



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : B01J 13/00, C04B 35/26		A1	(11) International Publication Number: WO 88/ 05337 (43) International Publication Date: 28 July 1988 (28.07.88)
(21) International Application Number: PCT/US88/00083 (22) International Filing Date: 14 January 1988 (14.01.88) (31) Priority Application Number: 003,899 (32) Priority Date: 16 January 1987 (16.01.87) (33) Priority Country: US (71) Applicant: CLARKSON UNIVERSITY [US/US]; Potsdam, NY 13676 (US). (72) Inventor: MATIJEVIC, Egon ; 94 Market Street, Potsdam, NY 13676 (US). (74) Agent: FARO, John, H.; Faro & Associates, 900 Glades Road, Fifth Floor, Boca Raton, FL 33431 (US).			(81) Designated States: AT (European patent), AU, BE (European patent), BR, CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent). Published <i>With international search report.</i>
(54) Title: PROCESS FOR PREPARATION OF MONODISPERSED BARIUM CONTAINING FERRITES			
(57) Abstract An improved process for preparation of well-defined monodispersed colloidal particles of barium containing ferrites. This process involves the formation of colloidal barium ferrite particles in aqueous media by phase transformation of a ferrous hydroxide gel in the presence of barium ions. In this process, a magnetite is initially formed in aqueous solution and barium substituted into the resultant particle by displacement of Fe^{2+}. This procedure is performed in a nonoxidizing atmosphere and under mildly caustic conditions. As the reaction proceeds to completion (aging) the system becomes decidedly more acidic. The colloidal particles produced in accordance with this invention are easily dispersible in aqueous media and, unlike magnetite, are superparamagnetic in response to a magnetic field. This procedure is in sharp contrast to more traditional methods of solid state transformations of the magnetite to ferrite at temperatures typically in excess of 1000°C.			

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**Title: PROCESS FOR PREPARATION OF MONODISPERSED
BARIUM CONTAINING FERRITES**

BACKGROUND OF THE INVENTION

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Field of the Invention - This invention relates to a process and to the composition of matter resulting from this process. More specifically, this invention is directed to a process for the
10 preparation of a colloidal dispersion of ferrite particles containing barium. The particles produced by this process have a very narrow particle size distribution and are superparamagnetic in their response to a magnetic field. These particles are useful in magnetic recording media; in separation of various constituents of
15 complex fluids (i.e. blood, cerebrospinal fluid or urine); and in certain diagnostic applications.

Description of the Prior Art - The preparation of colloidal particles
20 from inorganic substances has, until very recently, been a highly empirical "science". For the most part, the efficacy of such processes was quite subjective and generally the relative success or failure thereof required laborious trial and error in order to attain adequate process definition. More specifically, the efficacy
25 of a particular technique, even if it were reproducible to a degree, rarely produced a consistently acceptable product. The inability to achieve reproducible results from such processes has led many to regard the synthesis of inorganic colloidal particles as largely the domain of the empiricist.

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With the advent of more sophisticated analytical tools (i.e. electron microscopy), the fascination with inorganic colloidal particles, and more particularly, monodispersed inorganic
35 colloidal particles, has been rekindled. The initial interest in such materials was primarily as a scientific curiosity, however, more

recent developments have found them useful as supports for catalysts, in ceramics, pigments, films, recording media, coatings, in various diagnostic and therapeutic environments, as well as a myriad of other applications.

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The term "monodispersed" as used in the discussion of the prior art and throughout the balance of this disclosure is intended as referring to a population of particulate materials having a narrow particle size distribution.

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A survey of the various techniques for synthesis of monodispersed, inorganic colloidal particles has recently appeared in the technical literature, see Matijevic, E., "Monodispersed Colloids: Art and Science", Langmuir, Vol. 2, No. 1, pp. 12-20 (1986).

