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(54) Title: LIGAND MODIFIED POLY OXO-HYDROXY METAL ION MATERIALS, THEIR USES AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: Ligand-modified poly oxo-hydroxy metal ion materials and their uses are disclosed, in particular for nutritional, medical, cosmetic or biologically related applications for example for the treatment of a deficiency related to a component of the material or for the removal of an endogenous substance capable of binding to the material. The present invention further relates to processes for preparing the materials and optimising their physicochemical properties and their medical uses.

Ligand Modified Poly Oxo-hydroxy Metal Ion Materials, Their Uses and Processes For Their Preparation

Field of the Invention

5 The present invention relates to ligand-modified poly oxo-hydroxy metal ion materials and their uses, in particular for nutritional, medical, cosmetic or biologically related applications for example for the treatment of a deficiency related to a component of the material or for the removal

10 of an endogenous substance capable of binding to the material. The present invention further relates to processes for preparing the materials and optimising their physico-chemical properties and their medical uses.

15 Background of the Invention

Iron deficiency is the most common micronutrient deficiency in the world today, affecting more than 4 billion people globally. It is estimated that 2 billion people - over 30% of the world's population - are anaemic

20 (WHO, http://www.who.int/nut/ida.htm, accessed 20 December 2005). Iron deficiency is not a problem solely confined to the developing world. Epidemiological surveys performed in European countries show that iron deficiency concerns 10-30% of menstruating women and iron deficiency

25 anaemia (IDA) 1.5 to 14% (Hercberg et al., 2001; Goddard et al., 2005). Iron deficiency anaemia can result in decreased intellectual performance, decreased physical capacity, alterations in temperature regulation, alterations in the development of gestation, and

30 compromised immune and metabolic functions, all of which impact upon quality of life and health economics (Edgerton et al, 1979; Hercberg et al, 2001; Scholz et al, 1997). The standard first line treatment for simple mild IDA is, commonly, supplementation with oral ferrous sulphate.

More complex or severe iron deficiencies may be treated
with intravenous iron or blood transfusions, but
subsequent management is with oral iron preparations. In
spite of the widespread use of oral iron preparations

5   their effectiveness is poor. This is due to: (i) variable
absorption characteristics and (ii) side effects resulting
in poor compliance. Strategies for the prevention of iron
deficiency include the use of iron-fortified foods.
Commonly used fortificants include ferrous sulphate,

10   ferric chloride, ferric sodium EDTA and ferric
pyrophosphates. However, despite fortification
strategies, iron deficiency remains a common global
problem and, thus, cheap and effective supplements are
required.

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WO 2005/000210 describes the synthesis of high molecular
weight iron saccharidic complexes formed when freshly
precipitated iron hydroxides are subsequently aggregated
with sugar molecules to form secondary complexes. These

20   complexes are acknowledged to be agglomerated mixtures.

WO 03/031635 relates to an enzymatic method to prepare
calcium gluconate where the crystals are high purity and
high solubility.

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US 2005/0209322 describes a process for making sodium
ferric gluconate complexes for i.v. iron administration
that requires the initial step of preparing ferric
hydroxide with a subsequent step of reacting with the

30   ligand, sodium gluconate. US 2005/0209187 relates to a
similar process for making iron sucrose complexes rather
than iron gluconate complexes.

US 2003/0049284 describes a method for increasing the

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solubility of salts of alpha hydroxy carboxylic acids, by
reaction with an alpha amino acid, such that the material
would have improved nutritional supplementation
properties.

US 3,679,377 relates to the provision of an agronomically
effective source of iron in a plant nutrient solution as a
soluble ferric sulfato-hydroxyl complex anion.   The
materials produced are conventional ligand-metal ion
complexes.

DE 20 2005 014332 U1 discloses metal-organic nanopowders
for use in materials engineering such as the formation of
polymeric composites through injection spraying or coating
of the nanopowders into or onto an existing material.

Jugdaohsingh et al. (2004) describes a critical
precipitation assay that utilises a solution phase
reaction in which, at peri-neutral pH, organic acids
compete with the formation of the oxo-bridges between
aluminium atoms in the polymerisation process, limiting
the growth and decreasing the branching of the polyhydroxy
aluminium species (Jugdaohsingh et al. (2004); Powell et
al. (2004)).   The assay is usable because the efficiency
of the ligand in interrupting this process is related to
its affinity for aluminium.   It was also noted in this
work that during solution-phase growth of polyhydroxy
aluminium species, the 'competing ligand' becomes
incorporated within the polymer.

Summary of the Invention

Broadly, the present invention relates to processes for
preparing solid ligand-modified poly oxo-hydroxy metal ion
materials and optimising their physico-chemical

properties. The compositions generally comprise solid
ligand-modified poly oxo-hydroxy metal ion materials
represented by the formula $(M_xL_y(OH)_n)$, wherein M represents
one or more metal ions, L represents one or more ligands

5   and OH represents oxo or hydroxy groups, and may be used
in nutritional, medical, cosmetic or other biologically
relevant applications. These include delivery of the
materials *per se*, or the use of the materials for the
delivery of a component of the material, such as the metal

10   ion, as a supplement or fortificant or food additive, or
the use of the material to remove or inhibit a component
and ameliorate any undesirable effects that it may cause.

The solid ligand-modified poly oxo-hydroxy metal ion

15   materials disclosed herein constitute new forms of matter
that have not been described previously in the art for
such uses and which can be defined, *inter alia*, with
reference to structural, spectroscopic or compositional
parameters (i.e. using the analytical signatures of the

20   materials) or by the processes by which the materials have
been obtained. Thus, while metal oxo-hydroxide powders
are very well known in the field of inorganic chemistry,
in the present invention they are modified by biologically
compatible ligands (i.e. other than oxo or hydroxy groups)

25   to alter their physical and/or chemical properties to
produce new materials and for use in new applications. As
part of the unique processes used to optimise and produce
the materials, it is notable that (i) the materials are
recovered as a solid following precipitation from solution

30   (e.g. aqueous solution) and (ii) that the ligand
incorporation into the poly oxo-hydroxy metal ion solid
phase is, for at least one of the ligands involved,
through formal, identifiable bonding.

Thus, by way of example, the present invention differs
from the critical precipitation assay disclosed in
Jugdaohsingh et al. (2004) because that assay was carried
out in solution and the precipitated material was not

5   subsequently isolated or further employed. In contrast,
in the present invention, the formation of the polymers
continues to the point of precipitation and it is the
solid materials that are then characterised and used in a
variety of applications. Furthermore, the present

10   inventors have found that the dried solid phase materials
exhibit physico-chemical properties that are sensitively
dependent upon the exact solution conditions used in the
production of the material, for example the choice of
ligand(s) and their concentration versus that of the metal

15   ion. These materials are not, as might be expected,
simply metal oxides/hydroxides with subtly differing
degrees of crystallisation, and therefore subtly differing
material properties, but instead the ligand(s) incorporate
within the matrix of the poly oxo-hydroxy metal ion

20   precipitate through substitution of oxo or hydroxyl
groups. This is generally non-stoichiometric but,
nonetheless, occurs through formal bonding, and leads to
distinct and novel alterations in the chemistry,
crystallinity and material properties of the solid. Thus,

25   the compositions produced according to the present
invention are chemically novel entities and are not simply
the results of altering the degree of crystallinity of the
metal oxides/hydroxides. Surprisingly, the conditions of
precipitation do not easily predict the properties of the

30   solid, such as the conditions of its re-dissolution and,
for example, using this system it is perfectly possible to
precipitate a material at pH 7 which can also be
completely re-aquated at pH 7 using only a slightly larger
volume of solution or by making a subtle change to the

solution chemistry. Nonetheless, under the exact same
reaction conditions, material is formed with highly
reproducible properties. Thus, the idea underlying the
present invention is that this process can be used to
5   produce M:L:OH solids with precisely tailored physico-
chemical characteristics for multiple biological
applications such as in medicine, nutrition or cosmetics,
where specific material characteristics are required.
This approach has not been previously disclosed and it is
10 surprising that such subtle changes in the precipitation
process allow suitable changes in the solid phase that can
be used to produce such precisely tailored physico-
chemical (e.g. dissolution) characteristics or properties.

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Accordingly, in a first aspect, the present invention
provides a process for producing a solid ligand-modified
poly oxo-hydroxy metal ion material ($M_xL_y(OH)_n$) wherein:

M represents one or more metal ions selected from Ag^{2+},
20 Al^{3+}, Au^{3+}, Be^{2+}, Ca^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Eu^{3+}, Fe^{3+}, Mg^{2+}, Mn^{2+},
Ni^{2+}, Sr^{2+}, V^{5+}, Zn^{2+} and Zr^{2+},

L represents one or more ligands which comprise a
ligand selected from a carboxylic acid, maltol, ethyl
maltol, vanillin, bicarbonate, sulphate, phosphate,
25 silicate, borate, molybdate, selenate, tryptophan,
glutamine, proline, valine, histidine, folate, ascorbate,
pyridoxine, niacin, adipate, acetate, glutarate, dimethyl
glutarate, pimelate, succinate, benzoate and propionate, and
OH represents oxo or hydroxy groups,
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wherein the material has a polymeric structure and
wherein the gross solid ligand-modified poly oxo-hydroxy
metal ion material has one or more reproducible physico-
5   chemical properties and displays M-L bonding for at least
one ligand that can be detected by physical analytical
techniques,

wherein the polymeric structure in which the M, L and
oxo or hydroxy groups are distributed within the solid phase
10   structure is such that the substitution of the oxo or
hydroxy groups by the one or more ligands is substantially
random,

the process comprising:

(a) mixing the metal ions M and the ligands L at a
15   first pH(A) at which the components are soluble;

(b) changing the pH(A) to a second pH(B) to cause a
solid precipitate of the solid ligand-modified poly oxo-
hydroxy metal ion material to be formed; and

(c) separating, and optionally drying, the solid
20   ligand-modified poly oxo-hydroxy metal ion material produced
in step (b).

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By way of example, the materials produced by the processes
of the present invention may be employed in nutritional,
medical, cosmetic or other biologically relevant
applications. A preferred example of such an application

5   is the use of the material to deliver the material, or a
part thereof such as a metal ion or a ligand, to a
subject, for example to correct a deficiency in the
component or so that the component provide a beneficial
effect to the subject. An alternative example is the use

10   of a material to bind or sequester a component that may be
present in the system into which the material is
introduced, thereby to remove or inhibit that component
and ameliorate any undesirable effects that it may cause.
In view of this, the process may comprise the further step

15   of formulating the solid ligand-modified poly oxo-hydroxy-
metal ion material in a composition for administration to
a subject.

In any aspect of the present invention, the processes

20   disclosed herein may be employed to engineer or optimise
the physico-chemical properties of the material, for
example to control the dissolution profile or the
adsorption profile, or a similar property of the material,
and it is a considerable advantage of the processes

25   described herein that they are highly amenable to such
optimisation studies.

Accordingly, in a further aspect, the invention provides a
process for producing a solid ligand-modified poly oxo-

30   hydroxy metal ion material and optimising a desired physico-
chemical property of the material to adapt it for a
nutritional, medical, cosmetic or biologically related
application, wherein the solid ligand-modified poly oxo-
hydroxy metal ion material is represented by the formula
$(M_xL_y(OH)_n)$, wherein

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M represents one or more metal ions selected from Ag^{2+}, Al^{3+}, Au^{3+}, Be^{2+}, Ca^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Eu^{3+}, Fe^{3+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, Sr^{2+}, V^{5+}, Zn^{2+} and Zr^{2+},

L represents one or more ligands which comprise a ligand selected from a carboxylic acid, maltol, ethyl maltol, vanillin, bicarbonate, sulphate, phosphate, silicate, borate, molybdate, selenate, tryptophan, glutamine, proline, valine, histidine, folate, ascorbate, pyridoxine, niacin, adipate, acetate, glutarate, dimethyl glutarate, pimelate, succinate, benzoate and propionate, and

OH represents oxo or hydroxy groups,

wherein the material has a polymeric structure and wherein the gross solid ligand-modified poly oxo-hydroxy metal ion material has one or more reproducible physico-chemical properties and displays M-L bonding for at least one ligand that can be detected by physical analytical techniques,

wherein the polymeric structure in which the M, L and oxo or hydroxy groups are distributed within the solid phase structure is such that the substitution of the oxo or hydroxy groups by the one or more ligands is substantially random,

the process comprising:

(a) mixing the metal ion(s) M and the ligand(s) L in a reaction medium at a first pH(A) at which the components are soluble;

(b) changing the pH(A) to a second pH(B) to cause a solid precipitate of the ligand-modified poly oxo-hydroxy metal ion material to be formed;

(c) separating, and optionally drying, the solid ligand-modified poly oxo-hydroxy metal ion material produced in step (b);

(d) testing the desired physico-chemical characteristic(s) of the precipitated solid ligand-modified poly oxo-hydroxy metal ion material; and

(e) repeating steps (a) to (d) as required by varying one or more of:

(i) the identity or concentration of the metal ion(s) (M) and/or the ligand(s) (L) supplied in step (a); and/or

(ii) the ratio of metal ion(s) (M) to ligand(s) (L) supplied in (a); and/or

(iii) pH(A); and/or

(iv) pH(B); and/or

(v) the rate of change from pH(A) to pH(B); and/or

(vi) the presence or concentration of a buffer;

thereby to produce a solid ligand-modified poly oxo-hydroxy metal ion material having the desired physico-chemical property.

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Examples of possible metal ions and ligands are provided below. In some embodiments, the materials of the present invention may employ more than one species of metal ion or ligand, for example two, three, four or five different species of metal ion or ligand. In addition, in some embodiments, the ligand(s) L may also have some buffering capacity as described in more detail below.

As part of the process for optimising a desired physico-chemical property of the material to provide for its application, it may be desirable to vary physical or chemical reaction conditions used in the process for making the solid ligand-modified poly oxo-hydroxy metal ion material, for example the temperature of the reaction, the ionic content and strength of the solution, buffering capacity of the solution (e.g. using a buffer such as MOPS as in the examples), or the conditions and apparatus used to mix the reactants, to determine whether and how this affects one or more properties of the material.

In a further aspect, the present invention provides a process for making solid ligand-modified poly oxo-hydroxy metal ion materials for administration to a subject, the process comprising having optimised a solid ligand-modified poly oxo-hydroxy metal ion material according to the process as disclosed herein, the further step of manufacturing the solid ligand-modified poly oxo-hydroxy metal ion material in bulk and/or formulating it in a composition.

In one embodiment, the processes of the present invention have been employed by way of example to optimise and produce ferric iron compositions, e.g. for use as iron supplements, fortificants or therapeutics. As is

generally used in the art, supplements are nutritional
compositions that are taken by subjects to correct,
prevent or insure against a deficiency in a mineral or
other dietary component. A fortificant is somewhat

5   similar to a supplement but is generally applied to
compositions that are added routinely to foodstuffs to
improve their nutritional value, for example the addition
of iodide to table salt, B group vitamins to breakfast
cereals or iron to cereal products. In addition,

10   compositions may be used therapeutically, usually in the
context of preventing or treating a pathology or condition
caused by the deficiency in a mineral or other dietary
component. In the case of iron, the ferric iron
compositions disclosed herein may be employed as

15   supplements, fortificants or as therapeutic compositions,
for example in the treatment of iron deficiency in
pregnant or pre-menopausal women, cancer or inflammatory
disease. Such therapeutics are typically administered
orally or intravenously.

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Accordingly, in one aspect, the present invention further
provides a ferric iron composition for administration to a
subject which comprises a solid ligand-modified poly oxo-
hydroxy metal ion material represented by the formula

25      $(M_xL_y(OH)_n)$, wherein M represents one or more metal ions
that comprise Fe^{3+} ions, L represents one or more ligands
and OH represents oxo or hydroxy groups and wherein the
material has a polymeric structure in which the ligands L
are substantially randomly substituted for the oxo or

30   hydroxy groups, the solid ligand-modified poly oxo-hydroxy
metal ion material having one or more reproducible physico-
chemical properties and demonstrable M-L bonding using
physical analysis.

Generally a useful dietary iron supplement needs to share

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some characteristics of simple ferrous salts, namely cost
relatively little and be reasonably well absorbed, but at
the same time, be less redox active and hence lead to a
low incidence of side-effects. Some ferric salts do not

5   suffer from this disadvantage as they are already
oxidised, and are therefore less prone to redox activity
because the initiation of iron reduction in the
gastrointestinal lumen is less favourable than the
initiation of iron oxidation. Moreover, the controlled

10   mucosal reduction of ferric iron, via the mucosal protein
DcytB, may provide a rate-limiting step for the entry of
iron to the circulation, which would lower the production
of circulating non-transferrin bound iron (NTBI). NTBI
may lead to oxidative damage in the circulation,

15   endothelium and the more vascular organs. However, simple
ferric salts are not efficient supplements because their
rapid dissolution in the stomach is followed by
concentration-dependent oxo-hydroxy polymerisation in the
small bowel which inhibits their absorption. Thus, while

20   ferric iron salts, typically ferric chloride., have been
tried as fortificants in certain foods, these are poorly
absorbed at supplemental or therapeutic doses due to
uncontrolled delivery of ferric ions into the small bowel
at bolus doses. Chelation of ferric iron, for example

25   with maltol, may help overcome this small bowel solubility
issue for bolus doses, but has not proven commercially
viable due to production costs (WO 03/097627). In
addition there are concerns over the safety of chelators
such as maltol. The compositions disclosed herein are

30   engineered to overcome such absorption, safety, side
effect and production cost problems. Thus, these solid
ligand-modified poly oxo-hydroxy metal ion materials can
be tailored to have distinct dissolution profiles in the
stomach environment compared to the small bowel

environment. In this way, rapid dissolution in the
stomach that then leads to undesirable bolus delivery of
iron in the small bowel, as occurs for simple ferrous and
ferric salts, can be avoided in the design of these
5   materials. Both the pH of dissolution and the rate of
dissolution can be engineered to match requirements.
Potentially, these solid phase ligand-modified poly oxo-
hydroxy ferric iron materials could be tailored to 'sense'
iron requirements. Absorption of iron from the gut lumen
10   and into the circulation occurs in individuals who require
iron. In those who do not require iron there will be
little or no absorption and more iron will remain in the
lumen. The dissolution or disaggregation of these solid
phase ligand-modified poly oxo-hydroxy ferric iron
15   materials could be 'set' such that they dissolve or
disaggregate efficiently in an environment that is low in
aquated iron, but inefficiently in an environment that is
high in aquated iron. This again would help to reduce
side effects without compromising absorption in those who
20   need iron. Whether these materials are designed to
dissolve or disaggregate under gastrointestinal conditions
depends upon the optimal mode of iron absorption in the
gut as both soluble iron and very small aquated
particulate iron could both be absorbed but, either way,
25   the ligand-modified poly oxo-hydroxy ferric iron materials
could be so designed.

