispersion, it might be thought likely that a dispersion of ferromagnetic particles might cluster and so not distribute uniformly. In the case of parenterally administered dispersions, the occurrence of such clustering would have been considered dangerous to the patient and the use of ferromagnetic particles thus not considered suitable.

Furthermore, the strength of the field generated by a ferromagnetic particle is so much greater than that generated by paramagnetic particles that it would have been expected that the contrast effect produced in an nmr image by the presence of ferromagnetic particles in the sample under investigation would extend over such a distance as to be likely to blur the boundary on the image between tissue containing ferromagnetic particles and tissue not containing such particles, e.g. the walls of blood vessels or of the gastrointentinal tract for iv and orally administered particles respectively.

P. Mansfield and P.G. Morris in "Advances in Magnetic Resonance - Supplement 2" Ed. J.S. Waugh (1982) page 234, Academic Press N.Y. have suggested the oral administration of colloidal particles of pure iron in the form of an iron meal so that its progress could be tracked by the strong localised inhomogeneity produced. However, there is no indication as to whether T_1 or T_2 should be determined and no suggestion that the iron particles should impregnate tissues as compared with remaining as a plug of ferromagnetic material passing through the alimentary system.

Orally administrable particulate ferromagnetic compositions are also proposed in GB-A--1339537, although their suggested use is as X-ray contrast agents in place of conventional barium meals.

The use of certain ferromagnetic polymer particles for therapeutic and diagnostic purposes is suggested broadly in International Patent Application Publication No. WO 83/03920 which describes the preparation of monodisperse ferromagnetic polymer particles. This publication refers to the use of such particles in (in vitro) cell separation whereby separation by centrifugation may be replaced by the much simpler method of magnetic extraction. It is also suggested that such particles may be used as carriers for pharmaceuticals which can then be transported to the desired location using a magnetic field.

R.S. Newbower (IEEE Transactions on magnetics Mag 9 (1973) 447) and M.P. Perry (Proceedings Int. Adv. Course Workshop (1977)) have described therapeutic and diagnostic applications in which a stable colloidal dispersion of ferromagnetic particles is introduced into the bloodstream. The particles can be guided magnetically to a vascular malfunction, e.g. a cerebral aneurysm, and may be held there by a magnetic field to seal the defect. Alternatively by disposing a permanent magnet about an artery a plug of ferromagnetic particles can be caused to form which halts blood flow in the artery; this may be beneficial during surgery where the artery could be damaged if sealed by clamping. A further use of the injected dispersion is for blood flow tracing as the dispersion can be detected by its magnetic susceptibility alone.

There has however been no suggestion in the prior art that particles of ferromagnetic materials could be used as T_2 contrast agents in nmr imaging.

In one aspect, the present invention provides the use of particles of a ferromagnetic material for the manufacture of an nmr contrast agent for use in a method of nmr imaging of a sample wherein a contrast agent is introduced into said sample and an image of said sample is generated, characterized in that said contrast agent comprises a plurality of particles of ferromagnetic particles, conveniently in the form of a dispersion of such particles, and in that said image is a T_2 dependent image, preferably a T_2 image.

In the method of the invention the T_2-reducing contrast effect of the particles is of particular interest and while nmr imaging may be used to generate separate intensity, T_2 and T_1 images, a considerable saving in

required computing time and capacity may be achieved by producing the T_2 image alone or the T_2 and either the T_1 or the intensity image.

In the method of the present invention, the relative magnitude of the contrast effect will be dependent on several sample-unrelated factors such as the particle density, their ferromagnetic content and the mean particle size. As a general rule the reduction in both T_1 and T_2 achieved by use of the contrast agent will increase with these factors. However, the relative reduction of T_2 and T_1 may be particularly sensitive to ferromagnetic content and particle size with increasing ferromagnetic content causing a relatively higher reduction in T_2 and with the relative reduction in T_2 being smaller as particle size decreases.

The mean particle size will conveniently be less than 50 μm, preferably 0.002 to 50 μm and advantageously from 0.1 to 20 μm. For parenteral administration mean particle size will preferably be in the range of 0.1 to 10 μm while for administration directly into the digestive tract (e.g. orally) or into the bladder, the uterus, the biliary duct or the parotid duct, the particularly preferred range will be 5 to 20 μm. The ferromagnetic content of the particles will suitably be from 0.1 to 100%, preferably from 0.5 to 50%, by weight.

The particles may comprise any ferromagnetic material, such as pure iron or magnetic iron oxides such as magnetite, gamma-Fe_2O_3, manganese, cobalt or nickel ferrites and may if desired include non-ferromagnetic coatings or matrices, e.g. polymer coatings, for example to avoid chemical reaction between the sample and the particles or to aid dispersion. Where it is desired to use particles having a polymer coating or matrix within which the particles of ferromagnetic materials are distributed, the particles are preferably prepared according to the method of J. Ugelstad et al. (see for example International Patent Application Publication No. WO 83/03920). To be suitable for routine in vivo imaging, the particles should not be radioactive.

Nmr imaging is particularly valuable as a diagnostic tool as it makes it possible to image tissue and organs in vivo . Different organs and different tissues, e.g. cancerous and normal tissues within the same organ, exhibit different characteristic proton intensities and T_1 and T_2 relaxation times. Thus the contrast agents are particularly useful in nmr imaging diagnosis.

In a preferred aspect, the method of the invention is a method of nmr imaging of a human or non-human animal body (or of tissue extracted therefrom) in which method the nmr contrast agent, conveniently in the form of a dispersion, is introduced into the region to be imaged and T_2 dependent images, preferably T_2 images, suitable for use in diagnosis are generated of body tissue or sites.