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The procedures which have been previously developed by the inventor for synthesis of inorganic colloidal dispersions of narrow particle size distribution have been described in detail in a number of papers which have appeared in the technical literature, see for example, Matijevic, E., Ann. Rev. Mater. Sci. (1985), 15, 483 & Matijevic, E., Acc. Chem. Res. (1981), 14, 22. Two of the procedures described in the above article can be conveniently grouped into the following categories: (1) precipitation from homogenous solution (i.e. forced hydrolysis, controlled release of anions and controlled release of cations); and (2) phase transformations. What is, however, to be appreciated is that each of the above procedures will have one or more shortcomings or advantages for synthesis of a specific colloidal material. Thus, the production of an acceptable product, in accordance with each of the processes from the same starting materials, is both highly unpredictable and unlikely. More specifically, in order to produce colloidal particles of specific

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characteristics, both of the above procedures may have to be attempted before one can be identified as potentially useful or efficacious. At that point, additional refinement will be required before an acceptable product is attainable.

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In the procedures involving precipitation of inorganic compounds from homogenous solutions, the precursors to the formation of the solid phase are, in most instances, one or more solute
10 complexes. This procedure is, thus, based upon the control of kinetics of the complexation reaction in order to achieve a single burst of nuclei, which are then allowed to grow uniformly, resulting in particles of narrow size distribution. Where the constituent solutes are generated at the proper rate, their even
15 distribution onto existing nuclei results in the least increase in total free energy of the dispersion, thus, controlling the growth of such particles by proper control of particle charge. Control of the charge on such particles is traditionally achieved by adjustment in pH or through the introduction of additives. In the absence of
20 such control of charge, aggregation of such particles will result.

In a phase transformation procedure, a precipitate is initially prepared. The form of precipitate is generally other than in the
25 desired colloidal form. This precipitate is then subsequently changed, through crystallization, recrystallization or dissolution/precipitation into the desired form of dispersed matter. A most common example of this procedure is sol-gel transformation. The mechanisms involved in these transformations are not generally
30 well understood and, thus, the results are not readily predictable. It is also difficult to recognize if a phase transformation has in fact occurred since the initial state (form) of the dispersed matter may be either so short lived or so finely dispersed, the transition from one state to another is difficult to detect. The literature
35 does describe the preparation of spherical magnetite particles by phase transformation techniques. Analogous techniques have

also been used in the preparation of cobalt, nickel and cobalt/nickel ferrites, see for example Regazzoni, A. E.; Matijevic, E., Corrosion (1982), 38, 212; Tamura, H. and Matijevic, E., Colloid Interface Sci. (1982), 90,100; Regazzoni, A. E.; Matijevic, E.,
5 Colloids Surf. (1983) 6, 189.

Because of the nature of the colloidal particles, and the various methods used in their preparation, their physical properties are
10 often unpredictable. For example, in the preparation of colloidal magnetite and ferrites, their respective crystal structure can often vary and so to the response of such materials to magnetic fields. The production of barium ferrite powders has traditionally involved the phase transformation of large particles of barium
15 ferrite at elevated temperature, see for example Haneda, K, et al., J. Am. Cer. Soc. (1974) 57, 354. During production, the ferrite is milled and calcined at elevated temperatures to reduce particle size from multidomain to single-domain.

20 The majority of procedures used in the preparation of barium ferrites have involved some sort of phase transformation of these particles in the dry state, e.g. Tenzer, R.K., J. App. Phys. (1963) 34, 1267. A number of other investigators have been successful in
25 the preparation of barium ferrites from aqueous media; however, none of these so-called "wet" procedures have resulted in particles of uniform size distribution. It has been recently demonstrated that colloidal magnetite and some ferrites, having a narrow particle size distribution, can be produced by
30 crystallization of ferrous hydroxide gels in the presence of a mild oxidizing agent.

Because of their high anisotropic values caused by their crystal
35 structure, hexagonal barium ferrites have found application as permanent magnetic materials, recording tapes and the like. This

large anisotropy makes it difficult to reverse this tendency of the particles in the direction of magnetization. Also because of such high anisotropic values (typically 0.3 J/cm^3), the particles are single domain and very difficult to demagnetize, particularly
5 where the particle size is kept below values (0.2 micrometers). As is thus readily appreciated, the relative strength and permanency of the magnetic forces between these particles renders them essentially unsuitable for formation of stable colloidal dispersions in fluid media.