In a further aspect, the present invention provides the
use of a composition of a solid ligand-modified poly oxo-
30   hydroxy metal ion material ($M_xL_y(OH)_n$) as obtainable by the
processes disclosed herein for the preparation of a
medicament for therapeutic delivery of the metal ion to
the subject. Alternatively, the present invention
provides a solid ligand-modified poly oxo-hydroxy metal

ion material $(M_xL_y(OH)_n)$ as obtainable by the processes disclosed herein for the delivery of the metal ion to a subject.

5   Examples of the uses of the solid ligand-modified poly oxo-hydroxy metal ion materials disclosed herein include, but are not limited to, uses as: dietary mineral supplements and fortificants; therapeutic mineral supplements (e.g. as administered by i.v. and oral

10   routes); drugs, nutrients or cosmetic carriers/co-complexes; phosphate binding agents; other binding or sequestering applications; food additives; anti-perspirants; sun-protection agents; vaccine adjuvants; immuno-modulatory agents; direct cosmetic applications

15   including exfoliating agents; bone and dental filler/cements; implant materials including brachytherapy, and imaging and contrast agents.

     Embodiments of the present invention will now be described

20   by way of example and not limitation with reference to the accompanying figures and examples.

Brief Description of the Figures

Figure 1: Examples of the effects of weak (succinate,

25   closed square), intermediate (malate, open circle) and strong (maltol, closed triangle) ligands on the formation of solid ligand-modified poly oxo-hydroxy metal ion material (A) and the disaggregation of the wet solid materials in buffers at pH 6 (black bars) and pH 4 (grey

30   bars) (B), using the method described in "screening assay". The ratios indicated are M:L ratios that were selected for formation of the materials. The iron concentration in the initial solution (prior to precipitation) was 27mM.

Figure 2: Effect of different ligands on the evolution of
precipitation of solid ligand-modified poly oxo-hydroxy
metal ion materials with increasing pH as described in
5   titration protocol: no ligand (open circle), tartaric acid
(closed square) and malic acid (closed triangle). All
were prepared in 50mM MOPS and 0.9% w/v NaCl. The iron
concentration in the initial solution (prior to
precipitation) was 27mM.

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Figure 3: Example of the effect of varying the pH of the
final solution during the preparation of the solid ligand-
modified poly oxo-hydroxy metal ion materials on the
disaggregation of these wet materials at different pHs in
15   the buffers indicated. The materials, namely FeOHM-1:2-
MOPS50, were prepared following the preparation protocol
described in Methods with 0.9% w/v NaCl and final pH 6
(grey bars), pH 7 (striped bars) or pH 8 (black bars). The
percentage precipitation obtained was 10%, 30% and 48%
20   respectively. The iron concentration in the initial
solution (prior to precipitation) was 27mM.

Figure 4: Example of how the presence of an electrolyte in
the preparation of the solid ligand-modified poly oxo-
25   hydroxy metal ion materials can affect the disaggregation
of the material at four different pHs in the buffers
indicated. Materials were prepared following the
preparation protocol described in Methods and oven dried.
The materials, namely FeOHT-4:1-MOPS50, were prepared at a
30   final solution pH of 6.5 and formed in the absence of
electrolyte (grey bars, n=2) or in the presence of 0.9%
w/v NaCl (stripped bars, n=1); the percentage
precipitation obtained was 97% and 98% respectively (A).
The material, namely FeOHT-2:1-Niacin50, were prepared at

a final solution pH of 3.2 in the absence of electrolyte
(grey bars, n=2) or in the presence of 0.9% w/v KCl (black
bars, n=2); the percentage precipitation obtained was 88%
and 91% respectively (B). The iron concentration in the
5 initial solution (prior to precipitation) was 27mM.

Figure 5: Example of how drying the solid ligand-modified
poly oxo-hydroxy metal ion materials can affect its
disaggregation at four different pHs in the buffers
10 indicated. The materials, namely FeOHT-4:1-MOPS50, was
prepared following the preparation protocol described in
method with a final solution pH of 6.5 in the absence of
electrolyte. The percentage precipitation obtained was
97%. The solid phase was divided into three aliquots and
15 either oven dried (grey bars, n=2), or freeze-dried (black
bars, n=2) or used wet (stripped bars, n=2). Note: some
error bars are too small to be viewed. Data shown in grey
bars have been shown previously in Figure 4A. The iron
concentration in the initial solution (prior to
20 precipitation) was 27mM.

Figure 6: Example of the effect of "ligand B" on the
evolution of precipitation of the solid ligand-modified
poly oxo-hydroxy metal ion material with increasing pH in
25 presence (i) or absence (ii) of "ligand A", namely
tartaric acid, at M:L$_A$ ratio 4:1. "Ligand B" showed were
either 50mM adipic acid (squares) or 50mM MOPS
(triangles). All titrations were performed following the
protocol described in the methods and in the absence of
30 electrolyte. The iron concentration in the initial
solution (prior to precipitation) was 27mM.

Figure 7: Example of the effect of ligand B on the

disaggregation of oven dried solid ligand-modified poly
oxo-hydroxy metal ion materials in four different buffers.
Tartrate-modified poly oxo-hydroxy ferric materials at
M:L_A ratio 4:1, with tartrate being ligand A (L_A), were
5   prepared in the presence of different ligands B being 50mM
MOPS (grey bars, n=2), 20 mM benzoic acid (black bars,
n=3) or 50mM niacin (stripped bars, n=3) following the
preparation protocol described in Methods in the absence
of electrolyte. The percentage precipitation obtained was
10   97%, 94% and 100% respectively. Note: some error bars are
too small to be viewed. The data indicated in grey bars
have been shown previously in Figure 4A and 5.

Figure 8. Energy dispersive X-ray microanalysis (EDX) of a
15   ligand-modified poly oxo-hydroxy metal ion material
(FeOHT-3:1-Ad20) showing the composition of the material
to be predominantly Fe and O with incorporation of C plus
very small additions of Na and Cl from the electrolyte
used (the Cu signal is due to the support grid).
20

Figure 9. Typical infrared spectra of solid ferric oxo-
hydroxide in (A), the tartrate-modified ferric oxo-
hydroxide in (B) (i.e. the ligand-modified poly oxo-
hydroxy metal ion material; FeOHT-4:1) and tartaric acid
25   in (C). The band corresponding to the C=O stretch of
tartaric acid (1712 cm^{-1} in spectrum C) is replaced by two
bands (1356 and 1615 cm^{-1} in spectrum B) showing the
presence of bonding between the carboxylate group of
tartaric acid and iron in the FeOHT-4:1 material. Note
30   also the presence of a broad band circa 3350 cm^{-1} due to -
OH stretch in spectra A and B.

Figure 10. Percentage of iron disaggregation (without
ultrafiltration, A) and dissolution (with ultrafiltration,

B) after simulated passage through the stomach for the
time indicated. Prior art is shown in closed symbols,
namely ferric oxo-hydroxide (closed squares), Maltofer
(closed circles), ferrous sulphate (closed triangles).

5   The ligand-modified poly oxo-hydroxy metal ion materials
are shown in open symbols, namely FeOHT-3:1-Ad20 (open
diamonds) and FeOHM-4:1-Bic25 (open triangles). Error
bars represent STDEV (note that certain error bars are too
small to be visible).

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Figure 11. Aberration corrected high angle annular dark
field scanning transmission electron microscopy
(superSTEM) high resolution images showing that organised,
crystalline regions are less frequently discernible in
15   ligand-modified poly oxo-hydroxy metal ion materials (e.g.
FeOH-TRP15 (B) and especially in FeOHT-2:1-TRP15 (C)) than
in similar sized unmodified ferric iron oxo-hydroxide (A).

Figure 12. X-ray diffraction pattern of Maltofer (A) and
20   the ligand-modified poly oxo-hydroxy metal ion material
FeOHT-3:1-Ad20 (B) showing a clear presence of iron oxo-
hydroxide crystal structure in Maltofer and a clear lack
of detectable crystalline structure in FeOHT-3:1-Ad20,
apart from the co-precipitated electrolyte, sodium
25   chloride. Reference lines for iron oxide and sodium
chloride are shown below each graph for clarity.

Figure 13: Examples of the serum iron increase (A) and
percentage iron absorption (B) in human volunteers
30   following ingestion of ferrous sulphate, ferric oxo-
hydroxide or different solid ligand-modified poly oxo-
hydroxy ferric materials. A: ferrous sulphate (open
triangle, n=30); FeOHT-3:1-Ad20 (+ symbol, n=4); FeOHT-
2:1-TRP15 (- symbol, n=4); FeOHAdipate100 (x symbol, n=2);

FeOHHistidine100 (closed square, n=2); FeOHM-4:1-Bic25
(open square, n=3); FeOHGluconic20 (closed triangle, n=3);
FeOHT-2:1-Niacin50 (open circle, n=3); FeOH (closed
circle, n=2). B: Percentage iron absorption (calculated

5   as the red blood cell incorporation of ^{58}Fe divided by
0.80) from ferric oxo-hydroxide or the solid ligand-
modified poly oxo-hydroxy ferric materials (black bars)
compared with estimated absorption of iron from ferrous
sulphate for the same group of study participants (open

10   bars). Error bars represent the SEM. Number of each
pairing vary from 2 to 4, except for ferrous sulphate in
the FeOHHistidine100 group which was 1.

Figure 14: Disaggregation of iron during simulated passage

15   through the stomach and duodenum from (A) prior art
compounds: ferric pyrophosphate (Closed diamond), ferric
chloride (Closed square), ferric tri-maltol (Closed
triangle), ferrous bisglycinate (Open square); and (B) a
selection of compounds tested in our *in vivo* study in

20   Figure 13: ferrous sulphate (Open square), FeOHT-3:1-Ad20
(Open diamond) and FeOHM-4:1-Bic25 (Closed circle). For
details of the protocol see In vitro gastrointestinal
digestion assay in the Methods.

25   **Figure 15:** Examples of the effect of different ligands, at
differing M:L ratios, on the percentage of iron
disaggregation (A) and on the percentage of iron
dissolution (B) of solid ligand-modified poly oxo-hydroxy
metal ion materials, after 30 minutes incubation at

30   gastric pH 1.2 (black bars, n=3) or 60 minutes incubation
at intestinal pH 7.0 (open bars, n=3); error bars
represent standard deviations.

Figure 16: Evolution of the formation of the ligand-

modified poly oxo-hydroxy ferric materials, namely FeOHT-
2:1-Ad20, with increasing pH, as described in the
titration protocol in Methods, and expressed as the
percentage of total iron in the starting solution.

5   Percentage iron in the aggregated material is shown by the
closed triangles while the percentage of iron in both the
aggregated and aquated particulate materials is shown by
the closed square. Note: the remaining iron (i.e. the
iron that is not in the aggregated or aquated particulate

10   form) is in the soluble phase.

Figure 17: Example of the effect of ligand, M:L ratio, and
final solution pH of formation on the disaggregation of
the tartrate-modified poly oxo-hydroxy ferric materials

15   through the modified *in vitro* gastrointestinal digestion
assay described in methods. Bars represent the particle
size distribution of the disaggregated materials as a
percentage of total iron in solid phase. Size ranges
determined were <5nm (stripped section), 5-20nm(grey

20   section), 20-300 nm (black section), and 1-10 μm (white
section).

Detailed Description

The Metal Ion (M)

25   The solid ligand-modified poly oxo-hydroxy metal ion
materials may be represented by the formula $(M_xL_y(OH)_n)$,
where M represents one or more metal ions. Normally, the
metal ion will originally be present in the form of a salt
that in the preparation of the materials may be dissolved

30   and then induced to form poly oxo-hydroxy co-complexes
with ligand (L) some of which is integrated into the solid
phase through formal M-L bonding, i.e. not all of the
ligand (L) is simply trapped or adsorbed in the bulk
material. The bonding of the metal ion in the materials

can be determined using physical analytical techniques
such as infrared spectroscopy where the spectra will have
peaks characteristic of the bonds between the metal ion
and the ligand (L), as well as peaks characteristic of
5   other bonds present in the material such as M-O, O-H and
bonds in the ligand species (L). Preferred metal ions (M)
are biologically compatible under the conditions for which
the materials are used and are readily precipitatable from
aqueous solution by forming oxo-hydroxides. Examples of
10   metal ions include iron, calcium, magnesium, zinc, copper,
manganese, chromium and aluminium ions. A particularly
preferred metal ion is ferric iron (Fe^{3+}).

By way of reference to the ferric iron compositions
15   disclosed herein, the presence of formal bonding is one
aspect that mainly distinguishes the materials from other
products such as "iron polymaltose" (Maltofer) in which
particulate crystalline iron oxo-hydroxide is surrounded
by a sugar shell formed from maltose and thus is simply a
20   mixture of iron oxo-hydroxide and sugar at the nano-level
(Heinrich (1975); Geisser and Müller (1987); Nielsen et al
(1994; US Patent No: 3,076,798); US20060205691). In
addition, the materials of the present invention are metal
poly oxo-hydroxy species modified by non-stoichiometric
25   ligand incorporation and should therefore not be confused
with the numerous metal-ligand complexes that are well
reported in the art (e.g., see WO 03/092674, WO
06/037449). Although generally soluble, such complexes
can be precipitated from solution at the point of
30   supersaturation, for example ferric trimaltol, Harvey et
al. (1998), WO 03/097627; ferric citrate, WO 04/074444 and
ferric tartrate, Bobtelsky and Jordan (1947) and, on
occasions, may even involve stoichiometric binding of
hydroxyl groups (for example, ferric hydroxide saccharide,

US Patent No: 3,821,192). The use of hydroxyl groups to balance the charge and geometry of metal-ligand complexes is, of course, well reported in the art (e.g. iron-hydroxy-malate, WO 04/050031) and unrelated to the solid

5 ligand-modified poly oxo-hydroxy metal ion materials reported herein.

Without modification, the primary particles of the materials have metal oxide cores and metal hydroxide

10 surfaces and within different disciplines may be referred to as metal oxides or metal hydroxides. The use of the term 'oxo-hydroxy' or 'oxo-hydroxide' is intended to recognise these facts without any reference to proportions of oxo or hydroxy groups. Hydroxy-oxide could equally be

15 used therefore. As described above, the materials of the present invention are altered at the level of the primary particle of the metal oxo-hydroxide with at least some of the ligand L being introduced into the structure of the primary particle, i.e. leading to doping or contamination

20 of the primary particle by the ligand L. This may be contrasted with the formation of nano-mixtures of metal oxo-hydroxides and an organic molecule, such as iron saccharidic complexes, in which the structure of the primary particles is not so altered.

25

The primary particles of the ligand-modified poly oxo-hydroxy metal ion materials described herein are produced by a process referred to as precipitation. The use of the term precipitation often refers to the formation of

30 aggregates of materials that do separate from solution by sedimentation or centrifugation. Here, the term "precipitation" is intended to describe the formation of all solid phase material, including aggregates as described above and solid materials that do not aggregate

but remain as non-soluble moieties in suspension, whether
or not they be particulate, colloidal or sub-colloidal
(nanoparticulates). These latter solid materials may also
be referred to as aquated particulate solids.

5

In the present invention, reference may be made to the
modified metal oxo-hydroxides having polymeric structures
that generally form above the critical precipitation pH.
As used herein, this should not be taken as indicating

10   that the structures of the materials are polymeric in the
strict sense of having a regular repeating monomer unit
because, as has been stated, ligand incorporation is,
except by co-incidence, non-stoichiometric. The ligand
species is introduced into the solid phase structure by

15   substituting for oxo or hydroxy groups leading to a change
in solid phase order. In some cases, for example the
production of the ferric iron materials exemplified
herein, the ligand species L may be introduced into the
solid phase structure by the substitution of oxo or

20   hydroxy groups by ligand molecules in a manner that
decreases overall order in the solid phase material.
While this still produces solid ligand modified poly oxo-
hydroxy metal ion materials that in the gross form have
one or more reproducible physico-chemical properties, the

25   materials have a more amorphous nature compared, for
example, to the structure of the corresponding metal oxo-
hydroxide. The presence of a more disordered or amorphous
structure can readily be determined by the skilled person
using techniques well known in the art. One exemplary

30   technique is X-ray diffraction (XRD) which will produce an
X-ray diffraction pattern for the ferric iron materials
exemplified herein having poorly identifiable peaks for L
or MO/MOH, XRD relying on a regular arrangement of atoms
to diffract the X-rays and produce a pattern.

Alternatively or additionally, a decrease in the
crystallinity of the structure of the material may be
determined by high resolution transmission electron
microscopy. High resolution transmission electron
5   microscopy allows the crystalline pattern of the material
to be visually assessed. It can indicate the primary
particle size and structure (such as d-spacing) and give
some information on the distribution between amorphous and
crystalline material. Using this technique, it is
10 apparent that the chemistry described above increases the
amorphous phase of our described materials compared to
corresponding materials without the incorporated ligand.
This may be especially apparent using high angle annular
dark field aberration-corrected scanning transmission
15 electron microscopy due to the high contrast achieved
while maintaining the resolution thus allowing the surface
as well as the bulk of the primary particles of the
material to be visualised.

20 The reproducible physico-chemical property or
characteristic of the materials of the present invention
will be dependent on the application for which the
material is intended. Examples of the properties that can
be usefully modulated using the present invention include:
25 dissolution (rate, pH dependence and pM dependence),
disaggregation, adsorption and absorption characteristics,
reactivity-inertness, melting point, temperature
resistance, particle size, magnetism, electrical
properties, density, light absorbing/reflecting
30 properties, hardness-softness, colour and encapsulation
properties. Examples of properties that are particularly
relevant to the field of supplements, fortificants and
mineral therapeutics are physico-chemical properties
selected from one or more of a dissolution profile, an

23

adsorption profile or a reproducible elemental ratio. In

this context, a property or characteristic may be

reproducible if replicate experiments are reproducible

within a standard deviation of preferably ± 10%, and more

5   preferably ± 5%, and even more preferably within a limit

of ± 2%.