The administration of the contrast agent may be parenteral, suitably achieved by injection (e.g. i.v.), oral (e.g. by ingestion), rectal or by introduction through a catheter into the bladder uterus, biliary duct or parotid duct. However, administration to body sites from which the contrast agent may be discharged from the body without passing through body tissue, e.g. administration to the gut, the bladder, the uterus etc, is preferred. Where the organs to be imaged are the liver, spleen, bone marrow etc. i.v. administration will be preferred. It has been found in animal experiments that elimination of iv administered ferromagnetic particles from the blood is extremely rapid.

The particles may comprise free particles of ferromagnetic materials or particles of ferromagnetic materials embedded in or coated with a non-ferromagnetic matrix or coating. For parenteral administration the coating or matrix material is preferably a biodegradable polymer while for administration directly into the digestive tract or into the bladder, uterus etc, the coating or matrix material is preferably a biotolerable polymer and especially preferably a non-biodegradable polymer, e.g. a cellulose derivative.

In a still further aspect, the invention provides the use of particles of ferromagnetic material and a viscosity enhancing agent and/or a surfactant for the manufacture of an nmr contrast agent for use in a method of diagnosis proctised on the human or non-human animal body which method includes generation of a T_2 dependent image, preferably a T_2 dependent image, preferably a T_2 image, and diagnosis using said image.

In another aspect, the invention provides a package comprising the nmr contrast agent of the invention in a container therefor together with instructions for the use thereof in a method of nmr imaging.

The contrast agent, if for parenteral administration, is advantageously a dispersion in a sterile physiologically acceptable medium, e.g. isotonic aqueous solutions which may contain surfactants such as for example polysorbate®80. For parenteral administration the particles of ferromagnetic materials are preferably embedded in or coated by a biodegradable polymer whose degradation products are physiologically acceptable.

The contrast agent, if for administration directly to the digestive tract (e.g. orally) or to the bladder, uterus etc, is advantageously dispersed in a physiologically acceptable medium, e.g. aqueous solutions containing surfactants and/or viscosity increasing substances such as for example cellulose derivatives.

Using such a viscosity enhancing agent, the contrast agent may be caused to coat the walls of the

digestive tract and so make feasible contrast enhancement of images of the intestines. Using orally administered paramagnetic contrast agents, contrast enhancement of the digestive tract is not readily achieved beyond the stomach.

Where the contrast agent is for administration directly into the digestive tract (e.g. orally) or into the bladder, uterus, etc, it is especially preferred that the particles should be of about the same specific gravity as the surrounding fluid (gastro-intestinal fluid or urine) and particles having specific gravity of 1.07 are preferred.

For administration into the digestive tract or the bladder the particles of ferromagnetic materials are preferably embedded in or coated by a biotolerable polymer, i.e. a polymer which is physiologically acceptable and either non-biodegradable or biodegradable to yield degradation products which are physiologically acceptable. Non-biodegradable polymers are particularly preferred as the particles of ferromagnetic materials released by polymer degradation may be soluble in the gastro-intestinal fluid or if very fine may be absorbed by the body. Dissolution of the particles of ferromagnetic materials may release paramagnetic ions thereby reducing the contrast effect in the proton intensity image as the T_1 reducing effect of paramagnetic material tends to increase the proton intensity whereas the T_2 reducing effect of ferromagnetic material tends to decrease the proton intensity (see hereinafter for the dependence of proton intensity I on T_1 and T_2).

Particularly suitably the contrast agents comprise particles of ferromagnetic materials embedded in or coated by a polymer free from adsorbed or absorbed drugs. The particle sizes and ferromagnetic contents are preferably within the ranges specified above.

The particles in the nmr contrast agents of the invention are administered dispersed in a dispersion medium. Thus before administration uniform particle dispersion is preferably achieved by shaking and sonication. For simplicity, the term "dispersion" is used herein to relate to true dispersions, suspensions and colloids.

The concentrations of the particles of ferromagnetic materials in the contrast agent will be dependent on the administration form and on the particular organs or tissue to be studied. Advantageously the dosage should be sufficient to produce a concentration of 0.1 mmol of the ferromagnetic metal (e.g. Fe) per kilogram of the organ to be studied at the organ in question. Generally total dosages will be in the range of 10^{-4} to 10^{1} mmol of the ferromagnetic metal (e.g. Fe) per kg bodyweight, preferably 10^{-3} to 10^{-1} mmol/kg. The dispersions themselves conveniently contain about 0.1 to 10% by weight of particles of ferromagnetic material as a whole.

The particles in the parenterally administerable contrast agents of the invention are preferably substantially uniform in particle size to achieve uniform contrast in equivalent tissue areas. In general, particle diameters range from 0.002 to 50 μm and, for parenteral administration, a standard deviation in diameter of less than 10% is particularly preferred. For administration directly into the digestive tract particle size should not be so low as possibly to result in the particles being absorbed from the tract.

In diagnosis using nmr images, the nmr image or picture that is generated can be based upon the different T_2 values of neighbouring tissues. By reducing T_2 in a tissue, it will be possible to get a contrast enhancement.

The particulate form of the ferromagnetic material in the contrast agent makes it possible for the agent to be tissue specific. Particularly suitable target organs for intravascularly administered particles are the liver and spleen due to the reticuloendothelial system. One possible application of parenterally administered particles may be to diagnose primary cancer and metastases in the liver.

The liver is the organ in the abdomen with the shortest relaxation times (T_1 and probably T_2 also). Generally, tumors have longer relaxation times (T_1 and T_2) than normal tissues. Forty percent of the liver cells are made up of reticuloendothelial cells. Intravenously injected particles are distributed macroscopically uniformly within a normal liver. In both hepatomas and metastases the capability to pick up particles is reduced or does not exist. Intravenously administered particles may thus selectively reduce T_2 in normal liver tissue. T_2 in normal liver tissue is smaller than T_2 in liver cancer tissue and in surrounding tissues, and so further reduction of T_2 in the normal liver tissue by the use of the contrast agents will raise the contrast between normal liver tissue and cancer liver tissue making diagnosis simpler. The ability to diagnose metastases in the liver at an early stage is very important, because more than 30% of all cancer forms result in liver metastases, and often it is possible to diagnose the metastases in the liver before the primary tumor can be detected.