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For the above and related reasons, ferrites produced in the above manner have had rather limited application, and then only in industrial applications. Where attempts have been made to adapt
15 such materials to the biological environments, (i.e. separation processes) the results have largely been unsatisfactory for the reasons indicated previously (i.e. instability of dispersion). Where such colloidal materials do in fact have an affinity for a cellular analyte, the relatively strong magnetic forces between
20 the particles can be destructive of the adsorbed cells when the particles form aggregates. The unsatisfactory nature of these prior art materials is further manifest when an attempt is made at separation of the magnetic particles and the cellular analyte. Generally, such separation cannot be effected without incurring
25 modification or destruction to the analyte physiology and integrity. Because of these and associated shortcomings, it is apparent that currently available materials would not be suitable in the separation processes involving complex fluids, notably, complex biological fluids such as blood, cerebrospinal fluid or
30 urine.

OBJECTS OF THE INVENTION

- 5 It is the principle object of this invention to remedy the above as well as related deficiencies in the prior art.

10 It is another object of this invention to provide a reproducible, energy efficient process for the synthesis of monodispersed barium containing ferrite particles.

15 It is yet another object of this invention to provide a reproducible process for the synthesis of a class of ferrites which are useful in the separation of constituents of complex fluids, notably, biological fluids.

20 It is still yet another object of this invention to provide a process for the synthesis of a class of ferrites whose magnetic properties can be tailored to the separation of constituents of biological fluids without altering the native characteristics or physiology of such constituents.

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It is a further object of this invention to provide a process for the synthesis of a class of ferrites which are useful in separation processes and, once separated, are redispersible in aqueous media.

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It is yet a further object of this invention to provide a class of ferrite material which can form a stable colloidal dispersion and is, thus, useful in a variety of separation processes, notably those involving complex biological fluids.

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SUMMARY OF THE INVENTION

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The above and related objects are achieved by providing a process for the preparation of well-defined monodispersed particles of barium containing ferrites. This process involves the phase transformation of ferrous hydroxide gel, in a nonoxidizing atmosphere. This gel is then contacted with barium nitrate solution. The nitrate salt acts as a mild oxidizing agent, thus, promoting the phase transformation of the gel to barium containing ferrite particles. During this conversion process, barium is incorporated within the crystal lattice of the ferrite particle. The resultant crystalline materials have a narrow particle size distribution, and a cubic morphology.

These crystalline particles are unique among ferrites in that they are readily dispersible in an aqueous medium and are superparamagnetic in response to magnetic fields. The introduction of barium ions into the ferrite crystalline lattice is believed to attenuate the magnetic properties of these materials, thus, accounting for reduced particle/particle interactions (aggregation). This attenuation of magnetic properties of the ferrite can be controlled within limits, depending upon the relative concentration of barium ions introduced into these crystalline materials. These modified ferrite particles have surface characteristics which are favorable for the adsorption of protein (i.e. cellular materials), and yet maintain the stability of the dispersion in aqueous fluids. These particles exhibit superparamagnetic response in the presence of a magnetic field, thus, enable their relatively gentle aggregation within the fluid dispersion. The adsorbed protein or cell can, thus, be separated along with the barium ferrite particle without alteration or destruction of the native physical and/or physiological

characteristics of the adsorbed material. After such separation from the dispersion, the barium ferrite particle/protein complex can be redispersed in fluid media and subjected to quantitative or qualitative analysis. Alternatively, the complex can be treated to effect dissociation of the adsorbed materials from the barium ferrite particles, and the particles thereupon separated from the fluid and recycled.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a reproduction of a photomicrograph depicting the monodispersed barium containing ferrite particles of this invention.