The dissolution profile of the solid ligand-modified poly

oxo-hydroxy metal ion materials can be represented by

10   different stages of the process, namely disaggregation and

dissolution. The term dissolution is used to describe the

passage of a substance from solid to soluble phase. More

specifically, disaggregation is intended to describe the

passage of the materials from a solid aggregated phase to

15   an aquated phase that is the sum of the soluble phase and

the aquated particulate phase (i.e. solution plus

suspension phases). Therefore, the term dissolution as

opposed to disaggregation more specifically represents the

passage from any solid phase (aggregated or aquated) to

20   the soluble phase.

Preferred specific examples of the metal ions (M) include,

but are not restricted to, Groups 2, 3 and 5 metals of the

periodic table, the transition metals, heavy metals and

25   lanthanoids. Examples include, but are not restricted to:

Ag^{2+}, Al^{3+}, Au^{3+}, Be^{2+}, Ca^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Eu^{3+}, Fe^{3+}, Mg^{2+},

Mn^{2+}, Ni^{2+}, Sr^{2+}, V^{5+}, Zn^{2+}, Zr^{2+}. Moreover, many of these

metal cations take on different oxidation states so it

will also be appreciated that these examples are not

30   restricted to the oxidation states shown. In many cases,

the solid ligand-modified poly oxo-hydroxy metal ion

materials comprise a single species of metal ion, for

example Fe^{3+}.

The Ligand (L)

In the solid phase ligand-modified poly oxo-hydroxy metal ion- species represented by the formula $(M_xL_y(OH)_n)$, L represents one or more ligands or anions, such as

5   initially in its protonated or alkali metal form, that can be incorporated into the solid phase ligand-modified poly oxo-hydroxy metal ion material. Typically, this is done to aid in the modification of a physico-chemical property of the solid material, e.g. as compared to a poly oxo-

10   hydroxylated metal ion species in which the ligand(s) are absent. In some embodiments of the present invention, the ligand(s) L may also have some buffering capacity. Examples of ligands that may be employed in the present invention include, but are by no means limited to:

15   carboxylic acids such as adipic acid, glutaric acid, tartaric acid, malic acid, succinic acid, aspartic acid, pimelic acid, citric acid, gluconic acid, lactic acid or benzoic acid; food additives such as maltol, ethyl maltol or vanillin; 'classical anions' with ligand properties

20   such as bicarbonate, sulphate and phosphate; mineral ligands such as silicate, borate, molybdate and selenate; amino acids such as tryptophan, glutamine, proline, valine, or histidine; and nutrient-based ligands such as folate, ascorbate, pyridoxine or niacin. Typically

25   ligands may be well recognised in the art as having high affinity for a certain metal ion in solution or as having only low affinity or not be typically recognised as a ligand for a given metal ion at all. However, we have found that in poly oxo-hydroxy metal ion materials,

30   ligands may have a role in spite of an apparent lack of activity in solution. Typically, two ligands of differing affinities for the metal ion are used in the production of these materials although one, two, three, four or more ligands may be useful in certain applications.

25

For many applications, ligands need to be biologically
compatible under the conditions used and generally have
one or more atoms with a lone pair of electrons at the

5   point of reaction. The ligands include anions, weak
ligands and strong ligands. Ligands may have some
intrinsic buffering capacity during the reaction. Without
wishing to be bound by a particular explanation, the
inventors believe that the ligands have two modes of

10   interaction: (a) substitution of hydroxy groups and,
therefore, incorporation with a largely covalent character
within the material and (b) non-specific adsorption (ion
pair formation). These two modes likely relate to
differing metal-ligand affinities (i.e. strong ligands for

15   the former and weak ligands/anions for the latter). There
is some evidence in our current work that the two types of
ligand are synergistic in modulating dissolution
characteristics of the materials and, perhaps, therefore,
in determining other characteristics of the material. In

20   this case, two ligand types are used and at least one
(type (a)) is demonstrable as showing metal binding within
the material. Ligand efficacy, probably especially for
type (b) ligands, may be affected by other components of
the system, particularly electrolyte.

25

The ratio of the metal ion(s) to the ligand(s) (L) is also
a parameter of the solid phase ligand-modifiedpoly oxo-
hydroxy metal iron material that can be varied according
to the methods disclosed herein to vary the properties of

30   the materials. Generally, the useful ratios of M:L will
be between 10:1, 5:1, 4:1, 3:1, 2:1 and 1:1 and 1:2, 1:3,
1:4, 1:5 or 1:10.

Hydroxy and oxo groups

The present invention may employ any way of forming
hydroxide ions at concentrations that can provide for
hydroxy surface groups and oxo bridging in the formation
of these poly oxo-hydroxy materials. Examples include but
5   are not limited to, alkali solutions such as sodium
hydroxide, potassium hydroxide and sodium bicarbonate,
that would be added to increase [OH] in an ML mixture, or
acid solutions such as mineral acids or organic acids,
that would be added to decrease [OH] in an ML mixture.
10

Conditions used in the process
The exact conditions of mixing and precipitation of the
solid ligand-modified poly oxo-hydroxy metal ion material
will vary depending upon the desirable characteristics of
15 the solid material. Typical variables are:
(1)   Starting pH (i.e. the pH at which M and L are
mixed). This is always a different pH to that at which
oxo-hydroxy polymerisation commences. Preferably, it is a
more acidic pH, more preferably below a pH of 2.
20 (2)   The pH at which oxo-hydroxy polymerisation
commences. This is always a different pH to that of the
starting pH. Preferably, it is a less acidic pH and most
preferably above a pH of 2.
(3)   Final pH. This will always promote precipitation and
25 may promote agglomeration of the solid ligand-modified
poly oxo-hydroxy metal ion material and preferably will be
a higher pH than the pH at which oxo-hydroxy
polymerisation commences. It will be appreciated by the
skilled person that where a pH difference exists between
30 commencement of oxo-hydroxy polymerisation and the final
pH value, addition of further M, L, OH⁻, H⁺, excipients or
other substances may be undertaken before the final pH
value is achieved.
(4)   Rate of pH change from commencement of oxo-hydroxy

polymerisation to completion of reaction. This will occur within a 24 hour period, preferably within an hour period and most preferably within 20 minutes.

Concentrations of M and L. While the concentration of OH

5   is established by the pH during oxo-hydroxy polymerisation, the concentrations of total M and total L in the system will be fixed by the starting amounts in the ML mix and the final solution volume. Typically, this will exceed 10^{-6} molar for both M and L and more

10   preferably it will exceed 10^{-3} molar. Concentrations of M and L are independent and chosen for one or more desired characteristics of the final material and especially so that the concentration of M is not too high such that the rate of oxo-hydroxy polymerisation occurs too rapidly and

15   prevents L incorporation. Similarly the concentration of L will not be too high to prevent metal oxo-hydroxy polymerisation. For example, the ligand-modified poly oxo-hydroxy materials in which M is ferric iron are produced preferably with iron concentrations of the

20   initial solution below 300 mM and most preferably below 200 mM, providing ranges of ferric iron concentrations between between 1mM and 300mM, more preferably between 20mM and 200mM, and most preferably of about 40mM.

(5)   Solution phase. The preferred solution for this work

25   is aqueous and most preferably is water.

(6)   Buffer. The solution may have a buffer added to help stabilise the pH range of oxo-hydroxy polymerisation. Buffers may be inorganic or organic, and in some embodiments will not be involved in formal bonding with

30   the metal ion(s) M of the solid phase material. Alternatively, one or more of the ligands L involved in formal bonding with the metal ion(s) M of the solid phase material may have some buffering capacity that is additionally favourable in achieving the desired

composition of the final material. Buffer concentrations
are less than 500 mM, preferably less than 200 mM and most
preferably less than 100 mM.

(7)   Temperature. The preferred temperature is above 0
5   and below 100°C, typically between room temperature (20-
30°C) and 100°C, most typically at room temperature.

(8)   Ionic strength. Electrolyte such as, but not limited
to, potassium chloride and sodium chloride, may be used in
the procedure. The ionic strength of the solution may thus
10   range from that solely derived from the components and
conditions outlined in (1)-(8) above or from the further
addition of electrolyte which may be up to 10% (w/v),
preferably up to 2%, and most preferably <1%.

(9)   Extent of mixing of the components. This issue
15   mainly relates to degree of stirring and preferably
stirring is achieved such that the starting solutions
(i.e. M, L and buffer) are rapidly mixed and maintained
homogenous throughout.

20   It will be apparent to those skilled in the art that while
the above variables may all control the physico-chemical
nature of the precipitate, further variables such as the
collection system and/or excipients used for the recovery
of the precipitate, which may involve purposeful
25   inhibition of agglomeration, its drying and its grinding
may subsequently affect the material properties. However,
these are general variables to any such system for solid
extraction from a solution phase. After separation of the
precipitated material, it may optionally be dried before
30   use of further formulation. The dried product may,
however, retain some water and be in the form of a
hydrated solid phase ligand-modified poly oxo-hydroxy
metal ion material. It will be apparent to those skilled
in the art that at any of the stages described herein for

recovery of the solid phase, excipients may be added that
mix with the ligand-modified poly oxo-hydroxy metal ion
material but do not modify the primary particle and are
used with a view to optimising formulation for the
5   intended function of the material. Examples of these
could be, but are not limited to, glycolipids,
phospholipids (e.g. phosphatidyl choline), sugars and
polysaccharides, sugar alcohols (e.g. glycerol), polymers
(e.g. polyethyleneglycol (PEG)) and taurocholic acid.
10

Formulations and Uses
The solid phase materials of the present invention may be
formulated for use in a range of biologically relevant
applications, including formulation for use as
15 pharmaceutical, nutritional, cosmetic, or personal hygiene
compositions. The compositions of the present invention
may comprise, in addition to one or more of the solid
phase materials of the invention, a pharmaceutically
acceptable excipient, carrier, buffer, stabiliser or other
20 materials well known to those skilled in the art. Such
materials should be non-toxic and should not interfere
with the efficacy of the solid phase materials for the
application in question.

25 The precise nature of the carrier or other component may
be related to the manner or route of administration of the
composition. These compositions may be delivered by a
range of delivery routes including, but not limited to:
gastrointestinal delivery, including orally and per
30 rectum; parenteral delivery, including injection; dermal
delivery including patches, creams etc; mucosal delivery,
including nasal, inhalation and via pessary; or by implant
at specific sites, including prosthetics that may be used
for this purpose or mainly for another purpose but have

this benefit.

Pharmaceutical compositions for oral administration may be
in a tablet, capsule, powder, gel or liquid form. A
5   tablet may include a solid carrier such as gelatin or an
adjuvant. Capsules may have specialised properties such
as an enteric coating. Liquid pharmaceutical compositions
generally include a liquid carrier such as water,
petroleum, animal or vegetable oils, mineral oil or
10   synthetic oil. Physiological saline solution, dextrose or
other saccharide solution or glycols such as ethylene
glycol, propylene glycol or polyethylene glycol may be
included. Where the solid ligand-modified poly oxo-
hydroxy metal ion material needs to be maintained in a
15   solid form, e.g. to control the delivery of a component of
the material, it may be necessary to select components of
the formulation accordingly, e.g. where a liquid
formulation of the material is made.

20   For intravenous, cutaneous or subcutaneous injection, or
injection at the site of affliction, the active ingredient
will be in the form of a parenterally acceptable aqueous
solution or suspension which is pyrogen-free and has
suitable pH, isotonicity and stability. Those of relevant
25   skill in the art are well able to prepare suitable
solutions using, for example, isotonic vehicles such as
Sodium Chloride Injection, Ringer's Injection, Lactated
Ringer's Injection. Preservatives, stabilisers, buffers,
antioxidants and/or other additives may be included, as
30   required.

The materials and compositions used in accordance with the
present invention that are to be given to an individual
are preferably administered in a "prophylactically

effective amount" or a "therapeutically effective amount"
(as the case may be, although prophylaxis may be
considered therapy), this being sufficient to show benefit
to the individual (e.g. bioavailability). The actual
5   amount administered, and rate and time-course of
administration, will depend on the nature and severity of
what is being treated. Prescription of treatment, e.g.
decisions on dosage etc, is within the responsibility of
general practitioners and other medical doctors, and
10   typically takes account of the disorder to be treated, the
condition of the individual patient, the site of delivery,
the method of administration and other factors known to
practitioners. Examples of the techniques and protocols
mentioned above can be found in Remington's Pharmaceutical
15   Sciences, 20th Edition, 2000, Lippincott, Williams &
Wilkins. A composition may be administered alone or in
combination with other treatments, either simultaneously
or sequentially, dependent upon the condition to be
treated.

20

Examples of the uses of the solid ligand-modified poly
oxo-hydroxy metal ion materials disclosed herein include,
but are not limited to, uses as: dietary mineral
supplements and fortificants; therapeutic mineral
25   supplements (e.g. as administered by i.v. and oral
routes); drugs, nutrients or cosmetic carriers/co-
complexes; phosphate binding agents; other binding or
sequestering applications; food additives; anti-
perspirants; sun-protection agents; vaccine adjuvants;
30   immuno-modulatory agents; direct cosmetic applications
including exfoliating agents; bone and dental
filler/cements; implant materials including brachytherapy,
and imaging and contrast agents.

Ligand-modified poly oxo-hydroxide materials may be used
as supplements for nutritional or medical benefit. In
this area, there are three main examples:

5   (i) Therapeutic (prescription) supplements, which are
generally administered by the oral or i.v. routes for the
treatment of indications including iron deficiency
anaemia, iron deficiency and anaemia of chronic disease.
The therapeutic administration of materials of the present
10   invention may be in conjunction with other therapies and
especially with the concomitant use of erythropoietin.

(ii) Nutritional (self prescribed/purchased supplements)
which are usually for oral delivery.
15

(iii) Fortificants. These may be traditional forms- in
terms of being added to food prior to purchase - or more
recent fortificant forms such as 'Sprinkles' which are
added (like salt or pepper) to food at the time of
20   ingestion.

In all formats, but most especially for fortificants,
subsequent formulation, such as addition of a protective
coating (e.g. lipid), may be necessary to make the
25   material compatible with its intended usage. In addition,
any of these supplemental forms can be co-formulated,
either by incorporation within the material through use of
co-formulated material(s) as ligand(s) or through
trapping/encapsulation of said materials, or simply
30   through co-delivery of said materials.

As described herein, one particular application of the
solid ligand-modified poly oxo-hydroxy metal ion materials
of the present invention is for the treatment of mineral

deficiencies, for example iron deficiency. In an
alternative application the materials may be employed to
bind or sequester a component present in an individual.
By way of example, the ferric iron compositions disclosed
5   herein may be used to deliver iron to an individual for
use in the prophylaxis or treatment of iron deficiency or
iron deficiency anaemia which may be suspected, or
diagnosed through standard haematological and clinical
chemistry techniques. Iron deficiency and iron deficiency
10   anaemia may occur in isolation, for example due to
inadequate nutrition or due to excessive iron losses, or
they may be associated with stresses such as pregnancy or
lactation, or they may be associated with diseases such as
inflammatory disorders, cancers and renal insufficiency.
15   In addition, there is evidence that the reduced
erythropoiesis associated with anaemia of chronic disease
may be improved or corrected by the effective delivery of
systemic iron and that co-delivery of iron with
erythropoietin or its analogues may be especially
20   effective in overcoming reduced erthropoietic activity.
Thus, by way of further example, the ferric iron
compositions disclosed herein may be used to deliver iron
to an individual for use in the treatment of sub-optimal
erythropoietic activity such as in anaemia of chronic
25   disease. Anaemia of chronic disease may be associated
with conditions such as renal insufficiency, cancer and
inflammatory disorders. As noted above, iron deficiency
may also commonly occur in these disorders so it follows
that treatment through iron supplementation may address
30   iron deficiency alone and/or anaemia of chronic disease.
It will be recognised by those skilled in the art that the
above examples of the medical uses of iron supplements are
by no means limiting.

Experimental Description

Introduction

Inorganic mineral-based materials have widespread
biological applications that include: dietary supplements,

5   phosphate binding agents, antacids, immune adjuvants
(alum) and antiperspirants (alum). These are often co-
formulated in such a way that the mineral physico-chemical
properties, such as rates of dissolution and/or
disaggregation, are modestly altered in an attempt to

10   improve their efficacy. We have however developed a
procedure whereby the actual structure, at the level of
the primary particle (the primary unit within the lattice
structure), can be modified within oxide/hydroxide
minerals. This nano-structuring can lead to profound

15   changes in mineral characteristics and can be tuned to
provide mineral with precisely specified physico-chemical
characteristics. Moreover the methodology is cheap and
can be applied on as large a scale as required. The
modifying agents are all biologically compatible, food

20   grade ligands allowing rapid introduction of novel
materials to human subjects. An exemplar of these
materials is the production of a novel class of iron
supplements that may have therapeutic parenteral and oral
applications, as well as widespread roles as fortificants

25   and dietary supplements.

With supplements, we believe that one desirable property
is that the rate of nutrient absorption mimics that seen
for the same nutrient when ingested in a food. For

30   example, with iron, the rate of dietary iron absorption
can be controlled through the rate of iron dissolution.
In the following examples, we have produced a number of
different solid ligand-modified poly oxo-hydroxy metal ion
materials using the process of the present invention, with

the aim of identifying compositions that release iron in a
controlled fashion. The aim is that the rate of
dissolution will allow the ferric iron to be donated to
the mucosal reductase (DcytB) in a fashion that prevents

5   build up of iron in the lumen or bolus absorption into the
circulation- neither of which are desirable. Thus the
ferric iron compositions of the present invention should
have lower gastrointestinal side effects as they will not
undergo facile redox cycling in the gut. In addition,

10   there is scope to design the compositions to dissolve
differently at gastric pH versus intestinal pH. There is
also the possibility of tailoring the compositions to
dissolve at different rates depending upon the
concentration of iron in the local solution (e.g. the gut

15   lumen), such that the compositions may 'sense' iron
requirements of the environment and thus iron requirements
of the individual. The remaining, unabsorbed luminal iron
would be largely unavailable for undesirable redox
reactivity within the lumen and would pass harmlessly into

20   the faeces.

Nomenclature of materials
Throughout the examples the $FeOHL_A$-i:j-L_Bk nomenclature
was adopted to describe the preparation for ligand-

25   modified poly oxo-hydroxy ferric iron materials; where L_A
refers to the ligand with higher solution affinity and L_B
to the ligand with lower solution affinity for iron. The
ratio i:j refers to the molar ratio between iron (Fe) and
ligand A (L_A) and k refers to the concentration (mM)of

30   ligand B(L_B)in solution prior to the precipitation of
ligand-modified poly oxo-hydroxy ferric materials. Where
only a weaker ligand (ligand B) was present the
nomenclature used was FeOH L_Bk. For example, the material
defined as FeOHT-3:1-Ad20 was prepared using a molar ratio

of three Fe to one tartrate and a concentration of adipate
of 20 mM. The iron concentration in solution was 40 mM
unless stated otherwise in the figure legends.