The effect of the use of the contrast agents in the diagnosis of liver cancers using nmr imaging is illustrated schematically in the accompanying drawings, in which:

Figure 1 is a schematic representation of a T_2 dependent image of a transverse cross section of the body through a liver which contains a metastasis;

Figure 2 is a schematic representation of a T_2 dependent image of the cross section of Figure 1 following introduction into the liver of a contrast agent comprising particles of a ferromagnetic material;

Figure 3 is a schematic representation of a T_2 dependent image of a cross section of the body through the bladder after introduction into the bladder through a catheter of a contrast agent comprising particles of a ferromagnetic material; and

Figure 4 is a schematic representation of the T_2 dependent image of a transverse cross-section of a rabbit abdomen.

Referring to figures 1 and 2, these show a cross section through the abdomen 1, arms 4 and liver 2. The liver is shown as containing a metastasis 3. The shading of the body areas corresponds to the local T_2 value with light shading indicating a T_2 of 70 ms, medium shading 40 ms and heavy shading 10 ms.

Referring to Figure 3, the particle containing urine 5 enables the contour of the bladder wall 6 to be visualized and the presence of a tumour 7 to be detected.

Referring to Figure 4, this shows a schematic representation of an nmr image produced on a scan through a rabbit abdomen using the spin-echo technique (repetition time 500 ms (TR), echo time 50 ms (TE)) after oral administration to the rabbit of 100 μmol Fe/kg of the suspension of Example 6 hereinafter. The scan enables the large intestines 9 and the small intestines 10 which contain the contrast agent to be differentiated clearly from muscle 8.

The contrast enhancement achieved with the particles of ferromagnetic materials depends upon the pulse sequences and pulse parameters used in measuring the nmr image in question. In addition to the effect on the T_2 image, the particles of ferromagnetic materials may alter the proton intensity image. The proton intensity is a function of both T_1 and T_2:

$$I = Hf(v)\exp(-a/T_2)(1-\exp(-b/T_1))$$

Where H is the local hydrogen concentration, a and b are parameters of the nmr instrument and f(v) is a function of both the speed at which the hydrogen nuclei move through the region being imaged and the fraction of the total number of nuclei that are moving. Thus an increase in T_1 reduces the intensity while an increase of T_2 increases the intensity. A selective T_2 agent will thus alter the proton intensity.

The invention will now be further illustrated by the following Examples:

Examples 1 - 6

Preparation of dispersions containing particles of ferromagnetic materials

Polymer particles carrying particles of a ferromagnetic material prepared according to the process of J. Ugelstad et al (WO 83/03920) and having the properties listed in Table I below were used in the preparation of the contrast agents.

General procedure for Examples 1 - 3

The particles were suspended in 8 ml sterile water (0.5% polysorbate®80). The suspension was sonicated and shaken for 30 minutes, centrifuged and the particles resuspended in a solution of bovine serum albumin (200 mg) in sterile water (8 ml). After shaking for 3 hours, the suspension was centrifuged, the particles washed with 0.9% NaCl (0.1% polysorbate®80) (2 x 8ml) and resuspended in the same suspension medium to 10 ml.

Example 1

57.7 mg particles (Type 1) (19.4% Fe)
10 mg Polysorbate®80
ad 10 ml 0.9% aqueous NaCl solution

Example 2

1000 mg Particles (Type 2) (30.2% Fe)
20 mg Polysorbate®80

ad 20 ml 0.9% aqueous NaCl solution

Example 3

1000 mg Particles (Type 3) (29.2% Fe)
20 mg Polysorbate®80
ad 20 ml 0.9% aqueous NaCl solution

General procedure for Examples 4 and 5

The particles were suspended in 0.9% NaCl (0.3% polysorbate®80) to 10ml. The suspensions were sonicated and shaken for 10 minutes.

Example 4

765 mg Particles (Type 3) (29.2% Fe)
30 mg Polysorbate®80
ad 10 ml 0.9% aqueous NaCl solution

Example 5

740 mg Particles (Type 2) (30.2% Fe)
30 mg Polysorbate®80
ad 10 ml 0.9% aqueous NaCl solution

Example 6

(Suspension for administration directly to the digestive tract or the bladder.)

Carboxymethylcellulose (92 mg) and polysorbate® 80 (4 mg) were added to water (3.5 ml). The stirred mixture was warmed to 80° C.

After cooling, 1187 mg of particles (Type 3) were added and the suspension was homogenized by vigorous shaking and 15 minutes sonication.

Table I

Particle Type	% Fe	µm diameter	Particle Surface
1	19.4	3	porous
2	30.2	1.5	porous
3	29.2	3	porous
4	5.0	0.8	hydrophilic
5	2.0	0.8	hydrophilic
6	0.5	0.8	hydrophilic
7	0.5	0.8	hydrophilic
8	0.5	0.8	hydrophilic
9	32.9	1.5	porous
10	18.2	1.5	porous
11	9.4	1.5	porous
12	12.0	2.5	hydrophilic
13	30.0	3.0	hydrophilic
14	7.2	15.0	PFA +
15	9.8*	3.0	porous
16	6.8++	3.0	porous

* 9.8% Fe, 4.3% Mn

++ 6.8% Fe, 1.7% Mn

\+ polyfurfuryl alcohol layer

Experimental Results:

Measurements of T_1 and T_2

Nmr measurements were performed for protons at a frequency of 10.7 MHz with pulse sequences: ($90^\circ - \tau - 90^\circ$) and ($90^\circ - \tau - 180^\circ - \tau$) for T_1 and T_2 respectively.

The temperature was 37° C.

The suspensions containing particles of a ferromagnetic material were homogenized by sonication and vigorous shaking.