DESCRIPTION OF THE INVENTION INCLUDING PREFERRED EMBODIMENTS

This invention provides a reproducible process for the synthesis of colloidal particles of narrow particle size distribution from barium salts and a ferrous hydroxide gel. Colloidal particles are prepared from the above materials by phase transformation, in an inert atmosphere, of gelatinous ferrous hydroxide, in the presence of barium salts. This phase transformation is conducted under mild oxidizing conditions and in an aqueous environment.

This process initially involves the formation of ferrous hydroxide from a ferrous salt (i.e. ferrous chloride) and a stock solution of potassium hydroxide and potassium nitrate. The combination of the ferrous salt and the stock solution results in the formation of a ferrous hydroxide gel suspension which is stable at a slightly acidic pH (approximately 6.4). When barium salts (i.e. barium

nitrate) are added to the gelatinous ferrous hydroxide, the phase transformation of the gel to crystalline ferrite particles is initiated. Upon continued aging, this gelatinous precipitate undergoes a phase transformation to produce ferrite particles
5 containing barium with cubic crystal lattice. The mildly acidic conditions affect the rate and degree of oxidation of the hydroxide gel to the corresponding crystalline ferrites.

10 The conditions prevailing during the initial formation of the hydroxide, and its subsequent phase transformation, are critical to the process of this invention in order to avoid the formation of hematite. Once the gelatinous precipitate is formed, it is aged at
15 elevated temperatures (approximately 90°C) to effect the phase transformation to the desired tolerance. The magnetic particles which are ultimately recovered from the reaction mass are readily identifiable, easily redispersible in aqueous media, and have superparamagnetic properties in response to the magnetic
20 field.

The materials which are suitable for use in this process are preferably reagent grade chemicals. Ferrous hydroxide ($\text{Fe}(\text{OH})_2$) is initially formed by combining aqueous solutions of the ferrous
25 salt with an aqueous solution containing a source of hydroxide ions. The quantity of ferrous salt solution combined with the alkali is carefully adjusted to produce a ferrous hydroxide solution of slightly acidic (pH approximately 6.4) character.

30 Once the ferrous hydroxide solution is prepared, it is contacted with an aqueous solution of a suitable barium salt (i.e. $\text{Ba}(\text{NO}_3)_2$). The two solutions are combined in an inert atmosphere (e.g. argon or nitrogen) and permitted to interact at ambient (room)
35 temperature. After about 30 minutes, the interaction of the barium salt solution and the ferrous hydroxide results in the

incorporation of finite amounts of Ba^{2+} ions within the ferrous hydroxide gel (presumably by ion exchange). This suspension can thereafter be transferred to one or more sealed containers and aged at elevated temperatures until the phase transformation of the gel to the solid particles has been completed.

In the preferred embodiments of this invention, the following ranges of concentrations of materials and process conditions have produced ferrites containing barium consistent with the objectives of this invention:

FeCl_2 : 0.05 - 0.20 mol dm^{-3}

KOH : 0.05 - 0.20 mol dm^{-3}

$\text{Ba}(\text{NO}_3)_2$: 0.05 - 0.50 mol dm^{-3}

KNO_3 : 0.20 mol dm^{-3}

Aging temperature was kept at 90°C

Aging time: 4-48 hours.

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Upon completion of this aging process, the solid particles are removed from the sealed containers, and washed by resuspension in water. The magnetic properties of the colloidal particles permit their ready separation from other non-magnetic particles contained in the suspension. This separation is achieved by simply placing a magnet in contact with the side or bottom of the vessel containing the suspension, allowing the magnetic particles to collect on the interior of the vessel corresponding to the placement of the magnet and decanting the wash fluid containing the non-magnetic particles. This washing/decanting process can be repeated until essentially all non-magnetic particles and other water soluble materials are removed. The particles can thereafter be air dried or calcined. The particles obtained through this process in the foregoing manner are illustrated in Fig. 1. These particles are uniform and of a relatively narrow size distribution. The particle shape can vary from cuboidal to

hexagonal, whereas relative size remains essentially uniform. In the preferred embodiments of this invention, these particles are submicron in size and most preferably in the range of from 0.1 to 0.8 micrometers. As noted above, these particles, can be calcined
5 in the conventional manner to modify one or more of their physical properties.