5   **Materials**

All chemicals were purchased from Sigma-Aldrich, Dorset,
UK, unless otherwise specified. All laboratory ware was
in polypropylene. The materials used in the preparation
of the ligand-modified poly oxo-hydroxy ferric iron

10 materials for the *in vivo* study were prepared with food
grade chemicals or pharmaceutical grade chemicals also
from Sigma-Aldrich, with the exception of the ^{58}Fe
elemental iron used in the preparation of the ^{58}Fe ferric
chloride which was purchased from Chemgas, Boulogne,

15 France.

Methods

Screening assay

A series of dietary ligands was tested in a screening

20 assay for their effects on the formation of solid ligand-
modified poly oxo-hydroxy metal ion materials. Briefly,
in a centrifuge tube, a fixed volume of stock solution of
ferric iron (400mM FeCl$_3$ with 50mM MOPS, pH 1.4) was mixed
with varying volumes of a stock solution of ligand (400mM

25 with the exception of maltol which was 200mM, plus MOPS at
50mM and 0.9% NaCl) to obtain the desired metal: ligand
ratio. The volumes were then equally adjusted to parity
with a solution of 50mM MOPS and 0.9% NaCl. All the
solutions obtained at this stage were fully soluble at pH

30 < 2.0. A small aliquot was taken to confirm the starting
iron concentration and then the pH was raised to ~6.5 by
drop-wise addition of concentrated NaOH to avoid high
volume changes. After centrifugation at 2500 rpm for 10
minutes, an aliquot of supernatant was taken to analyse

the iron remaining in solution. The remaining supernatant
was discarded and a fixed volume of dissolution buffer at
pH 6 (MOPS 10mM) or pH 4 (Acetic acid 10mM) was then added
to the wet solid of each tube and incubated overnight at

5   room temperature. The tubes were then centrifuged (2500
rpm for 10 minutes) and an aliquot of supernatant taken to
determine the iron that was disaggregated. The iron
concentration in each aliquot was measured by ICPOES
analysis.

10

Titration experiments   .
An acidic concentrated stock solution of iron (as ferric
chloride) was added to a solution containing either the
ligand A, ligand B or both ligand A and B at appropriate

15   concentrations to obtain the desired M:L ratios. In some
cases 0.9% w/v of electrolyte (for example NaCl or KCl)
was also added. The solution was mixed thoroughly and an
aliquot collected for analysis of the "starting iron"
concentration. The pH of the solution was always <2.0 and

20   the iron fully solubilised. Next the pH was slowly
increased by drop-wise addition of a concentrated solution
of NaOH with constant agitation until the mixture reached
a basic pH (generally >8.0). At different points during
the titration, a homogeneous aliquot (1mL) of the mixture

25   was collected and transferred to an Eppendorf tube. Any
aggregate formed was separated from the solution by
centrifugation (10 minutes at 13000 rpm). The iron
concentration in the supernatant was assessed by ICPOES.
In some cases the supernatant was analysed for the

30   presence of aquated particulate iron and the size
distribution was measured (see below). When aquated
particulate iron was present, the supernatant was
ultrafiltrated (Vivaspin 3,000 Da molecular weight cut-off
polyethersulfone membrane, Sartorius Stedium Biotech GmbH,

Goettingen, Germany) and the iron concentration in the
filtrate, i.e. "soluble iron", was analysed by ICPOES.

Preparation of solid ligand-modified poly oxo-hydroxy
5 *ferric iron materials*
The materials were prepared following a protocol similar
to the titration experiment described above. Briefly, an
acidic concentrated stock solution of iron was added to a
solution containing either the ligand A, ligand B or both
10 ligand A and B. In some cases 0.9% w/v of electrolyte was
also added. The "starting pH" of the solution was always
<2.0, and the iron fully solubilised. The pH was then
slowly increased by drop-wise addition of a concentrated
solution of NaOH with constant agitation until reaching
15 the desired final pH.

When preparing the solid material as a pellet, the entire
mixture was then transferred to a centrifuge bottle and
spun at 4500 rpm for 15 minutes. The supernatant was
20 discarded and the aggregated solid phase collected in a
petri dish. When necessary, the solid was then dried in
an oven at 45 °C for a minimum of 8 hours. Alternatively,
the mixture (precipitate and supernatant) was freeze-dried
at -20 °C and 0.4 mbar.

25

When preparing the solid material as aquated particulate
material, the total mixture was either freeze-dried as
above, or concentrated by ultrafiltration (Vivaspin 3000
Da molecular weight cut-off polyethersulfone membrane,
30 Sartorius Stedium Biotech GmbH, Goettingen, Germany) and
then air dried in an oven at 45 °C for a minimum of 8
hours. In some cases the mixture was dialysed (1,000 Da
regenerated cellulose membrane Spectra/pro 7, Cole-Parmer,
London, UK) in water to remove excess iron, ligands and

electrolytes before undergoing one of the drying processes
described above.

5   When using bicarbonate as ligand B a variation of this
protocol was used to avoid release of CO_2 from
transformation of bicarbonate at acidic pH. The starting
solution containing ligand A (when applicable) and
bicarbonate was prepared at pH 8.5. The appropriate
volume of acidic concentrated stock solution of iron was
10 then added drop-wise in conjunction with NaOH pellets
(progressively added to the mixture as required) in order
to always maintain a pH >7.5. The final pH of the
preparation was 8.5.

15 *Disaggregation assay*
Known amounts of solid ligand-modified poly oxo-hydroxy
ferric iron materials were added into tubes (about 3 mg
iron per tube). Then, 3 mL of buffer (see below) were
added and the tubes shaken vigorously and incubated at
20 room temperature overnight. After centrifugation at 4500
rpm for 15 minutes to separate the aggregated solid phase
from the aquated phase, an aliquot of supernatant was
collected to measure the disaggregated iron concentration.
The remaining supernatant was discarded. The mass of
25 remaining material (i.e. the wet pellet) was recorded.
Concentrated HNO_3 was added to this pellet and the new
mass recorded. The tubes were left at room temperature
until all the pellet dissolved and an aliquot was
collected for ICPOES analysis to determine the iron
30 concentration in the wet pellet.

The buffers were either 50mM MOPS with 0.9% NaCl at pH
7.0; 50mM Maleic acid with 0.9% NaCl at pH 5.8-6.0 and
1.8-2.2; 50mM sodium acetate/ 50mM acetic acid glacial

with 0.9% NaCl at pH 4.0-4.5.

In vitro gastrointestinal digestion assay

An amount of the solid ligand-modified poly oxo-hydroxy
ferric iron materials or control iron materials namely
ferrous sulphate, ferric chloride, or unmodified ferric
oxo-hydroxide, equivalent to 60mg elemental iron, were
added to a synthetic gastric (stomach) solution (50 mL of
2 g/L NaCl, 0.15 M HCl and 0.3mg/mL porcine pepsin) and
incubated at 37°C for 30 minutes with radial shaking.
Then 5 mL of the resulting gastric mixture was added to 30
mL of synthetic duodenal solution (containing 10g/L
pancreatin and 2g/L NaCl in 50mM bicarbonate buffer pH
9.5). The final volume was 35 mL and the final pH was
7.0. The mixture was incubated at 37°C for 60 min with
radial shaking. Homogeneous Aliquots (1mL) were collected
at different time points during the process and
centrifuged at 13,000 rpm for 10 minutes to separate the
aggregate and aquated phases. The supernatant was
analysed for iron content by ICPOES. At the end of the
experiment, the remaining solution was centrifuged at
4,500 rpm for 15 min and the supernatant analysed for Fe
content by ICPOES. The mass of remaining material (i.e.
the wet pellet) was recorded. Concentrated HNO_3 was added
to this wet pellet and the new mass recorded. The tubes
were left at room temperature until all the pellet
dissolved and an aliquot was collected for ICPOES analysis
to determine the quantity of iron that did not
disaggregate / dissolve. The starting amount of iron was
calculated from the iron in the wet pellet plus the iron
in the supernatant.

To differentiate between soluble iron and aquated
particulate iron in the supernatant, at each time point,

this fraction was also ultrafiltered (Vivaspin 3,000 Da
molecular weight cut-off polyethersulfone membrane,
Sartorius Stedium Biotech GmbH, Goettingen, Germany) and
again analysed by ICPOES.

5

The gastrointestinal digestion of commercial iron
preparations was also tested with this assay using the
dose of total iron recommended by the manufacturers:
Ferric pyrophosphate 14mg (Lipofer, Boots); ferrous
10   bisglycinate 20mg (Gentle iron, Solgar); ferric-hydroxide
polymaltose complex 80mg (Maltofer, Ferrum Hausmann);
ferric tri-maltol 30mg (Trimaltol, Iron Unlimited).

Modified in vitro gastrointestinal digestion assay
15   The particle size of the ligand-modified poly oxo-hydroxy
ferric iron materials under simulated gastric and
intestinal conditions was determined using an adapted "*in
vitro* gastrointestinal digestion assay" in which no
protein was in solution. The absence of proteins was
20   required to measure particle size as these interfere with
the measurement but the procedure was otherwise identical
to the "*in vitro* gastrointestinal digestion assay" with
extra aliquots being collected at various time points for
the determination of particle size.

25

*Inductively Coupled Plasma Optical Emission Spectroscopy
analysis (ICPOES)*
Iron contents of solutions or solids (including wet
solids) were measured using a JY2000-2 ICPOES (Horiba
30   Jobin Yvon Ltd., Stanmore, U.K.) at the iron specific
wavelength of 259.940 nm. Solutions were diluted in 5%
nitric acid prior to analysis while solids were digested
with concentrated HNO_3. The percentage of iron in
solution or solid phase was determined by the difference

between the starting iron content and either the iron in
the soluble phase or the iron in the solid phase depending
on the assay.

5   *Determination of particle size*
     The size distribution of micron-sized particles was
     determined using a Mastersizer 2000 with a Hydro-µP
     dispersion unit (Malvern Instruments Ltd, Malvern, UK) and
     nano-sized particles were determined with a Zetasizer Nano
10   ZS (Malvern Instruments Ltd, Malvern, UK). Mastersizer
     measurements required no sample pre-treatment whereas
     centrifugation was needed to remove large particles prior
     to Zetasizer measurements.

15   **Structural analysis**
     Transmission Electron Microscopy and Energy Dispersive X-
     ray Analysis (EDX)
     Powder samples were analysed by first dispersing the
     powder in methanol and then drop-casting on standard holey
20   carbon TEM support films. Commercial tablets were
     similarly analysed but were first crushed to release the
     powder. Analysis were undertaken by the Institute for
     Materials Research, University of Leeds, UK.

25   *Scanning Transmission Electron Microscopy*
     Powder samples were analysed by first dispersing the
     powder in methanol and then drop-casting on standard holey
     carbon TEM support films. Commercial tablets were
     similarly analysed but were first crushed to release the
30   powder. Analysis were undertaken by aberration-corrected
     scanning transmission electron microscopy (Daresbury;
     superSTEM).

     Infrared Analysis (IR)

IR spectra were collected using a DurasamplIR diamond ATR
accessory with a Nicolet Avatar 360 spectrometer with a
wavelength range of 4000-650cm^{-1} and resolution of 4cm^{-1}.
Analysis were undertaken by ITS Testing Services (UK) Ltd,
5   Sunbury on Thames, UK.

X-Ray Diffraction Analysis

Samples were analysed as dry powders. Commercial tablets
10 were crushed to release the powder. Analysis was by X-ray
diffraction analysis at the University of Cambridge using
a Philips X'Pert PW3020 (theta/2theta, 2 motors) with up
to 14 hour scan time and 5-70° 2theta on CuKalpha.

15 **In vivo absorption study**

Subjects

Healthy young women (aged 18-45 years) with mild iron
deficiency anaemia (defined as haemoglobin between 10-11.9
g/dL plus either serum ferritin below 20µg/L or
20 transferrin saturation below 10%); or clear iron
deficiency (defined as serum ferritin below 12µg/L) were
recruited to take part in the study. Exclusion criteria
were pregnancy or lactation and known coeliac disease,
moderate/severe anaemia (haemoglobin levels <10 g/dL),
25 cardiovascular disease, chronic respiratory disease,
chronic liver disease, renal disease, chronic infection,
or chronic inflammation. Other exclusion criteria were:
surgery in the past three months, cancer diagnosis in the
last ten years, known history of hereditary
30 haemochromatosis or haemoglobinopathies, current
medication that could alter iron metabolism, recent blood
donation/heavy blood loss (in the past 3 months).
Subjects who regularly consume vitamin and mineral
supplements were asked to discontinue supplementation 2
35 weeks before the screening for the study. Written

informed consent was obtained from all subjects. The study
protocol was approved by the Suffolk Local Research Ethics
Committee.

5   *Study design*
     The experimental treatment was either a single dose of
     ^{58}Fe labeled ligand-modified poly oxo-hydroxy ferric iron
     material (60 mg total iron) or ferrous sulphate (65 mg
     total iron). Ferrous sulphate is used as a reference dose
10   to control for individuals who are poor absorbers (defined
     as those who have no significant net area under the curve
     (AUC) for plasma iron following ferrous sulphate
     ingestion). A crossover study design was used with each
     volunteer acting as her own control.
15
     Fe absorption was based on erythrocyte incorporation of
     the ^{58}Fe stable-isotope label 14 days after the intake of
     labelled iron test compounds. The test compounds and the
     reference compound (ferrous sulphate) were taken (with or
20   without breakfast), under strictly standardised conditions
     and close supervision, after an overnight fast with 14
     days interval. No intake of food or fluids (apart from
     water) was allowed for 4 h after the iron compound intake.

25   Ten blood samples (12 mL) were taken during each of the 2
     visits to determine the absorption of Fe at the following
     times: before intake and 30, 60, 90, 120, 180, 210 and 240
     minutes after intake of the iron compound. An additional
     blood sample was taken at baseline (before intake) to
30   confirm iron status (full blood count, ferritin, soluble
     transferrin receptor, transferrin saturation) and
     determine erythrocyte ^{58}Fe incorporation.

     Total serum iron concentration was analysed by a standard

clinical chemistry procedure based on the method by Smith et al using the chromophore Ferene®.

RBC incorporation of ^{58}Fe was determined using an Elan DRC
5   Plus Inductively Coupled Plasma Mass Spectrometer (Perkin Elmer Sciex, Beaconsfield, UK). The sample introduction system consisted of a V-groove nebuliser, a double-pass spray chamber, a demountable quartz torch, and a quartz injector (2 mm internal diameter). Platinum-tipped
10   sampler and skimmer cones (Perkin Elmer Sciex, Beaconsfield, UK) were used for all analyses. Baseline whole blood samples were collected from participants in the study immediately prior to administration of a 60 mg oral Fe supplement labelled with 2mg ^{58}Fe, and a second
15   blood sample was collected 14 days after administration. Whole blood was diluted 100-fold with an aqueous solution containing 0.5% Triton X-100, 1% butan-1-ol, 0.5% ammonia, and 0.007 % nitric acid. Instrument conditions were tuned for optimum signal sensitivity (via the measurement of
20   ^{24}Mg, ^{115}In and ^{238}U isotopes), minimum oxide formation (via the measurement of the ^{140}Ce and ^{155}Gd isotopes to allow monitoring of the degree of CeO formation at m/z = 155) and minimum doubly charged ion formation (via the measurement of the ^{138}Ba and ^{69}Ga isotope signals to allow
25   monitoring of the degree of ^{138}Ba^{2+} formation at m/z = 69). Further adjustment was then performed to reduce mass bias between ^{58}Fe and ^{57}Fe (approximately 5%). Detector voltages were dropped from the typical -2400 and 1550 V to -1725 and 1050 V for analogue and pulse stages,
30   respectively.

Preparation of ^{58}Fe labelled ferric chloride solution
A solution of ^{58}Fe labelled ferric chloride was prepared by dissolving 100 mg ^{58}Fe enriched elemental iron

(Chemgas, Boulogne, France) in 4 mL 37% HCl in a pear-
shaped glass flask attached to a condenser and heated at
48°C in a water bath. The temperature was raised
gradually over time to keep the solution boiling as the
5   concentration of chlorine dropped. When the elemental
iron powder was dissolved, 0.5 mL of 30% hydrogen peroxide
were added to oxidize ferrous iron to ferric iron. The
flask was then sealed, once the oxidation reaction
finished, i.e. once the formation of O_2 bubbles stopped.
10   The concentration of iron in the final solution was
determined by ICPOES and the Ferrozine assay was used to
confirm the absence of ferrous iron.

Preparation of the [58]Fe labelled ligand modified poly
15   *oxo-hydroxy ferric iron material*
The chosen ligand-modified poly oxo-hydroxy ferric iron
materials enriched with [58]Fe were prepared following the
protocol described above (see *Preparation of solid ligand-*
modified poly oxo-hydroxy ferric iron materials) using a
20   ferric chloride stock solution containing 3.5% w/w [58]Fe (2
mg of [58]Fe per 60 mg total iron in the ingested solid
material) from the [58]Fe labelled ferric chloride solution
discussed above.

25   **Results and discussion**
Effect of Ligand A
A series of ligands, namely maltol, succinic acid, citric
acid, lactic acid, tartaric acid, malic acid, gluconic
acid, aspartic acid, glutamic acid, histidine and
30   glutamine, were studied for their effect on ferric poly
oxo-hydroxide precipitation from solution.

Initially, the ligands were all tested using the screening
assay described above at ratios of 1:1 to 1:5 and

classified in three groups. The first group, "strong
ligands", were ligands found to inhibit the formation of
80% of the solid material at ratio 1:1 and included
gluconic acid, citric acid and maltol. The second group,

5   "weak ligands", were ligands found to have little effect
on the amount of solid material formed (<10% at all the
ratios tested) and included aspartic acid, succinic acid,
lactic acid, glutamic acid and histidine. The third
group, "intermediate ligands", were ligands found to have

10   an influence, between strong and weak ligands, on the
amount of solid material formed at, at least, one of the
ratios tested and included malic acid, tartaric acid and
glutamine.