The in vitro experiments were performed in the following solutions:

1)	Distilled and ion-exchanged water	68.76	vol. %
	Glycerol	31.75	vol. %
2)	Distilled and ion-exchanged water	53	weight %
	Glycerol	31.4	weight %
	Gelatin	15.0	weight %
3)	Human plasma		
4)	Heparinized blood (rabbit)	67.0	vol. %
	Homogenized liver (rabbit)	33.0	vol. %
5)	1% Methylcellulose in water.		

The in vivo experiments were performed as follows:

Particle suspensions were injected i.v. in rats and rabbits. Blood samples were taken at various points of time. The animals were killed and the relaxation times (T_1 and T_2) in both the blood samples and the various organs were measured.

In vitro measurements

The relaxation times (T_1 and T_2) have been measured in different samples with various monodisperse polymer particles carrying particles of ferromagnetic materials and with various commercially available particles of ferromagnetic materials and are summarized in Tables II, III and IX below. The ferromagnetic material in the particles includes various magnetic iron oxides and other ferrites. The size of the particles varied from 0.01 µm to 100 µm and their ferromagnetic content from 0.5 to 100 %.

Table II

Example No.	Particle Type	Particle diameter (μm)	Amount of Fe in particle (%)	Concentration of Fe in sample (mmol/kg)
7	4	0.8	5.0	0.1
8	4	0.8	5.0	0.2
9	5	0.8	2.0	0.1
10	5	0.8	2.0	0.2
11	6	0.8	0.5	0.1
12	7	0.8	0.5	0.1
13	8	0.8	0.5	0.1
14	9	1.5	32.9	0.1
15	2	1.5	30.2	0.1
16	10	1.5	18.2	0.1
17	11	1.5	9.4	0.1
18	12	2.5	12	0.1
19	13	3	30.0	0.1
20	3	3	29.2	0.1
21	1	3	19.4	0.1
22	14*	15	4.7	0.1
23	16	0.8	0	0

* Polyfurfuryl alcohol layer

Table II (Continued)

Example No.	SAMPLES							
	Distilled Water/ Glycerol		Human Plasma		Homogenized Liver and Blood		Distilled Water/ Glycerol/ Gelatin	
	T_1 (ms)	T_2 (ms)	T_1 (ms)	T_2 (ms)	T_1 (ms)	T_2 (ms)	T_1 (ms)	T_2 (ms)
7	1033	77	881	77	244	37		
8					178	23		
9	1054	128	942	92	407	56		
10					318	38		
11	602	50	481	42	187	30		
12	651	56	499	55				
13	774	69	573	68				
14	1685	169	1646	180				
15							812	46
16	1631	187	1507	139				
17	1679	548	1727	387				
18							835	60
19							866	49
20	1687	176	1618	173				
21							870	60
22							680	182
23	1706	658	1693	325				
Control	1710	800	1660	430	474	106	890	300

Table III

Example No.	Particle Type	% Fe	% Mn	[Fe] mmol/kg	[Mn] mmol/kg
24	15	9.8	4.3	0.1	0.045
25	16	6.8	1.7	0.1	0.025
26	Magnetite*	72.4	0	0.1	0.0

Table III (Continued)

	SAMPLE			
	1% Methylcellulose		Distilled Water/ Glycerol/Gelatin	
Example No.	T_1 (ms)	T_2 (ms)	T_1 (ms)	T_2 (ms)
24	1500	120	722	161
25	1590	289	523	214
26	2753	213	845	191
Reference**	3109	484	920	328

* Iron (II, III) oxide black, magnetic pure (Koch Light 3991-00, particle size 10 - 100 µm)

** Reference values for control with no added contrast agent.

As shown in Table IV below, the effect of the particles of ferromagnetic materials on the spin-lattice relaxation rates (R_1 which is equal to $1/T_1$) was moderate, while the spin-spin relaxation rates ($R_2 = 1/T_2$) were increased many times. An interesting observation is the relatively constant value of ratio R_{2R}/R_{1R} - ($T_2^*T_1/T_2T_1^*$ where T_1^* and T_2^* are the relaxation times in the absence of the contrast agent) in each solution. If the magnetic material is concentrated in few particles, like Type 2, no effect on R_1 has been observed while R_2 is increased 4 to 5 times. When the magnetic materials are distributed more homogeneously through the sample, as with Type 6, effects on both R_1 and R_2 are observed.

Fine powdered magnetic materials also show a remarkable effect on T_2 while monodisperse polymer particles with manganese ferrite seem to increase both R_1 and R_2 (Table III above).

Table IV below shows relative relation rates (R_{1R} and R_{2R}) and the ratio R_{2R}/R_{1R} in various suspensions of monodisperse polymer particles. The concentration is 0.1 mmol Fe/kg (5.6 ppm).

Table IV

			SAMPLE		
			Water/Glycerol		
Example No.	Particle Type	Relative amount of Fe per particle[1]	R_{1R}	R_{2R}	R_{2R}/R_{1R}
27	3	788	1.01	4.54	4.50
28	9	111	1.01	4.73	4.68
29	10	61.4	1.04	4.28	4.12
30	4	2.6	1.65	10.39	6.30
31	5	1.0	1.62	6.25	3.86
32	8	0.26	2.21	11.59	5.24
33	7	0.26	2.63	14.29	5.43
34	6	0.26	2.84	16.00	5.63

Table IV (Continued)

			SAMPLE		
			Plasma		
Example No.	Particle Type	Relative amount of Fe per particle[1]	R_{1R}	R_{2R}	R_{2R}/R_{1R}
27	3	788	1.02	2.49	2.43
28	19	111	1.01	2.39	2.37
29	20	61.4	1.10	3.09	2.81
30	4	2.6	1.88	5.58	2.97
31	5	1.0	1.77	4.67	2.65
32	8	0.26	2.90	6.32	2.18
33	7	0.26	3.33	7.81	2.35
34	6	0.26	3.45	10.24	2.96

1) relative amount of Fe per particle = d^3x
where d = particle diameter in μm
x = % Fe in the particle

Thus while paramagnetic compounds are particularly effective in reducing the spin-lattice relaxation time (T_1), we find particles of ferromagnetic materials to be especially effective in reducing the spin-spin relaxation time (T_2).