These particles are unique in a number of respects (in addition to
10 their narrow particle size distribution). The processing history and the introduction of barium ions into the ferrite crystalline lattice is believed to be responsible for attenuation of the magnetic properties of these materials, thus, accounting for reduced particle to particle interaction (aggregation). These
15 barium modified ferrite particles are, thus, capable of formation of stable colloidal dispersions in fluid media. The surface characteristics of the particles of these colloidal dispersions have a natural affinity for adsorption of protein (i.e. cells, ligands, steroids, hormones, etc.). This adsorption is accomplished while
20 maintaining the stability of the particle dispersion in the fluid medium.

The adsorption characteristics of the barium modified ferrites is
25 essentially surface charge dependent. The characteristic surface charge of these particles can be readily modified by adjustment in pH. The variation in surface charge follows a characteristic sigmoid curve. At a pH above the particles isoelectric point, the surface charge on these particles is positive; and at a pH below
30 the isoelectric point, the surface charge on these particles is negative.

Within the operational range of interest (pH 6-8), these particles
35 can rapidly and efficiently adsorb proteinaceous materials without adverse or destructive effect upon their physical and/or

physiological properties. This ability to effectively adsorb protein and its separation upon application of a magnetic field is unique to the barium modified colloidal particles of this invention. The effective adsorption of protein without disruptive effect upon the other constituents of the fluid dispersion is of critical importance not only to preservation of the adsorbed species, but also to the particulates and dissolved matter which remain within the fluid. This latter application involves the use of the colloidal particles as scavengers to remove undesirable components of a fluid sample (presumably interferents) prior to analysis of the residual material which remains in suspension. The particles, thus, have application in both industrial and biological environments, involving magnetic separation techniques of the type described in the following U.S. Patents: 4,001,288; 4,247,406; 4,018,886; 4,285,819; 4,147,767; 4,335,094; 4,152,210; 4,452,773; 4,169,804; 4,454,234; and 4,230,685 - all of which are hereby incorporated by reference in their entirety. The barium modified ferrites of this invention thus provide, for the first time, a practical and efficacious material which can perform reliably in such separation systems and yet are compatible with relatively simple, straightforward methodologies.

In a separation system of the type described in the above patents, the superparamagnetic colloidal barium ferrite particles obtained by this process can be used directly or modified by treatment with a binding material (i.e. antigen, antibody, binding protein, complement DNA), in accordance with conventional techniques described in the open literature. This treatment (coating) with these binding materials is performed under conditions which retain the desirable attributes of the barium ferrite particles. These untreated or treated particles can thereafter be combined with an industrial or biological fluid having one or more constituents capable of binding to the particles. After a suitable incubation period, the particles, and presumably the constituents of the fluid for which they are

specific, are then separated from the fluid utilizing conventional magnetic separation equipment and techniques. The materials separated from the fluid in this manner can either be discarded (if regarded as impurities) or recovered (if regarded as desirable constituents). In this latter instance, the particle and adsorbed constituents would simply be exposed to certain conditions (temperature and/or pH) to effect release (decoupling) of the desired constituent from the binding material. This decoupling of the adsorbed constituent allows for recycling of the ferrite particles.

The barium ferrites prepared in this manner are also suitable in other industrial and biological applications, including the use as recording media, as delivery systems for therapeutics (ceramic composition and the like).

EXAMPLES

The following materials and procedures were used in the preparation of the novel monodispersed particles of this invention. Parts and percentages appearing in such examples are by weight unless otherwise stipulated. Apparatus and techniques used in the preparation, characterization and evaluation of these particles are standard or as described hereinafter.

I. Synthesis Procedure - All chemicals were of reagent-grade quality and were used without further purification. The solutions were made up with doubly distilled water from an all-Pyrex apparatus. A stock solution of FeCl_2 (1 mol dm^{-3}) was prepared by dissolving $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ in water under argon atmosphere to prevent air oxidation of Fe^{2+} ion during storage. Argon was

purified from traces of carbon dioxide and oxygen by passing the gas through an alkaline pyrogallol solution.