15   In a second instance, six ligands from the three groups
described above were re-screened for their effects on both
the formation of ferric poly oxo-hydroxide precipitation
at varying M:L ratios, and the dissolution of the solid
materials formed in pH 6 and pH 4 buffers (see screening

20   assay above). As expected, the ligands had variable
effects on the percentage of poly oxo-hydroxy iron that
was precipitated depending upon (a) the group the ligand
belonged to and (b) the M:L ratio. Yet, the solid
materials formed, showed variable re-aquation properties

25   that were not predictable from the precipitation
behaviours. Examples of results using a strong affinity
ligand, namely maltol, a weak affinity ligand, namely
succinate, and an intermediate affinity ligand, namely
malate, are shown in Figures 1A and B. Re-dissolution

30   clearly depends upon the ligand and its ratio to iron
which may be expected. What is not expected is that the
strong ligand, maltol, did not promote any re-dissolution
of the iron at pH 6.0 in spite of the fact that soluble
iron-maltol complexes can be formed (for at least a

proportion of the iron) at this pH. Moreover, the
intermediate ligand, malate, allowed greater dissolution
of iron from the solid phase at pH 6.0 than the strong
ligand maltol - even when ratios were matched (c.f. 1:1).
5   Examples of further results with other ligands or ratios
are shown in Table 1.

Table 1: The effect of single ligands on poly oxo-hydroxy
iron precipitation and the re-dissolution of that iron.

Ligand	M:L ratio	% Fe precipitated at pH 6.5	% Fe disaggregated at pH 6	PH 4
Succinic acid	1:1	100	0	0
L-lactic acid	1:1	65	0	0
Maltol	3:1	55	0	13
Tartaric acid	5:1	85	36	100
Citric acid	5:1	42	0	0

10

Two ligands, namely malate and tartrate, that showed most
effects in the screening assay, were chosen for study in
greater detail. The re-dissolution profile was studied
using a more defined assay in four different buffers (see
15   Disaggregation Assay in Methods). The buffers contained
0.9% w/v electrolyte so that the results obtained would
reflect the behaviour of the material in a biological
ionic strength environment. Also the pH environments were
chosen to reflect different parts of the gastrointestinal
20   tract from gastric (pH 1.8) to intestinal (pH 7.0).
Firstly, the results shown in Table 2 confirmed that the
two ligands affected not only the precipitation but also
the disaggregation profile depending on the ratio used in
the preparation of the ferric poly oxo-hydroxide materials
25   as seen in the screening assay above. Generally,
increasing the ligand ratio decreased the formation of the

ligand-modified poly oxo-hydroxy ferric iron solid
material and increased the disaggregation profile.
However, the extent of the effect seen with one ligand did
not reflect the extent of the effect seen with another
5   ligand as illustrated here with malate and tartrate. The
results observed were reproducible as indicated in table 2
with malate at M:L ratio 1:2.

Table 2: Effect of malate and tartrate ratios on the
10   *percentage of iron precipitated as ligand-modified poly*
oxo-hydroxy ferric iron materials and the disaggregation
of the materials.

Ligand	M:L ratio	% Fe precipitated	% Fe disaggregated at pH			
			7.0	5.8	4.1	1.8
Malic	2:1	59	6	7	19	14
acid[a]	1:1	45	12	20	55	15
	1:2 (n=4)	27±10	6±4	49±5	63±5	18±4
Tartaric	4:1	99	13	61	99	22
acid[b]	3:1	91	71	100	100	28
	2:1	43	100	100	100	14

Ligand-modified poly oxo-hydroxy ferric iron materials
15   were prepared at pH 6.5 in 50mM MOPS and 0.9% NaCl.
Starting iron concentrations were 26.7mM. Precipitation
steps were either carried out in individual tubes (a) as
per the precipitation procedure described in Screening
Assay, or as a batch (b) as per the preparation of solid
20   ligand-modified poly oxo-hydroxy ferric iron materials
(see methods). Disaggregation of all materials was
performed according to the method outline in
Dissagregation assay (see methods).

25   Secondly, the effect of the ligand on the rate of

formation of the ligand-modified poly oxo-hydroxy ferric
iron materials was studied using the titration protocol
described in the methods section. Figure 2 shows the rate
of formation of the solid material with increasing pH.

5   The addition of malate was found to delay the formation of
the solid material compared to the absence of ligand.
This scenario is to be expected when a ligand competes
with the polymerisation of the poly oxo-hydroxy ferric
iron entity that results in the formation of the solid

10   material. However, unexpectedly, tartrate was found to
have a promoting effect on the formation of the solid
material at lower pH. This does not correlate with the
competition. scenario described above. In this case the
ligand, tartrate, appears to be enhancing the

15   precipitation. Another observation was that tartrate, at
basic pH (>7.5), did promote disaggregation of this
material. Indeed, Figure 16 shows a typical profile of
the formation of two solid phases, namely aggregated and
aquated tartrate-modified ferric poly oxo-hydroxide with

20   increasing pHs following the titration protocol described
in Methods. These results were also observed with other
ligands A and ligands B (results not shown).

The disaggregation profile of the ligand-modified poly

25   oxo-hydroxy ferric iron solid material formed at different
pHs was shown to vary as illustrated in Figure 3 for
malate. As the pH of preparation of the material
increases, the disaggregation profile decreases. This is
in accordance with an increase of polymerisation and

30   formation of oxo-bridges with increasing pH, probably
limiting the modification effect of the ligand on the
material.

The presence of 0.9% w/v electrolyte, as sodium (NaCl) or

potassium chloride (KCl), in the preparation of the
ligand-modified poly oxo-hydroxy ferric iron solid
materials was also studied. Figure 4A shows that the
presence of 0.9% NaCl did not affect the disaggregation
5   profile of the tartrate-modified poly oxo-hydroxy ferric
iron material at M:L ratio 4:1 compared to the same
material prepared without NaCl. Similarly, Figure 4B
shows that the presence of 0.9% KCl did change the
disaggregation profile of the tartrate-modified poly oxo-
10   hydroxy ferric iron material at M:L ratio 2:1 (solution
containing 50mM niacin).

Finally, the effect of drying ligand-modified poly oxo-
hydroxy ferric iron solid materials was studied with
15   respect to disaggregation. Drying the material generally
lead to a modest reduction in its disaggregation as
exemplified by the tartrate-modified poly oxo-hydroxy
ferric iron material at M:L ratio 4:1 which is illustrated
in Figure 5. Small, inconsistent differences were
20   observed between oven-drying and freeze-drying methods
(Figure 5).

Effect of ligand B
Almost all of the studies described above were carried out
25   with ligand-modified poly oxo-hydroxy ferric iron solid
materials produced in MOPS buffer. MOPS is often used in
metal speciation studies due to its very weak interaction
with most metal ions and hence it rarely interferes in the
formation of metal complexes. However, MOPS has a pKa of
30   7.2 and so has a buffering capacity around neutral pH.
Thus, although MOPS would not interact directly with iron
or prevent the formation of the solid material, it may
indirectly influence the formation of the solid by
controlling the rate of change in environmental pH. In

addition, the buffer used in the preparation of the
ligand-modified poly oxo-hydroxy ferric iron solid
materials should be safe for human consumption which MOPS
is not. Therefore, to study the influence of the buffer,

5   or ligand B, on the formation and re-dissolution
properties of the ligand-modified poly oxo-hydroxy ferric
iron solid materials, we selected a series of compounds
with buffering capacity at varying pH ranges; namely,
adipate, bicarbonate, acetate, glutarate, dimethyl

10   glutarate, pimelate, succinate, vanillin, tryptophan,
benzoate, propionate, borate, niacin and pyridoxine
hydrochloride. Figure 6 illustrates the effect of
changing MOPS for adipate on the rate of formation of the
tartrate-modified poly oxo-hydroxy ferric iron solid

15   material at M:L ratio 4:1 (Figure 6(i)), as well as its
effect on the otherwise un-modified poly oxo-hydroxy
ferric iron solid material (Figure 6(ii)). In both cases,
adipate had a promoting effect on the rate of formation of
the solid material.

20

Following these observations, the formation and
disaggregation profiles of the tartrate-modified oxo-
hydroxy ferric iron solid materials were studied using
varying M:L ratios. Adipate reduced the disaggregation

25   capacity of the materials formed (Table 3) compared to
MOPS (Table 2), except at gastric pH (pH 1.8) which showed
low disaggregation capacity with both buffers. In
contrast, in the case of malate-modified poly oxo-hydroxy
ferric iron materials, bicarbonate had a negative

30   influence on the percentage of precipitation and the
disaggregation capacity of the material (Table 2 and 3).
These effects fell off with lower concentrations of
adipate but not bicarbonate (Table 3, data in bold).

The influence of ligand B on the disaggreagtion profile of the tartrate-modified poly oxo-hydroxy ferric iron solid material is further illustrated in Figure 7 with niacin and benzoate.

5   *Table 3*

Material	M:L ratio	% Fe precipitated	% Fe disaggregated at pH		
			7.0	4.1	1.8
FeOHT-Ad50	2:1	41	43	76	17
	3:1	78	13	42	14
	4:1	91	9	50	26
	5:1	96	3	44	27
FeOHT-Ad20	**3:1**	**82**	**2**	**21**	**17**
FeOHM-Bic100	1:1	5	nd	nd	nd
	2:1	33	nd	nd	nd
	4:1	78	0	1	10
	5:1	81	0	0.5	6
FeOHM-Bic25	**4:1**	**83**	**0**	**1**	**3**

Tartrate-modified poly oxo-hydroxy ferric iron solid materials were prepared following the protocol "preparation of solid ligand-modified poly oxo-hydroxy

10   ferric iron materials" (see methods) at pH 4.0 in either 50mM adipate (Ad50) or 20mM adipate (Ad20) without the presence of an electrolyte. Malate-modified poly oxo-hydroxy ferric iron solid materials were prepared following the same procedure at pH 8.5 in either 100mM

15   bicarbonate (Bic100) or 25mM bicarbonate (Bic25) without the presence of an electrolyte. The disaggregation of the materials was performed according to the method outlined in Disaggregation assay (see method) using the non-dried material for FeOHT-Ad50 and FeOHM-Bic100 and the oven-

20   dried material for FeOHT-Ad20 and FeOHM-Bic25.

Structural analysis of the solid ligand-modified poly oxo-hydroxy ferric iron materials

The solid ligand-modified poly oxo-hydroxy ferric iron

5   materials prepared above differ from currently available
iron formulations in that they are not a simple inorganic
ferrous ion salt (e.g. ferrous sulphate), an iron complex
in which the metal is coordinated with organic ligand
(e.g. ferric trimaltol), nor an organic ligand coated iron

10   mineral particle (e.g. iron polymaltose or 'Maltofer').

The elemental analysis of particles from our solid ligand-
modified poly oxo-hydroxy ferric iron materials measured
by Energy dispersive X-ray analysis (EDX) clearly shows

15   the presence of carbon atoms in the iron- and oxygen-
containing particles (an example is shown in Figure 8).
Furthermore, the infrared spectrum of the material
demonstrates the presence of a covalent-like bond between
the ligand and the metal (Figure 9) in addition to the

20   abundant presence of hydroxy groups. This illustrates
that the ligand is incorporated into the structure of the
metal oxo-hydroxide lattice through formal bonding and not
simply adsorption or 'entrapment'. The changes to the
dissolution characteristics of the material can be readily

25   explained by the manner in which the ligand alters the
metal-oxo-hydroxide lattice. In freshly precipitated iron
oxo-hydroxide a ferrihydrite-like structure is observed
with some clear crystalline regions: the addition of
ligand B, in this case tryptophan, reduces the extent of

30   crystallinity while the addition of ligand A and B, in
this case trypotphan and tartrate, almost negate the
crystallinity entirely (Figure 11). Maltofer, which is an
organic ligand coated iron mineral particle, appeared more
like freshly precipitated iron oxo-hydroxide, indicating

that the ligand had not significantly modified its primary
structure. This comparison is best observed using X-ray
diffraction where iron hydroxide peaks are not detected
for a ligand-modified poly oxo-hydroxy ferric iron
5   material, but they are seen in Maltofer (Figure 12) albeit
broad and noisy peaks due to the very small size of the
primary particles (a few nanometres).

Gastrointestinal digestion of the solid ligand-modified
10   *poly oxo-hydroxy ferric iron materials*
We compared the disaggregation of some prior art and
commercial iron compounds to that of the ligand-modified
poly oxo-hydroxy ferric iron materials under simulated
gastrointestinal conditions (see Methods). The gastric
15   disaggregation (pH1.2) and the gastric dissolution
profiles of two of the ligand-modified poly oxo-hydroxy
ferric iron materials, in comparison with ferrous
sulphate, ferric oxo-hydroxide and iron polymaltose
(Maltofer), are shown in Figure 10. Ferrous sulphate
20   disaggregates and dissolves very well at acidic pH as is
expected for a metal salt. Conversely, Maltofer
disaggregates very rapidly in the gastric conditions
(after 5 minutes almost 80% of the iron is disaggregated)
but remains in an aquated particulate form (typically
25   around 20 nm diameter: results not shown) (Figure 10).
Percentage iron dissolution from Maltofer was less than 5%
although it should be noted that there can be a loss of up
to 10% of iron through binding to the ultrafiltration
membrane. In comparison, the two novel ligand-modified
30   poly oxo-hydroxy ferric iron materials had an intermediate
disaggregation profile compared to ferric oxo-hydroxide
and ferrous sulphate. In addition, the dissolution of
these materials closely paralleled the disaggregation
profile under gastric conditions although this need not be

the case for these novel materials. These data show a
clear difference between un-modified ferric oxo-hydroxide,
Maltofer, ferrous sulfate, and our ligand-modified poly
oxo-hydroxy ferric iron materials.

5

Disaggregation of some of our novel ligand-modified poly
oxo-hydroxy ferric iron materials under gastric and
intestinal conditions was also compared to dissagregation
of other commercially available iron compounds, namely

10   ferric pyrophosphate, ferric chloride, ferric trimaltol
and ferrous bisglycinate. The commercial compounds either
failed to disaggregate properly (e.g. ferric
pyrophosphate), or they disaggregated very rapidly (Figure
14). This rapid disaggregation, if paralleled by

15   dissolution, is believed to be responsible for giving rise
to bolus delivery of iron ions in the gut lumen and
likely, therefore, the occurrence of side effects. The
novel ligand-modified poly oxo-hydroxy ferric iron
materials showed a degree of controlled release although,

20   clear differences can be seen in the rates of
disagreggation for the novel materials, indicating that
their properties can be tailored as required (Figure 14).
It should be noted in Figure 14 that whether iron remains
in solution or not at pH 7.0 is merely a function of

25   whether chelators/ligands are present (as they will
naturally be in the gut) and so the data for ferrous
sulphate and ferric chloride (where no ligand is present
in the compound) should not be over-interpreted.   ·

30   Iron disaggregation and dissolution under both gastric and
intestinal conditions for some ligand-modified poly oxo-
hydroxy ferric iron materials that were tested further in
human volunteers (see below) are presented in Figure 15.
Again we show a range of different disaggregation and

dissolution profiles for the novel materials, illustrating the possibility of tailoring them as required.

5   A study of the particle size distribution after passage through the modified gastrointestinal digestive assay of some tartrate-modified poly oxo-hydroxy ferric iron material is shown in Figure 17. Changing the M:L ratio (first vs second bar), pH of preparation (second vs third bar) and type of ligand B (fourth bar) clearly affects the
10   size of particles obtained and therefore disaggregation/dissolution profiles. There is especially an increase in smaller particle sizes with increasing tartrate concentrations indicating less aggregation of the primary particles with increasing L content. In addition,
15   the higher the pH of preparation, the smaller the resulting particle size.

Iron absorption in humans of the solid ligand-modified poly oxo-hydroxy iron ferric materials
20   Seven ligand-modified poly oxo-hydroxy ferric iron materials have been assessed further for their absorption in human volunteers and the results compared with unmodified ferric oxo-hydroxide. A summary of the results is shown in Table 4.

25   *Table 4: In vivo absorption of different ligand-modified poly oxo-hydroxy ferric iron materials:*

Compound	Serum Fe increase at 180 min	% absorption
FeOHT-3:1-Ad20	9 ± 3	5.8 ± 0.9
FeOHM-4:1-Bic25	5.2 ± 0.6	1.9 ± 0.5
FeOHT-2:1-Niacin50	3 ± 2	2.8 ± 0.7
FeOHT-2:1-TRP15	8 ± 3	5 ± 1

FeOHGluconic20	4.3 ± 0.5	6 ± 2
FeOHHistidine100	6.0 ± 0.4	3 ± 2
FeOHAdipate100	8 ± 4	18 ± 1
FeOH	-1.3 ± 0.2 *	0.9 ± 1

Serum iron increase three hours after ingestion and percentage iron absorption (calculated as the red blood cell incorporation of 58Fe divided by 0.80) of solid ligand-modified poly oxo-hydroxy ferric iron materials.

5   Mean ± SEM (n ranges from 2-4); * for FeOH at 180min there was a decrease from the baseline serum iron value.

The serum absorption profiles of the compounds (Figure 13) show that the novel ligand-modified poly oxo-hydroxy

10 ferric iron materials have much lower rates of iron absorption than ferrous sulphate which may be advantageous as this will prevent systemic exposure and potential damage from transiently high levels of iron. There was clear iron absorption from all formulations (Figure 13)

15 and for at least one preparation this is estimated to be equivalent to ferrous sulphate. It is especially noteworthy that literature reports indicate that ferric polymaltose yields no detectable rise in serum iron following ingestion and, that absorption of iron is very

20 low (Kaltwasser et al, 1987) and would be consistent with our data for ferric oxo-hydroxide.

The compounds FeOHT-2:1-TRP15 and FeOHGluconic20 are examples of how changing the composition of these novel

25 materials changes their serum iron profile but maintains the same percentage of iron absorption (Figure 13) again indicating that the materials can be tailored to achieve desired outcomes.

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herein or filed with this application, including
references filed as part of an Information Disclosure
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The term "comprising" as used in this specification and
claims means "consisting at least in part of". When
interpreting statements in this specification and claims
which include "comprising", other features besides the
5   features prefaced by this term in each statement can also be
present. Related terms such as "comprise" and "comprised"
are to be interpreted in similar manner.

In this specification where reference has been made to
10   patent specifications, other external documents, or other
sources of information, this is generally for the purpose of
providing a context for discussing the features of the
invention. Unless specifically stated otherwise, reference
to such external documents is not to be construed as an
15   admission that such documents, or such sources of
information, in any jurisdiction, are prior art, or form any
part of the common general knowledge in the art.