The observed increase of R_2 in the presence of particles of ferromagnetic materials might be explained as follows:

In the T_2 relaxation process, no energy is transferred from the nuclei to the lattice. The nuclei in the excited and ground spin states exchange energy with each other, undergoing a spin transition that leaves the net spin state of the whole system unchanged: while one nucleus absorbs energy the cooperating nucleus releases energy.

It is the rate of loss of the transverse magnetization that determines the T_2 relaxation time. The transverse magnetization decreases because the nuclear magnetic moments get out of phase. This loss of coherence results from the fact that all nuclear magnetic moments do not have exactly the same precession frequency (due to different local magnetic fields). The decay rate observed (R_2^*) is a result to the true spin-spin relaxation rate (R_2) together with a contribution which is due to the local inhomogeneity of the magnetic field ($R_{2inh.}$)

$(R_2^*) = (R_2) + (R_{2inh.})$

The observed T_2^* (i.e. $1/R_2^*$) in a system is always smaller than the real value due to the different magnetic environments of the nuclei. By introducing particles of ferromagnetic materials, the local magnetic field inhomogeneities increase resulting in a decrease of the observed T_2^*.

In vivo measurements

Various suspensions of monodisperse polymer particles carrying particles of ferromagnetic materials have been intravenously administered to rats and rabbits and the relaxation times (T_1 and T_2) in different organs have been measured (post mortem). The obtained relaxation times are summarized in Tables V and VI below. By taking blood samples and measuring relaxation times at various points of time, the elimination of the particles from the vascular system could be followed. The particles were eliminated from the blood extremely rapidly: five minutes after i.v. administration, the particles were substantially eliminated from the vascular system.

As shown in Table VI, the relaxation times (T_2) in liver, spleen and lungs were strongly reduced. The relaxation time (T_2) in the kidneys was also decreased.

The effects of various amounts of the particles of ferromagnetic materials on the relaxation times (T_1 and T_2) have been studied. It was found that the rate of decrease of the observed relaxation times decreased with increasing concentrations of particles of ferromagnetic materials.

Table V Relaxation times (T_1 and T_2) in liver (rat) 1 hour after intravenous injection of particles of ferromagnetic materials.

Example No.	Particle Type	mmol Fe/kg bodyweight	T_1 ms	T_2 ms
35	1	0.1	219	22
36	1	0.1	212	23
		Reference values **	216	39

** control - with no contrast agent.

Table VI

Relaxation times (T_1 and T_2) in blood samples and different organs after intravenous injection of particles of ferromagnetic material.

		Blood		Bile	
Example No.	Injection	T_1 (ms)	T_2 (ms)	T_1 (ms)	T_2 (ms)
Control	None	1024	350 3200	2500-	
37	Particle* Type 3 0.5mmol/kg	925(5) 1047(60)	98(5) 218(60)	2787 (0-60) 3632 (60-120)	- -
38	Particle** Type 3 0.5mmol/kg	878(5) 1020(60)	149(5) 227(60)	- -	- -
39	Particle*** Type 2 0.5mmol/kg	-	78(5)	-	-
40	Particle* Type 2 0.5mmol/kg	995(5)	180(5)	-	-

The numbers in the brackets are minutes after the injection

*Killed after 2 hours

**Killed after 90 minutes

***Killed after 30 minutes

Table VI (Continued)

Example No.	Liver/0.9% NaCl (1:2) T_1 (ms)	Liver/0.9% NaCl (1:2) T_2 (ms)	Lung/0.9% NaCl (1:2) T_1 (ms)	Lung/0.9% NaCl (1:2) T_2 (ms)
Control	578	179	1039	240
37	369	5	613	11
38	539	15	687	7
39	167	3	345	6
40	284	5	308	6

Table VI (Continued)

Example No.	Kidneys/0.9% NaCl (1:2) T_1 (ms)	Kidneys/0.9% NaCl (1:2) T_2 (ms)	Spleen/0.9% NaCl (1:2) T_1 (ms)	Spleen/0.9% NaCl (1:2) T_2 (ms)
Control	1224	206	-	-
37	768	34	672	6
38	776	52	379	7
39	645	43	-	-
40	672	39	287	4

Toxicity

(a) Intravenous administration

Magnetically responding microspheres have been used for biophysical targeting of antitumor agents and other drugs. The toxicity of intravenously administered microspheres has been thoroughly studied. The toxicity of particles has been found to depend on both the size and the shape of the particles.

At present, there are no published studies describing the toxicity of intravenously administered magnetite. However, intensive human studies have been performed to evaluate the effects of inhaled material. These studies revealed that respiratory intake of moderately large quantities of iron oxides does not cause significant inflammation, fibrosis or alteration of pulmonary function. Based on these results, it may be reasonable to assume that intravascularly administered ferromagnetic compounds will also induce minimal inflammatory responses.

We have studied the acute toxicity of intravenously administered monodisperse particles carrying particles of ferromagnetic material. The mortality is summarized in Table VII below while Table VIII below shows the approximate i.v. LD_{50} of various particles in mice.

All injections were performed on male mice, strain NMRI, weighing 18-22 g, obtained from Bomholtgaard, Denmark. Injection site: Tail veins. Injection rate: 0.20 ml/10 sec. Observation period: One week.

The particle solutions were treated by sonication (15 minutes), prior to the injection.