- 5 A reactive solution is initially prepared from appropriate volumes of 5 mol dm⁻³ KOH and 2 mol dm⁻³ KNO₃ stock solutions. The individual components of this reactive solution were combined in a two-necked round bottom flask, equipped with a gas-outlet and a gas-inlet. Argon was bubbled for 2 hours through a solution of
10 desired concentrations of KOH and KNO₃ in oxygen free distilled water. Subsequently, a calculated amount of a 1 mol dm⁻³ FeCl₂ stock solution was added and bubbling of argon continued for 30 minutes. During this 30 minute period a dark green gelatinous precipitate is formed. A given volume of a 1 mol dm⁻³ Ba(NO₃)₂
15 solution was admixed to the dark-green precipitated Fe(OH)₂ and bubbling of argon was continued for another 30 minutes. Equal amounts of resulting dispersion were distributed into test tubes, which were immediately tightly closed and placed in a constant temperature oven preheated to 90°C for aging. The systems were
20 kept thermostated for 6, 24, and 48 hours. One tube was used to measure the initial pH of the suspension before aging.

- The solid reaction products obtained in the foregoing manner
25 consisted predominantly of a mixture of particles, the main fraction of which was magnetic. To separate the latter, the precipitate was first agitated in an ultrasonic bath, then the magnetic particles were retained at the bottom of the test tube with the aid of a magnet, while the remaining suspension of
30 nonmagnetic particles was decanted. The magnetic portion was resuspended again in doubly distilled water and the washing/decanting procedure repeated several times.

- 35 II. Characterization of Physical Properties - The particles obtained by the described Synthesis Procedure above appeared either

brown or black. Their shape was essentially cubic. The X-ray diffraction patterns were characteristic of barium ferrites as determined by comparisons to ASTM X-ray Data File, confirming the crystalline character of the resulting powders. Particle sizing
5 was performed by scanning electron microscopy (of dry powders). The surface charge characterization of these particles was determined by standard electrokinetic measurements, and surface chemical composition identified by IR spectroscopy. BET gas absorption techniques were used for determination of specific
10 surface area.

Magnetic properties were determined with a vibrating magnetometer on the original barium ferrite powders and on the
15 annealed solids. The coercivity before annealing ranged between 60 and 100 Oe and the saturation magnetization varied between 60 and 80 emu/g, while the squareness was between 0.12 and 0.18, depending on the sample.

20 The particles thus obtained could be physically modified by conventional treatment regimes. For example, to anneal the particles, the calcination was carried out at temperatures ranging between 300 and 900°C for 2-12 hours in air or in an air inert
25 atmosphere (argon). This treatment brought about some rounding of the crystal edges.

**EXAMPLE I - Synthesis of Barium Containing Ferrites Having
Narrow Particle Size Distribution**

- 5 (A) A colloidal dispersion was prepared in accordance with the above Synthesis Procedures utilizing the following materials and under the following conditions:

10 FeCl₂: 0.125 mol dm⁻³
KOH: 0.10 mol dm⁻³
KNO₃: 0.20 mol dm⁻³
Ba(NO₃)₂: 0.010 mol dm⁻³
Initial pH: 6.7, final pH: 2.8
15 Temperature: 90°C
Aging time: 48 hours

The dried powders obtained by the foregoing procedures were
20 readily redispersible in aqueous solutions. Their particle size ranged from between 0.1 and 0.8 μ m (cubic edge) and the size could be altered by varying the concentrations of the solutions used in this synthesis (as illustrated in Tables I & II). As
illustrated in these Tables, the chemical composition of the
25 particles also varied with experimental conditions. Thus, the content of the barium within the ferrite could be varied between 1 to 7% by weight. As noted previously, the substitution of Ba²⁺ for Fe²⁺ in the ferrite crystal lattice, at concentrations in the range of from about 1 to about 7% (w/w), is effective to alter the
30 magnetic properties of these crystalline materials and, thus, substantially reduce particle to particle interaction. This modification of the classical magnetic properties of ferrites, in accordance with the process of this invention, produces submicron particles of narrow size distribution that are capable of
35 formation of stable fluid dispersions.