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Claims:

1. A process for producing a solid ligand-modified poly oxo-hydroxy metal ion material ($M_x L_y (OH)_n$) wherein:

M represents one or more metal ions selected from Ag^{2+}, Al^{3+}, Au^{3+}, Be^{2+}, Ca^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Eu^{3+}, Fe^{3+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, Sr^{2+}, V^{5+}, Zn^{2+} and Zr^{2+},

L represents one or more ligands which comprise a ligand selected from a carboxylic acid, maltol, ethyl maltol, vanillin, bicarbonate, sulphate, phosphate, silicate, borate, molybdate, selenate, tryptophan, glutamine, proline, valine, histidine, folate, ascorbate, pyridoxine, niacin, adipate, acetate, glutarate, dimethyl glutarate, pimelate, succinate, benzoate and propionate, and

OH represents oxo or hydroxy groups,

wherein the material has a polymeric structure and wherein the gross solid ligand-modified poly oxo-hydroxy metal ion material has one or more reproducible physico-chemical properties and displays M-L bonding for at least one ligand that can be detected by physical analytical techniques,

wherein the polymeric structure in which the M, L and oxo or hydroxy groups are distributed within the solid phase structure is such that the substitution of the oxo or hydroxy groups by the one or more ligands is substantially random,

the process comprising:

(a) mixing the metal ions M and the ligands L at a first pH(A) at which the components are soluble;

(b) changing the pH(A) to a second pH(B) to cause a solid precipitate of the solid ligand-modified poly oxo-hydroxy metal ion material to be formed; and

(c) separating, and optionally drying, the solid ligand-modified poly oxo-hydroxy metal ion material produced in step (b).

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2.   The process of claim 1, further comprising formulating
the solid ligand-modified poly oxo-hydroxy metal ion
material in a composition for administration to a subject.

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3.   The process of claim 2, wherein the step of formulating
the material comprises adding an excipient.

4.   The process of claim 3, wherein the composition is for
10   use as a nutritional, medical, cosmetic or other
biologically applicable composition.

5.   The process of any one of claims 1 to 4, wherein the
composition is for delivery of the metal ion or the ligand
15   to a subject.

6.   The process of any one of claims 1 to 4, wherein the
composition is for sequestering or inhibiting a component
present using the solid ligand-modified poly oxo-hydroxy
20   metal ion material.

7.   The process of any one of the preceding claims, wherein
the pH(A) is above a pH at which oxo-hydroxy polymerisation
of the corresponding metal oxo-hydroxide commences.

25

8.   The process of any one of the preceding claims, wherein
the pH is changed from pH(A) to pH(B) by the addition of
alkali.

30   9.   The process of claim 8, wherein the alkali is added as
a solution of sodium hydroxide, potassium hydroxide or
sodium bicarbonate to increase the concentration of OH in
the mixture of step (b).

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10. The process of claim 8 or claim 9, wherein pH(A) is less than or equal to pH 2 and pH(B) is greater than or equal to pH 2.

5   11. The process of any one of claims 1 to 7, wherein the pH is changed from pH(A) to pH(B) by the addition of acid.

12. The process of claim 11, wherein the acid is added as a mineral acid or an organic acid to decrease the
10   concentration of OH in the mixture of step (b).

13. The process of claim 11 or claim 12, wherein pH(B) is less than or equal to pH 2 and pH(A) is greater than or equal to pH 2.

15

14. The process of any one of the preceding claims, wherein the one or more reproducible physico-chemical properties are selected from dissolution (rate, pH dependence and pM dependence), adsorption and absorption characteristics,
20   reactivity-inertness, melting point, temperature resistance, particle size, magnetism, electrical properties, density, light absorbing/reflecting properties, hardness-softness, colour and encapsulation properties.

25   15. The process of claim 14, wherein the reproducible physico-chemical property is reproducible within a limit of ± 10%

16. The process of claim 14, wherein the reproducible
30   physico-chemical property is reproducible within a limit of ± 5%.

17. The process of claim 14, wherein the reproducible physico-chemical property is reproducible within a limit of

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± 2%.

18. The process of any one of the preceding claims, wherein
the polymeric structure in which the M, L and oxo or hydroxy

5   groups are distributed within the solid phase structure is
such that the substitution of the oxo or hydroxy groups by
the one or more ligands is substantially random.

19. The process of any one of the preceding claims, wherein

10   the metal ion (M) is Fe^{3+}.

20. The process of any one of the preceding claims, wherein
the carboxylic acid ligand is selected from adipic acid,
glutaric acid, tartaric acid, malic acid, succinic acid,
aspartic acid, pimelic acid, citric acid, gluconic acid,

15   lactic acid and benzoic acid.

21. The process of any one of the preceding claims, wherein
the ligand has buffering properties or a buffer is present
in a medium for carrying out the process.

20

22. The process of claim 21, wherein the buffer is selected
from an inorganic buffer, such as borate, silicate or
bicarbonate, or an organic buffer such as MOPS, HEPES, PIPES
or TRIS, or a buffer selected from adipic acid, pimelic

25   acid, tryptophan or hydroxymethylcellulose.

23. The process of any one of the preceding claims, wherein
the composition is for use an iron supplement.

30   24. A process for producing a solid ligand-modified poly
oxo-hydroxy metal ion material and optimising a desired
physico-chemical property of the material to adapt it for a
nutritional, medical, cosmetic or biologically related
application, wherein the solid ligand-modified poly oxo-

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hydroxy metal ion material is represented by the formula $(M_xL_y(OH)_n)$, wherein

M represents one or more metal ions selected from Ag^{2+}, Al^{3+}, Au^{3+}, Be^{2+}, Ca^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Eu^{3+}, Fe^{3+}, Mg^{2+}, Mn^{2+},

5   Ni^{2+}, Sr^{2+}, V^{5+}, Zn^{2+} and Zr^{2+},

L represents one or more ligands which comprise a ligand selected from a carboxylic acid, maltol, ethyl maltol, vanillin, bicarbonate, sulphate, phosphate, silicate, borate, molybdate, selenate, tryptophan,

10   glutamine, proline, valine, histidine, folate, ascorbate, pyridoxine, niacin, adipate, acetate, glutarate, dimethyl glutarate, pimelate, succinate, benzoate and propionate, and

OH represents oxo or hydroxy groups,

wherein the material has a polymeric structure and

15   wherein the gross solid ligand-modified poly oxo-hydroxy metal ion material has one or more reproducible physico-chemical properties and displays M-L bonding for at least one ligand that can be detected by physical analytical techniques,

20   wherein the polymeric structure in which the M, L and oxo or hydroxy groups are distributed within the solid phase structure is such that the substitution of the oxo or hydroxy groups by the one or more ligands is substantially random,

25   the process comprising:

(a) mixing the metal ion(s) M and the ligand(s) L in a reaction medium at a first pH(A) at which the components are soluble;

(b) changing the pH(A) to a second pH(B) to cause a

30   solid precipitate of the ligand-modified poly oxo-hydroxy metal ion material to be formed;

(c) separating, and optionally drying, the solid ligand-modified poly oxo-hydroxy metal ion material produced in step (b);

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(d) testing the desired physico-chemical characteristic(s) of the precipitated solid ligand-modified poly oxo-hydroxy metal ion material; and

(e) repeating steps (a) to (d) as required by varying

5   one or more of:

(i) the identity or concentration of the metal ion(s) (M) and/or the ligand(s) (L) supplied in step (a); and/or

(ii) the ratio of metal ion(s) (M) to ligand(s) (L) supplied in (a); and/or

10   (iii) pH(A); and/or

(iv) pH(B); and/or

(v) the rate of change from pH(A) to pH(B); and/or

(vi) the presence or concentration of a buffer;

thereby to produce a solid ligand-modified poly oxo-

15   hydroxy metal ion material having the desired physico-chemical property.

25.   The process of claim 24, which further comprises varying a physical or chemical reaction condition used in

20   the process for making the solid ligand-modified poly oxo-hydroxy metal ion material.

26.   The process of claim 25, wherein the physical or chemical reaction condition is selected from the temperature

25   of the reaction, the rate of pH change or the use or the conditions used to mix the reactants.

27.   The process of any one of claims 24 to 26, wherein the first pH(A) is a pH below the pH at which oxo-hydroxy

30   polymerisation of the corresponding metal oxo-hydroxide commences.

28.   The process of claim 27, wherein pH(A) is less than or equal to pH 2 and pH(B) is greater than or equal to pH 2.

29. The process of any one of claims 24 to 28, wherein the pH is changed from pH(A) to pH(B) by the addition of acid.

5   30. The process of claim 29, wherein the acid is added as a mineral acid or an organic acid to decrease the concentration of OH in the mixture of step (b).

31. The process of any one of claims 24 to 26, wherein

10   pH(B) is less than or equal to pH 2 and pH(A) is greater than or equal to pH 2.

32. The process of any one of claims 24 to 31, wherein the pH change from pH(A) to pH(B) occurs in a 24 hour period or

15   less.

33. The process of any one of claims 24 to 32, wherein the concentrations of total metal ions (M) and total ligand (L) are greater than 10^{-6} molar.

20

34. The process of any one of claims 24 to 33, wherein the reaction medium is an aqueous solution.

35. The process of any one of claims 24 to 34, wherein

25   buffer stabilises the pH range of oxo-hydroxy polymerisation.

36. The process of any one of claims 24 to 35, wherein the buffer is selected from an inorganic buffer, such as borate,

30   silicate or bicarbonate, or an organic buffer such as MOPS, HEPES, PIPES or TRIS, or a buffer selected from adipic acid, pimelic acid, tryptophan or hydroxymethylcellulose.

37. The process of any one of claims 24 to 36, wherein the

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buffer concentrations are less than 500 mM.

38.   The process of any one of claims 24 to 37, wherein the
temperature of the reaction is between 0 and 100°C.

5

39.   The process of any one of claims 24 to 38, wherein the
ionic strength of the reaction medium is varied by addition
of electrolyte.

10   40.   The process of claim 24, wherein the components are
mixed in step (a) to form a homogeneous solution.

41.   A process for making a solid ligand-modified poly oxo-
hydroxy metal ion material for administration to a subject,
15   the process comprising having optimised a solid ligand-
modified poly oxo-hydroxy metal ion material according to
the process of any one of claims 24 to 40, the further step
of manufacturing the solid ligand-modified poly oxo-hydroxy
metal ion material in bulk and/or formulating it in a
20   composition.

42.   A ferric iron composition for use in therapy which
comprises a solid ligand-modified poly oxo-hydroxy metal ion
material represented by the formula $(M_xL_y(OH)_n)$, wherein M
25   represents one or more metal ions that comprise Fe^{3+} ions, L
represents one or more ligands and OH represents oxo or
hydroxy groups and wherein the material has a polymeric
structure in which the ligands L are substantially randomly
substituted for the oxo or hydroxy groups, the solid ligand-
30   modified poly oxo-hydroxy metal ion material having one or
more reproducible physico-chemical properties and
demonstrable M-L bonding using physical analysis.

43.   The ferric iron composition for use in therapy of claim

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42, wherein M is Fe^{3+} ions.

44.   The ferric iron composition for use in therapy of claim
42 or claim 43, wherein the substantially randomly solid

5   phase structure of the material produced by substitution of
hydroxy or oxo groups by the ligand L is determinable by an
X-ray diffraction pattern having no identifiable peaks for L
or MO/MOH.

10   45.   The ferric iron composition for use in therapy of any
one of claims 42 to 44, wherein the substantially randomly
solid phase structure of the material produced by
substitution of hydroxy or oxo groups by the ligand L is an
increase in the amorphousness of the structure of the

15   material as determinable by high resolution transmission
electron microscopy.

46.   The ferric iron composition for use in therapy of any
one of claims 42 to 45, wherein the reproducible physico-

20   chemical property is selected from one or more of a
dissolution profile, an adsorption profile or a reproducible
elemental ratio.

47.   The ferric iron composition for use in therapy of claim

25   46, wherein the reproducible elemental ratio is reproducible
within a limit of preferably ± 10%.

48.   The ferric iron composition for use in therapy of any
one of claims 42 to 47, wherein the infrared spectra further

30   comprises one or more peaks for the bonds between M-O, O-H,
and L alone.

49.   The ferric iron composition for use in therapy of any
one of claims 42 to 48, wherein the ligand L comprises

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tartarate or adipate or succinate.

50.   The ferric iron composition for use in therapy of claim
49, wherein the ligand L comprises tartarate and adipate.

51.   The ferric iron composition for use in therapy of claim
49, wherein the ligand L comprises tartrate and succinate.

52.   The ferric iron composition for use in therapy of any
one of claims 42 to 51, wherein the ratio M:L is between
about 1:5 and 5:1.

53.   The ferric iron composition for use in therapy of any
one of claims 42 to 52 which is FeOHAd100 and FeT-3:1-Ad20.

54.   The ferric iron composition for use in therapy of any
one of claims 42 to 53, wherein the composition is a
supplement, a fortificant or a food additive.

55.   The ferric iron composition for use in therapy of any
one of claims 42 to 54, wherein the material is used for the
therapeutic delivery of the metal ion or the ligand to a
subject.

56.   The ferric iron composition for use in therapy of any
one of claims 42 to 54, wherein the material is for use in
the therapeutic removal or inhibition of an endogenous
substance present in the subject that is capable of binding
to the solid ligand-modified poly oxo-hydroxy metal ion
material.

57.   Use of a composition of a solid ligand-modified poly
oxo-hydroxy metal ion material ($M_xL_y(OH)_n$) wherein:
        M represents one or more metal ions selected from Ag^{2+},

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Al^{3+}, Au^{3+}, Be^{2+}, Ca^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Eu^{3+}, Fe^{3+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, Sr^{2+}, V^{5+}, Zn^{2+} and Zr^{2+},

L represents one or more ligands which comprise a ligand selected from a carboxylic acid, maltol, ethyl

5   maltol, vanillin, bicarbonate, sulphate, phosphate, silicate, borate, molybdate, selenate, tryptophan, glutamine, proline, valine, histidine, folate, ascorbate, pyridoxine, niacin, adipate, acetate, glutarate, dimethyl glutarate, pimelate, succinate, benzoate and propionate, and

10   OH represents oxo or hydroxy groups,

wherein the material has a polymeric structure and wherein the gross solid ligand-modified poly oxo-hydroxy metal ion material has one or more reproducible physico-chemical properties and displays M-L bonding for at least

15   one ligand that can be detected by physical analytical techniques, and

wherein the polymeric structure in which the M, L and oxo or hydroxy groups are distributed within the solid phase structure is such that the substitution of the oxo or

20   hydroxy groups by the one or more ligands is substantially random for the preparation of a medicament for the treatment of mineral deficiency, metal deficiency, iron deficiency or anaemia.

25   58. A solid ligand-modified poly oxo-hydroxy metal ion material ($M_xL_y(OH)_n$) for use in therapy wherein:

M represents one or more metal ions selected from Ag^{2+}, Al^{3+}, Au^{3+}, Be^{2+}, Ca^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Eu^{3+}, Fe^{3+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, Sr^{2+}, V^{5+}, Zn^{2+} and Zr^{2+},

30   L represents one or more ligands which comprise a ligand selected from a carboxylic acid, maltol, ethyl maltol, vanillin, bicarbonate, sulphate, phosphate, silicate, borate, molybdate, selenate, tryptophan, glutamine, proline, valine, histidine, folate, ascorbate,

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pyridoxine, niacin, adipate, acetate, glutarate, dimethyl glutarate, pimelate, succinate, benzoate and propionate, and OH represents oxo or hydroxy groups,

wherein the material has a polymeric structure and

5   wherein the gross solid ligand-modified poly oxo-hydroxy metal ion material has one or more reproducible physico-chemical properties and displays M-L bonding for at least one ligand that can be detected by physical analytical techniques, and

10   wherein the polymeric structure in which the M, L and oxo or hydroxy groups are distributed within the solid phase structure is such that the substitution of the oxo or hydroxy groups by the one or more ligands is substantially random.

15

59.   The use or the solid ligand-modified poly oxo-hydroxy metal ion material for use in therapy of claim 58, wherein the metal ion (M) is Fe^{3+}.

20   60.   The use of claim 57 or the solid ligand-modified poly oxo-hydroxy metal ion material for use in therapy of claim 58, wherein the carboxylic acid ligand is selected from adipic acid, glutaric acid, tartaric acid, malic acid, succinic acid, aspartic acid, pimelic acid, citric acid, 25   gluconic acid, lactic acid and benzoic acid.

61.   The use of claim 57 or the solid ligand-modified poly oxo-hydroxy metal ion material for use in therapy of claim 58, wherein the ligand has buffering properties or a buffer 30   is present in a medium for carrying out the process.

62.   The use or the solid ligand-modified poly oxo-hydroxy metal ion material for use in therapy of claim 61, wherein the buffer is selected from an inorganic buffer, such as

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borate, silicate or bicarbonate, or an organic buffer such

as MOPS, HEPES, PIPES or TRIS, or a buffer selected from

adipic acid, pimelic acid, tryptophan or

hydroxymethylcellulose.