Table VII

Toxicity in mice of various monodisperse polymer particles of ferromagnetic material

Example No.	Particle Type (and administration mode)	%Fe in particle	Dose in mg particle /kg bodyweight	Mortality
41	4 (i.v.)	5	800	0 of 4
			1000	0 of 4
42	5 (i.v.)	2	1230	0 of 4
			1640	0 of 4
			2050	0 of 4
43	6 (i.v.)	0.5	600	0 of 2
			750	0 of 2
			900	0 of 2
			1200	0 of 2
			1500	7 of 7
44	7 (i.v.)	0.5	360	3 of 5
			540	2 of 5
			720	5 of 5
			810	5 of 5
			900	5 of 5
45	2 (i.v.)	30.2	500	0 of 5
			750	1 of 5
			1000	2 of 2
			1250	2 of 2
46	3 (i.v.)	29.2	750	0 of 2
			1250	0 of 4
			1500	0 of 4
			2000	4 of 4
			2250	3 of 4
			3000	2 of 2
47	3 (oral)	29.2	7810	0 of 5

Table VIII

Example No.	Particle Type	Particle diameter µm	% Fe in particle	Approximate LD_{50} mg particles/kg bodyweight
48	4	0.8	5	>1000
49	5	0.8	2	>2050
50	6	0.8	0.5	1350
51	7	0.8	0.5	450
52	2	1.5	30.2	750-1000
53	3	3.0	29.2	1500-2000

	Approximate LD_{50} mg Fe/kg bodyweight	Approximate LD_{50}/ED
48	>50	>360
49	>41	>290
50	6.8	49
51	2.3	16
52	230-300	1700-2100
53	440-580	3100-4100

The especially low LD_{50} values with particle Type 2 as compared with Type 3 and with Type 7 as compared with Types 4, 5 and 6 may be due to flocculation of the particles.

If all the particles were picked up by the reticuloendothelial cells in the liver, 0.14 mg Fe/kg bodyweight could be enough to give a contrast enhancement. (0.1 mmol Fe/kg liver, and the liver constitutes about 2.6% of the bodyweight). As shown in Table VIII, the estimated "safety factor" (approximate LD_{50}/effective dose (ED)) is large.

(b) Oral administration

The toxic properties of orally administered particulate ferromagnetic substances as magnetite and ferrites have been described. No changes in any of the biochemical and physiological parameters were observed when a single dosis of 2.0 g/kg bodyweight or 20 g/kg as repeated doses were given rats and mice.

We have studied the toxicity of orally administered monodisperse particles (Type 3). No sign of toxic effect was observed after 7.8 g particles/kg bodyweight.

During the first 24 hours 92.4% of the dose were recovered in the faeces.

The material is insoluble in water and thereby is not absorbed from the gastrointestinal tract. (The

polymer matrix for Type 3 particles is not biodegradable).

The invention is also illustrated by the following further Examples:

TABLE IX (In vitro test results)

Example No.	Particle type	Particle diameter (μm)	Amount of Fe in particle (%)
54	17 [1])	3.0	0.52
55	18 [2])	0.3 - 4.0	10.0
56	19 [3])	0.3 - 4.0	8.6
57	20 [4])	0.6	69.9
58	21 [5])	0.3 - 0.6	69.9
59	22 [6])	0.5 - 2.0	44.0
60	23 [7])	0.01-0.02	72.4

TABLE IX (continued)

Example No.	Concentration of Fe in sample* (mmol/kg)	T_1 (ms)	T_2 (ms)
54	0.25	291	48
55	0.25	1236	59
56	0.25	107	10
57	0.25	1356	182
58	0.25	1225	124
59	0.25	363	24
60	0.25	723	27
Control		1332	445

1) Monodisperse particles prepared according to the process of J. Ugelstad et al. (WO 83/03920). Density 1.07 g cm^{-3}.

2) Estrapor ® LMP 233 from Rhône-Poulenc, Paris, France.

3) Estrapor ® LMC 247 from Rhône-Poulenc, Paris, France.

4) γ-Fe_2O_3 (Bayferrox 8060 from Bayer AG, Leverkusen, W-Germany)

5) Black Iron Oxide (11557 from D.F. Anstead Ltd. Billericay, Essex, England)

6) Biomag M4200 (Advanced Magnetics Inc., Cambridge, Massachusetts, U.S.A.)

7) Ferrofluid (Ferrofluid Co., U.S.A.)

* Distillied and ion-exchanged water 77.3 weight %
Glycerol 13.6 weight %
Gelatin 9.1 weight %

Example 61 (Preparation of a suspension for oral administration)

Particles (Type 9)	3.04 g
Sodium polymetaphosphate	18.25 g
Saccharin sodium	1.0 g
Methyl parahydroxybenzoate	0.75 g
Potassium sorbate	1.0 g
Xanthan gum	3.0 g
Peppermint oil	2.0 g
Water	971.0 g

Methyl parahydroxybenzoate was dissolved in hot water (90 °C). The solution was cooled and xanthan gum was added, and the mixture was vigorously stirred for 1 h. Sodium polymetaphosphate, saccharin sodium, potassium sorbate and peppermint oil were dissolved, and finally the particles were suspended. The suspension was filled in a 1 litre bottle. The suspension contained 1.0 mg Fe/g.

Example 62 (Preparation of a suspension for oral use)

Magnesium aluminium silicate (e.g Veegum)	5.0 g
Liquid sorbitol 70%	478.0 g
Citric acid	1.0 g
Methyl parahydroxybenzoate	0.8 g
Orange essence	0.2 g
Ethanol	15.0 g
Particles (Type 21)	1.32 g
Water	498.6 g

Veegum was dispersed in water at 60 °C by high speed mixing for 1 hour. Liquid sorbitol and citric acid were added under continuous stirring. A solution of methyl parahydroxybenzoate and orange essence in ethanol was added and the particles were suspended under vigorous stirring. The suspension was filled in a 1 litre bottle. The suspension contained 1 mg Fe/g.