The following tables illustrate a series of preparations of barium modified ferrite particles. In certain instances, the relative concentrations of starting materials were varied and/or pH and/or aging times (Table I). The results of such variations are indicated in Table II. The results in Table II are specific for procedures involving an aging interval of twenty-four (24) hours.

TABLE I
EXPERIMENTAL CONDITIONS

<u>Initial conc. of sol./mol dm⁻³</u>					Initial	Aging
Ex.	FeCl ₂	KOH	KNO ₃	Ba(NO ₃) ₂	pH	time/hrs
II	0.125	0.200	0.200	0.010	6.92	6,24,48
III	0.125	0.100	0.200	0.200	6.55	6,24,48
IV	0.125	0.200	0.200	0.300	6.81	6,24,48

TABLE II
RESULTS AFTER 24 HOURS OF AGING

Ex.	Color of Precipitate	pH after aging	Test for Barium	Particles Shape	Particles size/micrometers
II	Brown	3.41	+	cubic	0.80
III	Brown	3.02	+	cubic	0.7-0.8
IV	Black	2.22	+	cubic	0.10-0.15

Note: In test for Ba, a "+" sign designates a system where barium was found in obtained precipitate.

The ability to produce acceptable barium modified ferrite particles is believed attributable, in part, to the relative concentrations in starting materials, which directly effect initial pH (the operative pH range being from about 7 to about 11).

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EXAMPLE V

10 A monoclonal antibody (MoAb) specific for a surface marker on human red blood cells, is directly adsorbed onto the colloidal barium ferrite particles of Example I. The particle size of the ferrite particle selected for use in the system was approximately 1.09 micrometers. Sufficient MoAb was contacted with the
15 colloidal particles to effect essentially complete saturations of the particle surface.

Antibody coated barium ferrite particles were then slurried with
20 a whole blood sample for a brief incubation period, a magnet placed in contact with the bottom of the container and magnetic particles allowed to collect upon the inside surface of the container opposite the magnet. After a relative brief interval, the fluid phase of the sample is substantially depleted of both red
25 blood cells and magnetic particles. The fluid phase is then aspirated from the sample container into a Coulter Model S-Plus cell counter and the sample subjected to analysis. The data available from such analysis permitted the identification of two discrete sub-populations of white blood cells. The ability to
30 effectively separate erythrocytes from a whole blood sample in the above manner, without the resort to lytic reagents, offers significant advantages in the recovery of the leukocyte population. More specifically, the magnetic separation which is effected in the above manner has been achieved without
35 substantial alteration in the physiological environment of the sample. Thus, the leukocytes have retained their native physical,

chemical and immunochemical properties. This can be critical in further differentiation of the leukocyte sub-populations from one another and in the continued vitality of these cells.

WHAT IS CLAIMED IS:

1. In a process for the preparation of colloidal particles of barium
5 ferrites by phase transformation of a gel at elevated
temperatures, the improvement comprising:

10 (a) forming a gelatinous dispersion from an aqueous
solution of a ferrous salt, potassium hydroxide and
potassium nitrate under non-oxidizing conditions;

(b) contacting said gelatinous dispersion with an aqueous
solution of a barium salt under non-oxidizing conditions;
and

15 (c) aging the dispersion/solution at elevated temperatures
for an interval sufficient to effect a phase transformation of
the gelatinous dispersion to crystalline solids having barium
incorporated within a ferrite crystal lattice.

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2. The improved process of claim 1, wherein the barium salt is a
barium nitrate.

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3. The improved process of claim 1, wherein the aging of the
gelatinous solids is performed at a temperature in the range of
from about 80 to about 90°C for a period sufficient to effect
essentially complete transformation of a barium ferrite gel to the
30 barium ferrite solid.