5

A
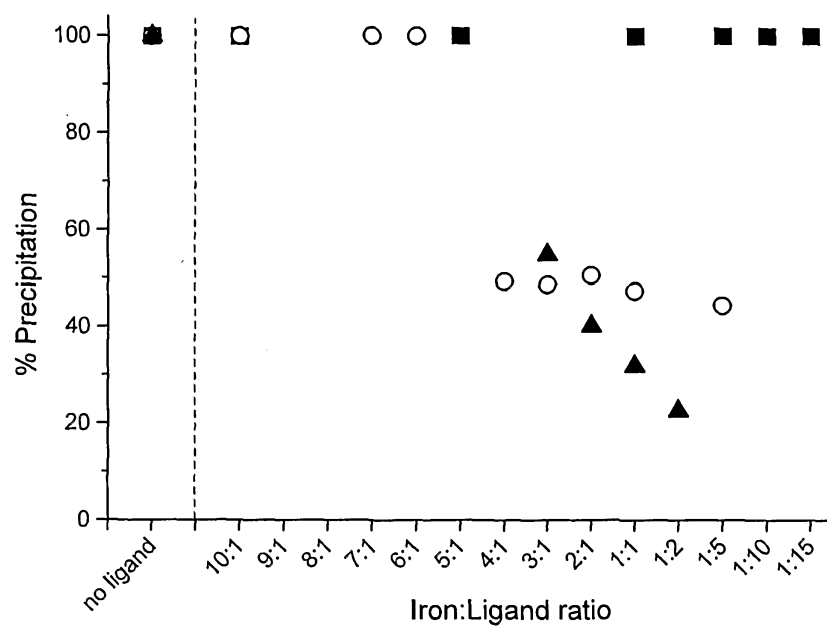
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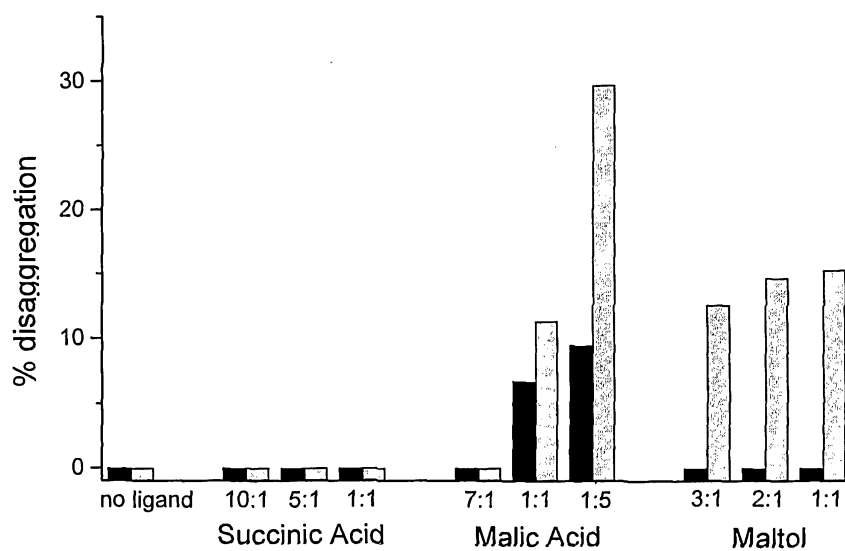
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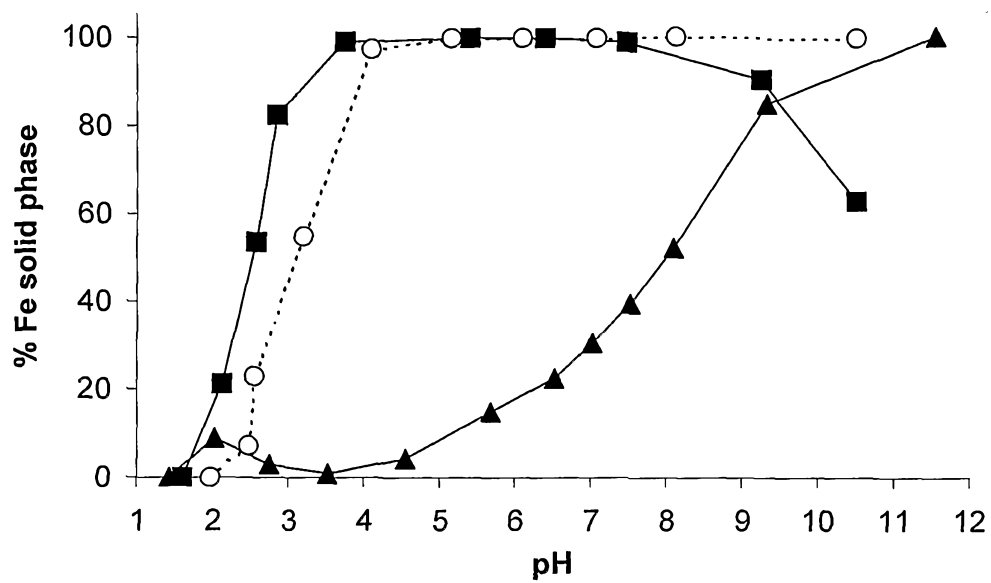
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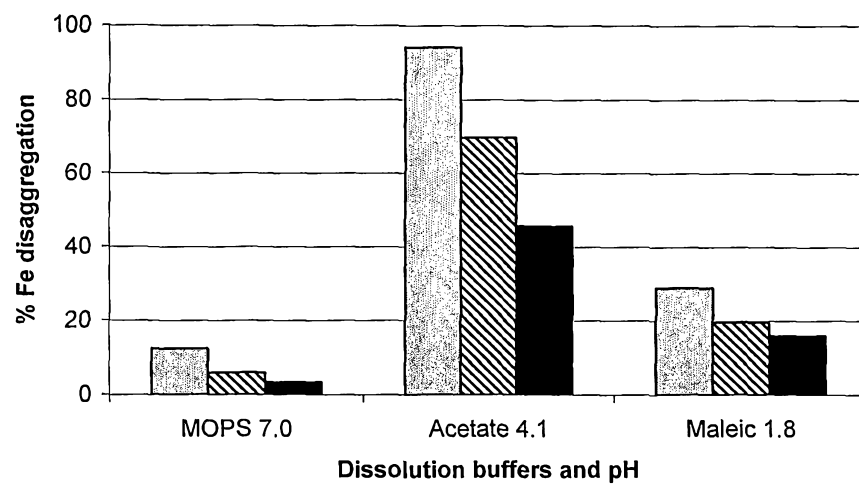
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A

B
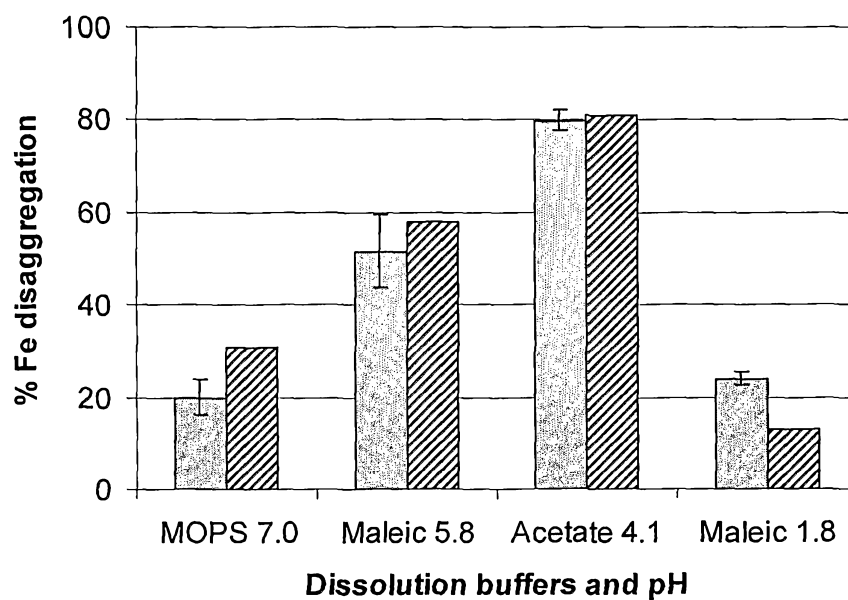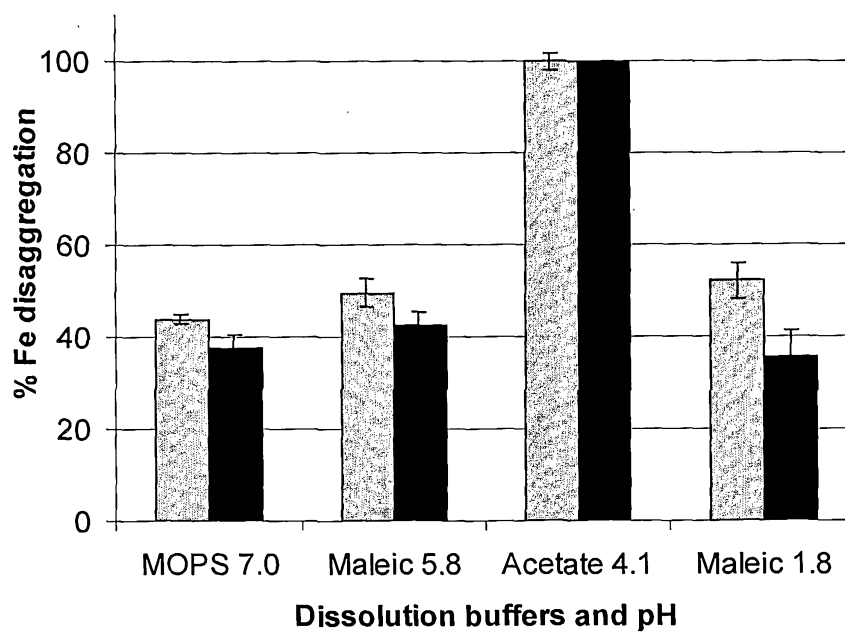
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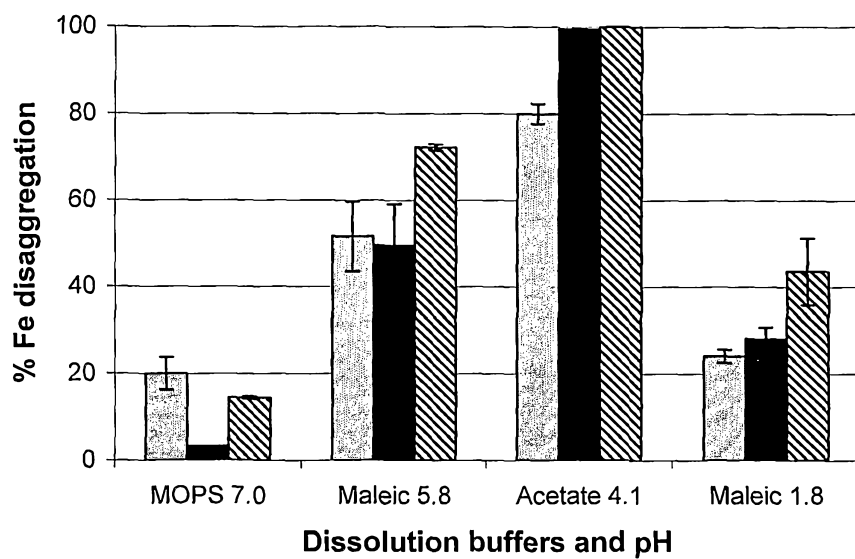
Figure 5

(i)
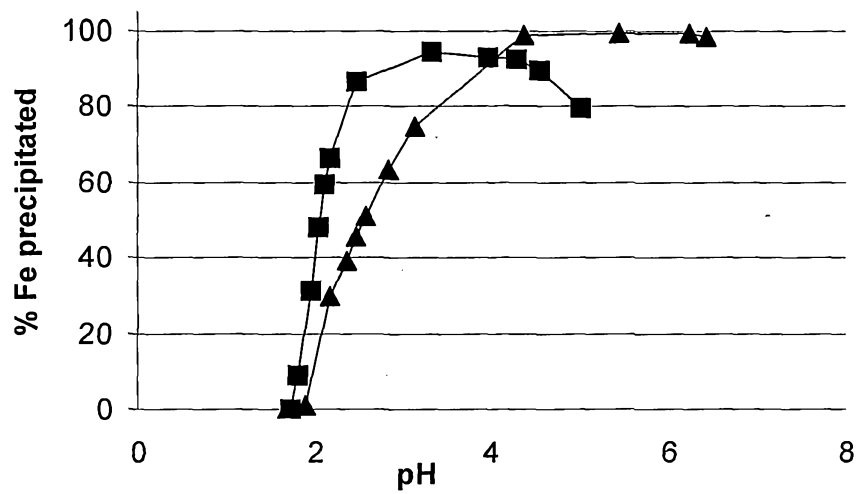
(ii)
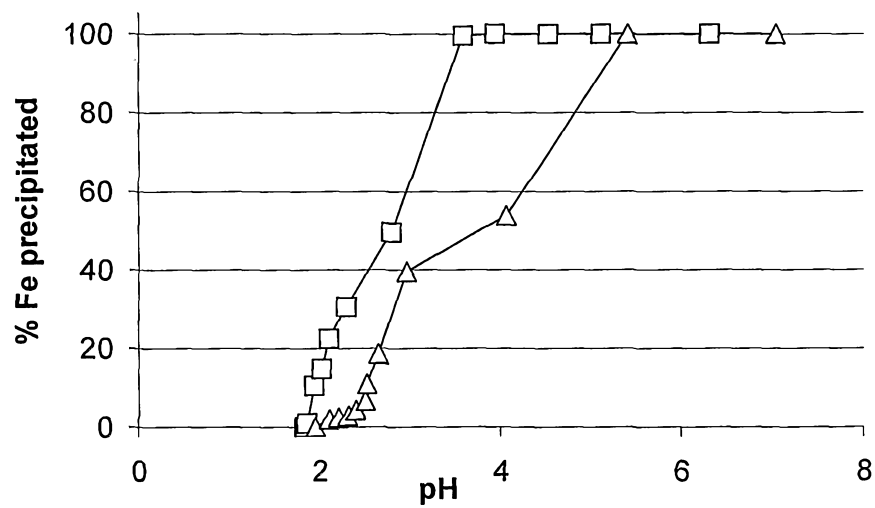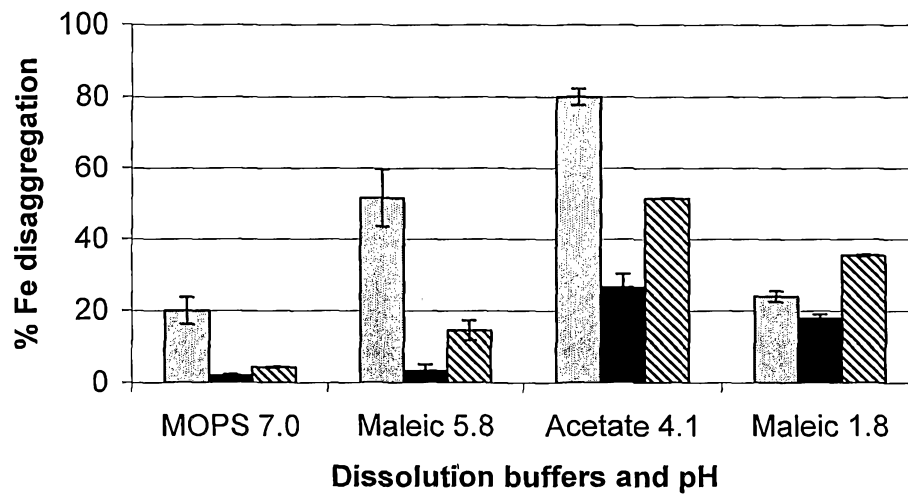
Figure 6

Figure 7
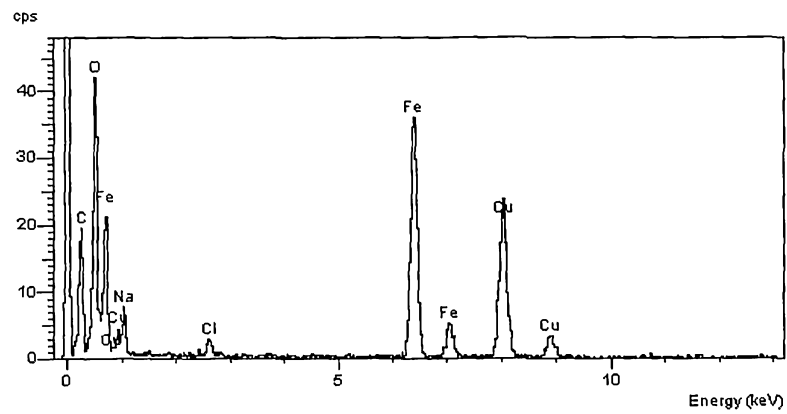
Figure 8

Figure 9

A

B
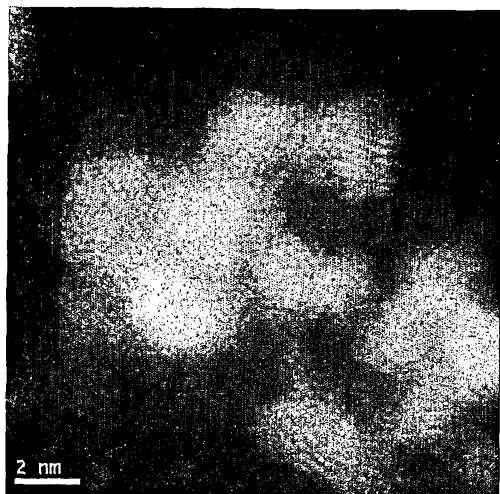

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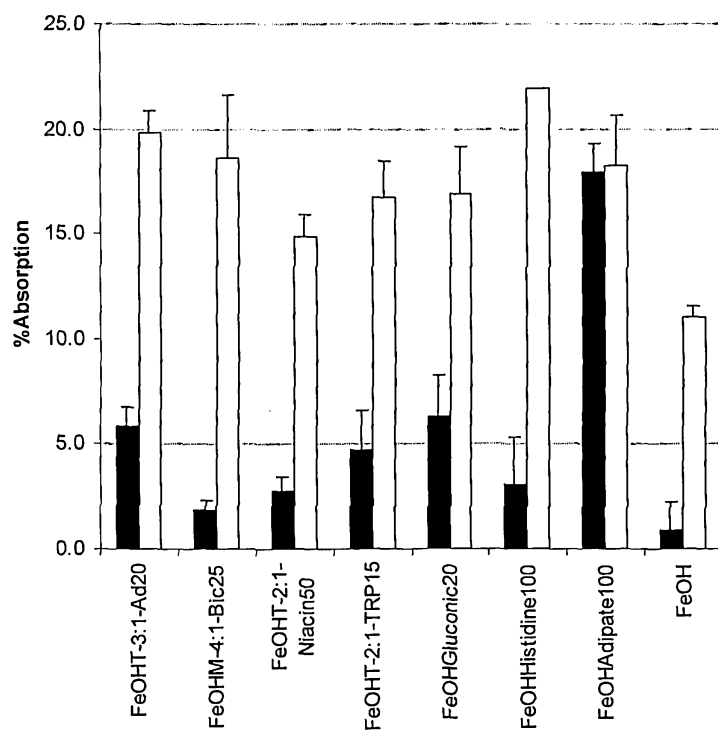
A