Example 63 (Preparation of a suspension for oral administration)

Particles (Type 8)	10	g
Hydroxyethyl cellulose	10.0	g
Methyl parahydroxybenzoate	0.8	g
Propyl parahydroxybenzoate	0.2	g
Ethanol	10.0	g
Saccharin sodium	1.0	g
Orange essence	0.3	g
Apricot essence	0.7	g
Water	967.0	g

Hydroxyethyl cellulose was dispersed in water with stirring for 2 hours. Saccharin sodium and a solution of the essences, methyl and propyl parahydroxybenzoate in ethanol were slowly added. The particles were dispersed in the solution under vigorous stirring. The suspension contained 0.05 mg Fe/g.

Example 64 (Preparation of a suspension for rectal administration (enema))

Methyl parahydroxybenzoate (85 mg) and propyl parahydroxybenzoate (15 mg) were dissolved in water (100 ml) at 90 °C. After cooling to 30 °C methyl cellulose (2 g) was added and the mixture was agitated for 2 hours. 1.0 g of particles (Type 5) was suspended. The suspension was filled in a 100 ml tube. The suspension contained 0.2 mg Fe/ml.

Example 65 (Preparation of a suspension for use in sialography/nmr-examination of the urine bladder and/or hysterosalpingography)

Particles (Type 17)	1.0	g
Polyoxyethylene polyoxypropylene copolymer (e.g. Pluronic® F68)	0.5	g
Sodium chloride	0.9	g
Sterile water	ad 100	ml

The particles were aseptically suspended in a sterile mixture of sodium chloride and Pluronic® in water. The suspension was filled into single dose containers. The suspension contained 52 mg Fe/l.

Example 66 (Preparation of suspension of coated particles for oral administration)

Solution A

Methacrylate esters copolymers (e.g. Eudragit® RS)	50	g
Talcum	50	g
Isopropanol	900	g

Talcum was suspended in a solution of Eudragit®RS in isopropanol under stirring.

100 g of the solution A were sprayed upon 500 g of magnetite particles (Example 26). The particles were rotated in a fluidised bed apparatus. The amounts and the temperature of the inlet air were adjusted so that the particles were kept at a temperature of 30° C and were sprayed continuously. The spraying was carried on until sufficient coating was obtained. The particles were dried overnight at ambient temperature and filled into single dose containers.

Solution B.

Cellulose gum	1.0	g
Sodium chloride	0.5	g
Methyl parahydroxybenzoate	0.1	g
Ethanol	2.0	g
Peppermint oil	0.5	g
Water	96.0	g

The cellulose gum, sodium chloride and peppermint oil and methyl parahydroxybenzoate in ethanol were dissolved in water.

Preparation of the final suspension:

100 ml of solution B were added to 2.8 g of the coated particles and the container was shaken until homogenous suspension. The suspension contained 20 mg Fe/ml. Example 67 -(Preparation of enterosolubly coated particles for oral use)

This suspension was prepared as described in Example 66. Eudragit®S was used instead of Eudragit®RS. The pH in the suspending solution (Solution B) was adjusted to 4 with 1N HCl.

Claims

1. Use of particles of a ferromagnetic material for the manufacture of an nmr contrast agent for use in a method of diagnosis practised on the human or non-human animal body which method includes generation of a T_2 dependent image and diagnosis using said image.

2. Use as claimed in claim 1 of particles of a ferromagnetic material embedded in or coated with a non-ferromagnetic matrix or coating of a non-biodegradable, biotolerable polymer.

3. Use as claimed in either of claims 1 and 2 of said particles and a viscosity enhancing agent and/or a surfactant for the manufacture of said contrast agent.

4. Use as claimed in any one of claims 1 to 3 of particles of a ferromagnetic material of 0.01 to 0.6 micrometers in size.

5. Use as claimed in claim 4 of particles of a ferromagnetic material of 0.01 to 0.02 micrometers in size.

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Solution A

Methacrylate esters copolymers (e.g. Eudragit®RS)	50 g
Talcum	50 g
Isopropanol	900 g

Talcum was suspended in a solution of Eudragit®RS in isopropanol under stirring.

100 g of the solution A were sprayed upon 500 g of magnetite particles (Example 26). The particles were rotated in a fluidised bed apparatus. The amounts and the temperature of the inlet air were adjusted so that the particles were kept at a temperature of 30 °C and were sprayed continuously. The spraying was carried on until sufficient coating was obtained. The particles were dried overnight at ambient temperature and filled into single dose containers.

Solution B.

Cellulose gum	1.0 g
Sodium chloride	0.5 g
Methyl parahydroxybenzoate	0.1 g
Ethanol	2.0 g
Peppermint oil	0.5 g
Water	96.0 g

The cellulose gum, sodium chloride and peppermint oil and methyl parahydroxybenzoate in ethanol were dissolved in water.

Preparation of the final suspension:

100 ml of solution B were added to 2.8 g of the coated particles and the container was shaken until homogenous suspension. The suspension contained 20 mg Fe/ml. Example 67 -(Preparation of enterosolubly coated particles for oral use)

This suspension was prepared as described in Example 66. Eudragit®S was used instead of Eudragit®RS. The pH in the suspending solution (Solution B) was adjusted to 4 with 1N HCl.

Claims

1. Use of particles of a ferromagnetic material for the manufacture of an nmr contrast agent for use in a method of diagnosis practised on the human or non-human animal body which method includes generation of a T_2 dependent image and diagnosis using said image.

2. Use as claimed in claim 1 of particles of a ferromagnetic material embedded in or coated with a non-ferromagnetic matrix or coating of a non-biodegradable, biotolerable polymer.

3. Use as claimed in either of claims 1 and 2 of said particles and a viscosity enhancing agent and/or a surfactant for the manufacture of said contrast agent.

4. Use as claimed in any one of claims 1 to 3 of particles of a ferromagnetic material of 0.01 to 0.6 micrometers in size.