4. The improved process of claim 3, wherein the aging of
gelatinous solids is performed in a sealed container.

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5. A composition comprising monodispersed particles having ferrite crystalline lattice, from about 1 to about 7 weight percent barium ions within said lattice, a particle size in the range from about 0.1 to about 1.0 micrometers superparamagnetic response to a magnetic field, a coercivity in the range of from about 60 and 100 Oe, essentially cuboidal in shape and capable of formation of a stable colloidal dispersion in aqueous medium.

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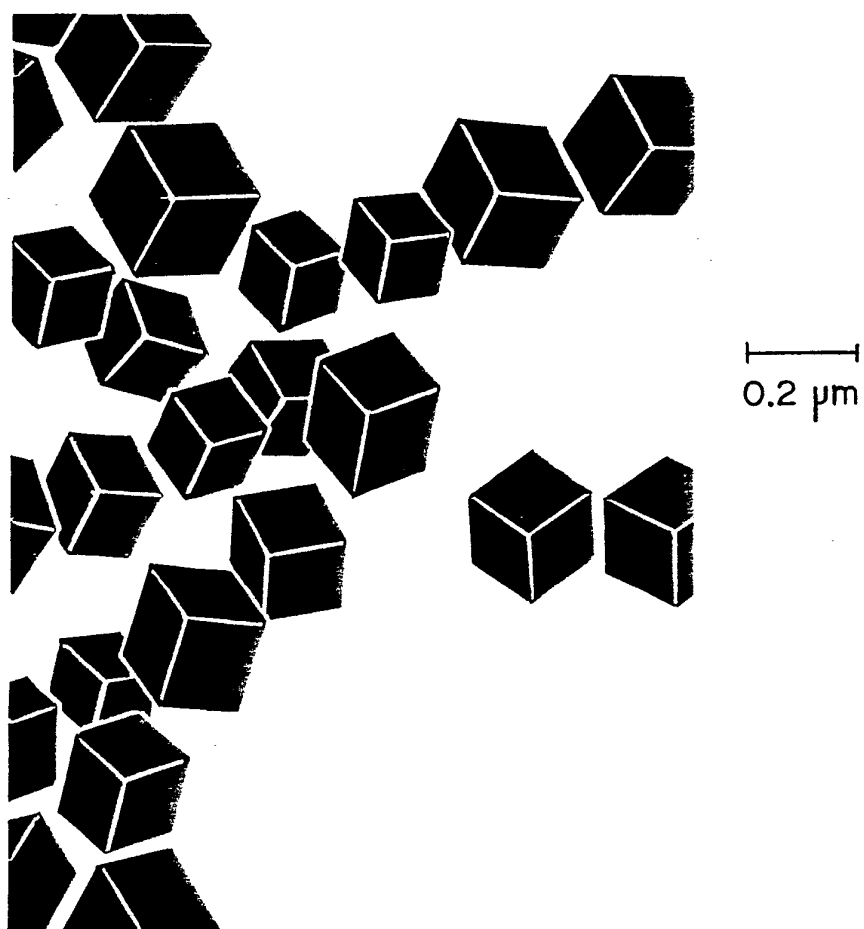


FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No PCT/US88/00083

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC(4) B01J 13/00, C04B 35/26 U.S.C1. 252/62.63		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
US	252/62.63, 313.1, 315.01; 423/594	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category *	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
X	US, A, 3,634,254 (MICHELI) 11 January 1972, see Table, Specimen numbers 1 and 2 and column 3, lines 52-56	5
A	US, A, 4,529,524 (NAGAI, HORIIISHI, KIYAMA and TAKADA) 16 July 1985, see the entire document.	1-5
* Special categories of cited documents: ¹⁵ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Δ" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ²	Date of Mailing of this International Search Report ²	
18 February 1988	12 APR 1988	
International Searching Authority ¹	Signature of Authorized Officer ²⁰	
ISA/US	Jack Cooper	