B

C

Figure 11

A

Iron hydroxide

B

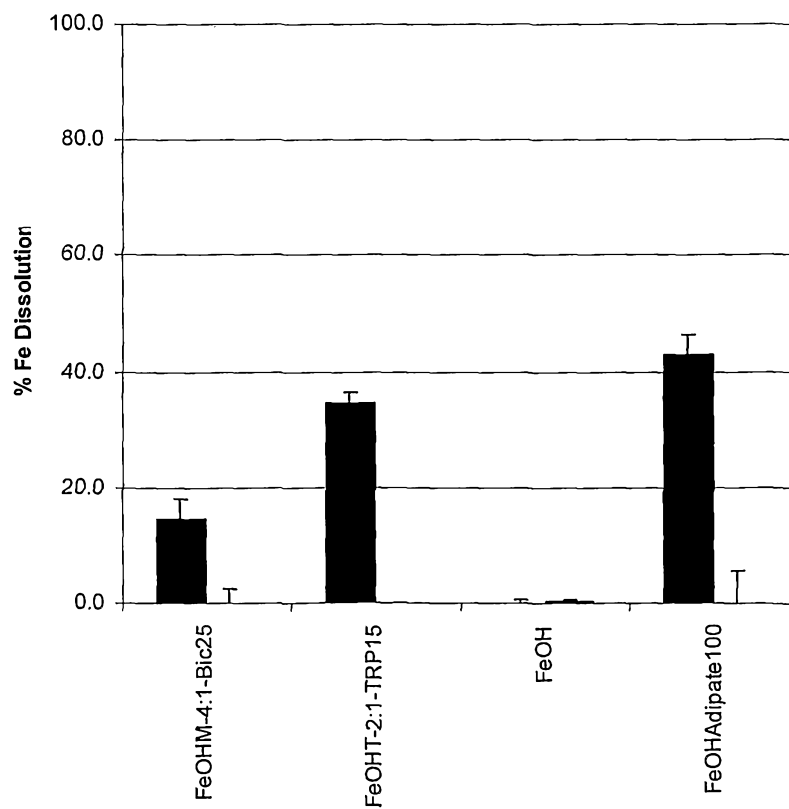Sodium chloride

Position [°2Theta]
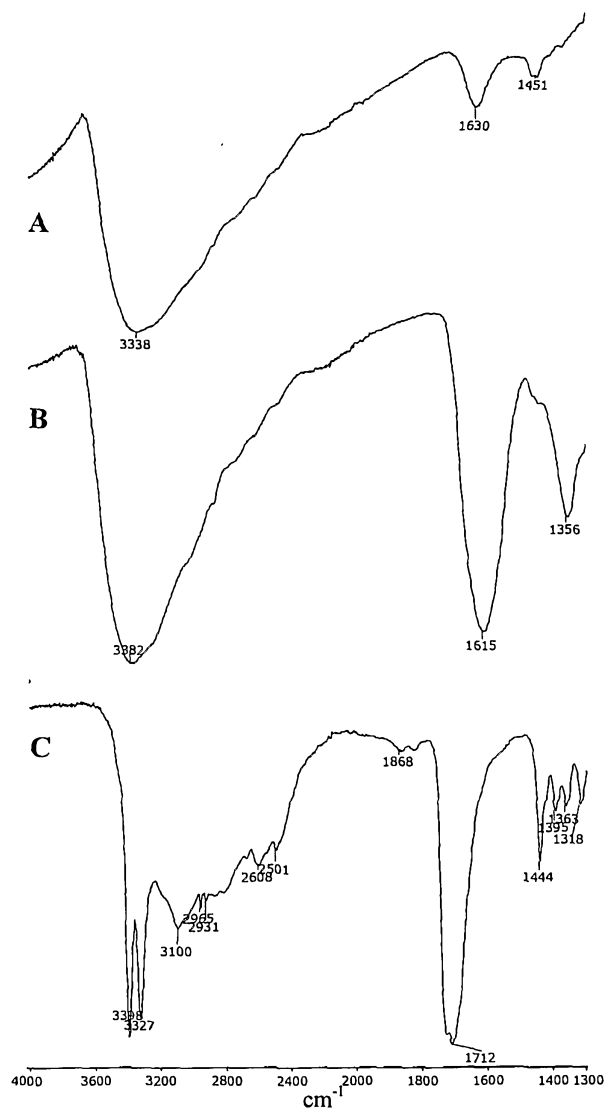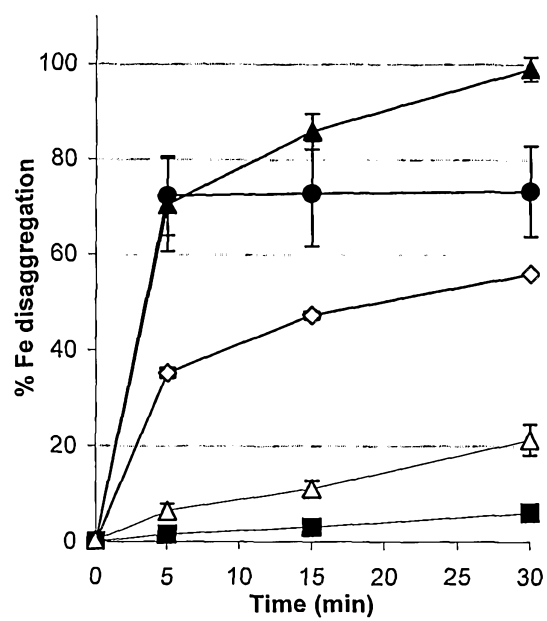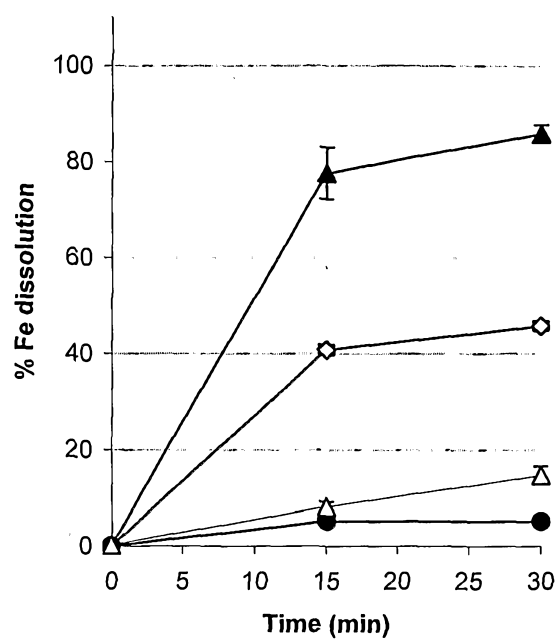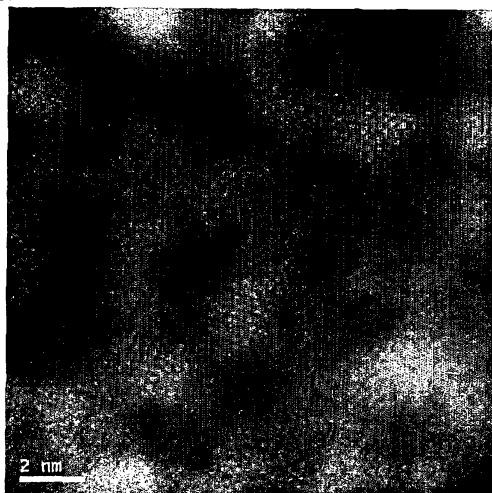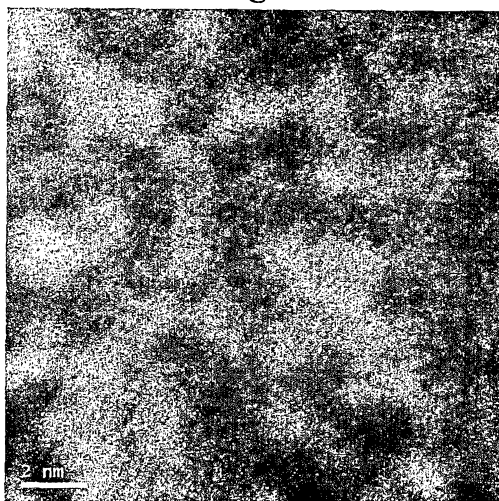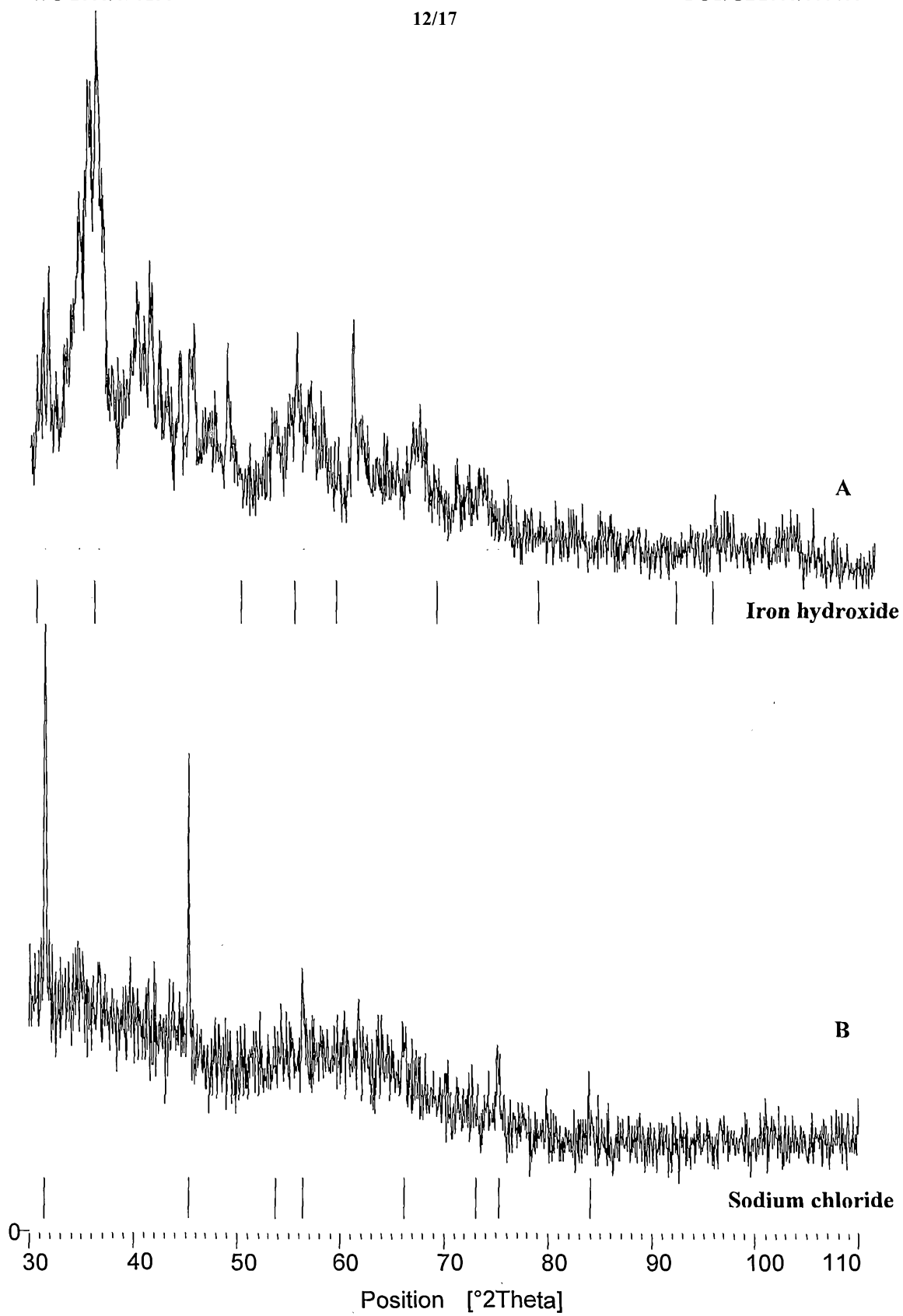
FIG 12

A
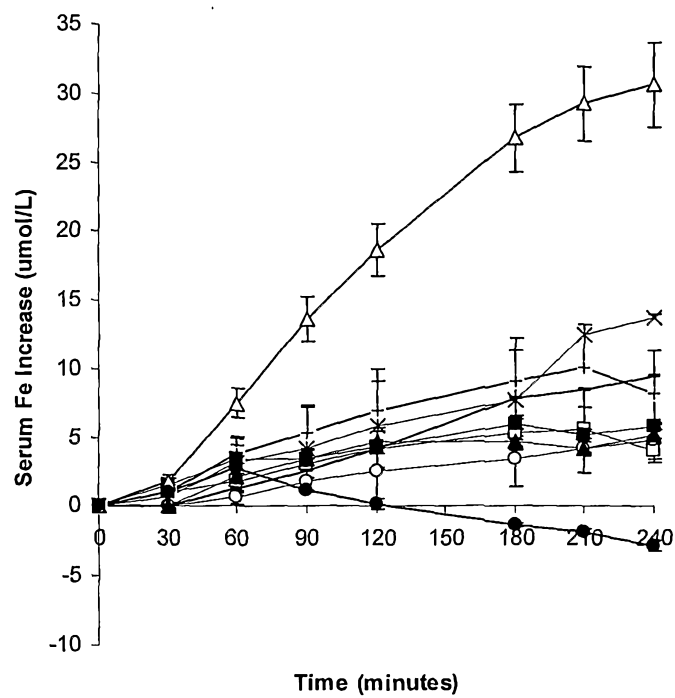
B

Figure 13

A

B
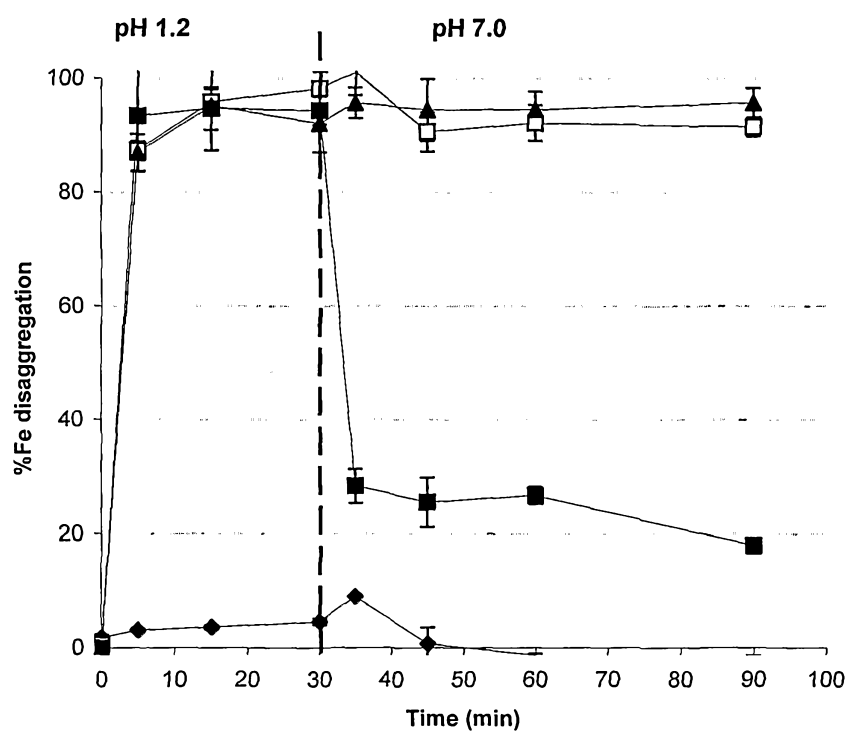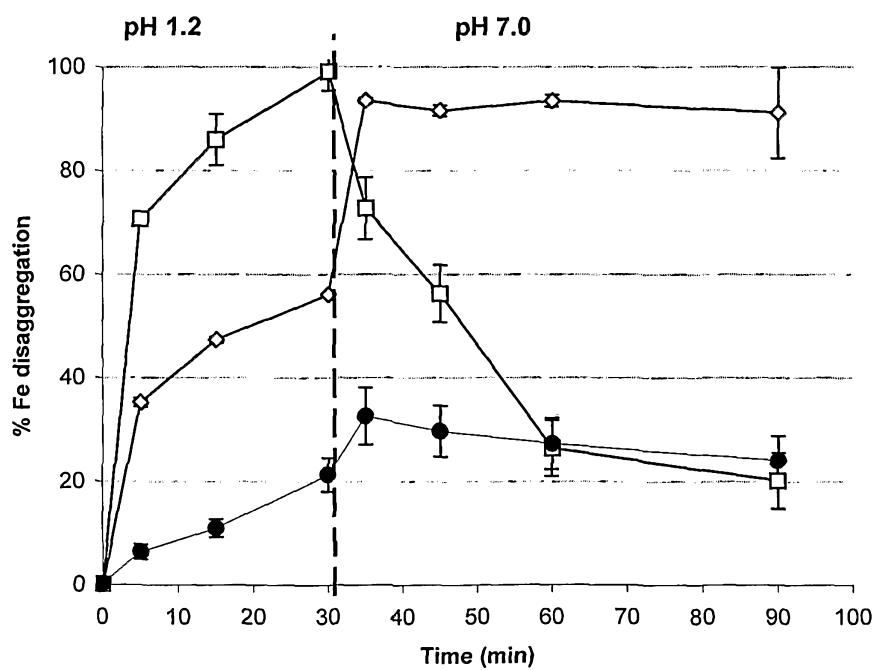
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A
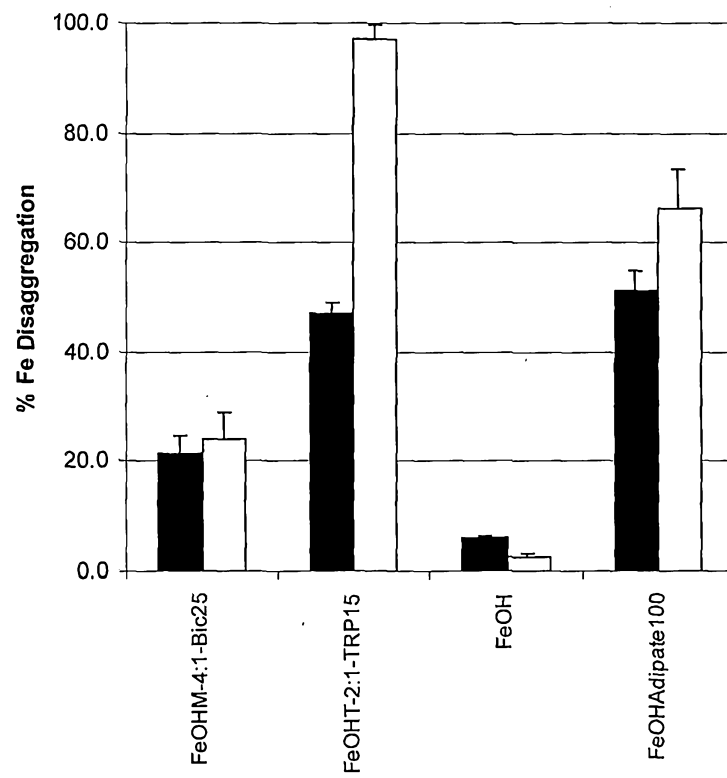
B

Figure 15

Figure 16

Figure 17