5. Use as claimed in claim 4 of particles of a ferromagnetic material of 0.01 to 0.02 micrometers in size.

6. Use as claimed in any one of claims 1 to 3 of particles of a ferromagnetic material of 0.002 to 50 micrometers in size.

7. Use as claimed in any one of claims 4 to 6 of uncoated particles of a ferromagnetic material.

8. Use as claimed in any one of claims 1 to 7 of particles of a ferromagnetic material which are particles of a magnetic iron oxide.

9. Use as claimed in claim 8 of particles of a ferrite.

10. Use as claimed in claim 8 of particles of a magnetite or of gamma-Fe_2O_3.

11. Use as claimed in any one of claims 1 to 10 for the manufacture of a said agent in a form adapted for parenteral administration.

12. Use as claimed in claim 11 for the manufacture of a tissue specific contrast agent.

13. Use as claimed in claim 1 of particles having a maximum dimension in the range 0.1 to 20 micrometers and having a ferromagnetic content of from 0.5 to 50% by weight.

Revendications

1. Utilisation de particules de matière ferromagnétique pour la fabrication d'un agent de contraste de résonance magnétique nucléaire destiné à être utilisé dans un procédé de diagnostic pratiqué sur l'organisme de l'homme ou de l'animal, ce procédé consistant à engendrer une image qui dépend de T_2 et à effectuer un diagnostic en utilisant cette image.

2. Utilisation, suivant la revendication 1, de particules d'une matière ferromagnétique enrobée ou revêtue d'une matrice non ferromagnétique ou revêtue d'un polymère non biodégradable et acceptable biologiquement.

3. Utilisation, suivant la revendication 1 ou 2, de ces particules et d'un agent augmentant la viscosité et/ou d'un agent tensio-actif pour la préparation de l'agent de contraste.

4. Utilisation, suivant l'une quelconque des revendications 1 à 3, de particules d'une matière ferromagnétique ayant une dimension comprise entre 0,01 et 0,6 micron.

5. Utilisation, suivant la revendication 4, de particules d'une matière ferromagnétique ayant une dimension de 0,01 à 0,02 micron.

6. Utilisation, suivant l'une quelconque des revendications 1 à 3, de particules d'une matière ferromagnétique ayant une dimension comprise entre 0,002 et 50 microns.

7. Utilisation, suivant l'une quelconque des reven dications 4 à 6, de particules non revêtues d'une matière ferromagnétique.

8. Utilisation, suivant l'une quelconque des revendications 1 à 7, de particules d'une matière ferromagnétique qui sont des particules d'oxyde de fer magnétique.

9. Utilisation, suivant la revendication 8, de particules d'un ferrite.

10. Utilisation, suivant la revendication 8, de particules de magnétite ou de gamma-fe_2O_3.

11. Utilisation, suivant l'une quelconque des revendications 1 à 10, pour la préparation de l'agent sous une forme adaptée à l'administration parentérale.

12. Utilisation, suivant la revendication 4, pour la préparation d'un agent de contraste spécifique au tissu.

* C L M S *

13. Utilisation, suivant la revendication 1, de particules ayant une dimension maximum comprise entre 0,1 et 20 microns et ayant une teneur en substance ferromagnétique de 0,5 à 50 % en poids.

Ansprüche

1. Verwendung von Teilchen eines ferromagnetischen Materials zur Herstellung eines NMR-Kontrastmittels zur Anwendung in einem am menschlichen oder tierischen Körper durchzuführenden Diagnoseverfahren, wobei das Verfahren auch die Erzeugung eines T_2 abhängigen Tomogramms und eine Diagnose unter Verwendung dieses Tomogramms umfaßt.

2. Verwendung gemäß Anspruch 1 von Teilchen eines ferromagnetischen Materials, die in eine nicht ferromagnetische Matrize eingeschlossen oder mit einer solchen überzogen sind oder mit einem biologisch nicht abbaubaren, biologisch verträglichen Polymeren überzogen sind.

3. Verwendung gemäß den Ansprüchen 1 und 2 der genannten Teilchen und eines die Viskosität erhöhenden Mittels und/oder eines oberflächenaktiven Mittels für die Herstellung des genannten Kontrastmittels.

4. Verwendung gemäß einem der Ansprüche 1 bis 3 von Teilchen eines ferromagnetischen Materials, deren Größe 0.01 bis 0.06 Mikrometer beträgt.

5. Verwendung gemäß Anspruch 4 von Teilchen eines ferromagnetischen Materials, deren Größe 0.01 bis 0.02 Mikrometer beträgt.

6. Verwendung gemäß einem der Ansprüche 1 bis 3 von Teilchen eines ferromagnetischen Materials, deren Größe 0.002 bis 50 Mikrometer beträgt.

7. Verwendung gemäß einem der Ansprüche 4 bis 6 von nicht überzogenen Teilchen eines ferromagnetischen Materials.

8. Verwendung gemäß einem der Ansprüche 1 bis 7 von Teilchen eines ferromagnetischen Materials. die aus magnetischem Eisenoxid bestehen.

9. Verwendung gemäß Anspruch 8 von Teilchen, die aus einem Ferrit bestehen.

10. Verwendung gemäß Anspruch 8 von Teilchen, die aus einem Magnetit oder aus Gamma= Fe_2O_3 bestehen.

11. Verwendung gemäß einem der Ansprüche 1 bis 10 zur Herstellung des genannten Mittels in einer für die parenterale Verabreichung geeigneten Form.

12. Verwendung gemäß Anspruch 11 für die Herstellung eines gewebsspezifischen Kontrastmittels.

13. Verwendung gemäß Anspruch 1 von Teilchen, die eine maximale Abmessung im Bereich von 0.1 bis 20 Mikrometern und einen ferromagnetischen Gehalt von 0.5 bis 50 Gewichtsprozenten aufweisen.