



- (51) **International Patent Classification:**
A61K 33/24 (2006.01) *C01B 17/64* (2006.01)
- (21) **International Application Number:**
PCT/GB2016/050133
- (22) **International Filing Date:**
21 January 2016 (21.01.2016)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
1501000.2 21 January 2015 (21.01.2015) GB
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(81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) **Title:** LANTHANUM THIOSULFATE AND METHODS OF PREPARATION OF THE SAME

(57) **Abstract:** There is provided compositions and methods of preparation of compositions that can be used for the treatment of diseases such as end stage renal disease and chronic renal insufficiency, and particularly to lanthanum and thiosulfate compositions, use of these compositions for the treatment of diseases such as end stage renal disease, chronic kidney disease and/or chronic renal insufficiency, and methods of preparation of the same.



WO 2016/116759 A1

Lanthanum Thiosulfate and Methods of Preparation of the Same

Field of the Invention

5 The present invention relates to the field of compositions and methods of preparation of compositions that can be used for the treatment of diseases such as end stage renal disease and chronic renal insufficiency, specifically to lanthanum and thiosulfate compositions, use of these compositions for the treatment of diseases such as end stage renal disease and chronic renal insufficiency, and methods of preparation of the same.

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Background of the Invention

In patients with end stage renal disease (ESRD), or chronic kidney disease (CKD), the kidneys are no longer capable of efficiently filtering and excreting wastes, resulting in increased concentrations of toxins and salts in the blood. ESRD patients normally require kidney dialysis to purify the blood of these unwanted materials. Phosphate normally enters a patient's serum by the ingestion of foods containing phosphates, which are very common in modern processed foods. Although phosphate is removed from a patient's blood, to some extent, during the kidney dialysis procedure, most kidney dialysis patients are not on daily dialysis and therefore require constant treatment for high levels of serum phosphate. Elevated phosphate levels are not only hazardous because they can lead to weakening of the bones and hardening of the arteries, but they are also independently associated with increased mortality on dialysis.

25 When circulating phosphate levels are high, calcium and phosphate combine to lower the production of vitamin D and activate parathyroid hormone to release calcium from the bones (a condition known as secondary hyperparathyroidism). If left untreated, this condition can result in renal osteodystrophy, which is similar to osteoporosis, and is frequently associated with significant bone disease, fractures, and bone pain. High calcium phosphate levels can also lead to cardiovascular disease (CVD), which is associated with atherosclerosis.

To minimize the risk of elevated serum phosphate levels, ESRD and CKD patients must restrict dietary phosphorus intake and use oral phosphate-binding drugs to reduce absorption of phosphate from the gastrointestinal tract. Calcium-based phosphate binders are often used, for example, but have negative side effects including hypercalcemia and long-term progressive cardiovascular and soft tissue calcification. Lanthanum-based

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phosphate binders are a good alternative to calcium-based phosphate binders, and are now a common treatment for elevated serum phosphate levels.

As mentioned above, elevated levels of calcium for patients with end stage renal disease, for example, can lead to the formation of calcium phosphate in the blood, leading to a variety of problems. Calcium binders are often administered to sequester the calcium, and these include thiosulfate salts, such as sodium thiosulfate, for example.

Typically, thiosulfate salts are administered parentally by slow intravenous infusion due to the poor bioavailability of thiosulfate salts if administered orally.

It is often the case that patients with end stage renal disease suffer from both elevated phosphate levels and elevated calcium levels, and therefore, may be required to take lanthanum-based phosphate binders orally, and to take thiosulfate-based calcium binders intravenously. Such a course of treatments is inconvenient for the patient as they are typically required to both take tablets comprising the phosphate binder, and to travel to a hospital or health centre for the intravenous administration of the calcium binder. Furthermore, intravenous administration requires the presence of a healthcare professional, and the treatment is uncomfortable for the patient.

Accordingly, there remains a need for a treatment that includes both a phosphate binder and a calcium binder in a simple treatment that can be self-administered by the patient without the requirement for a healthcare profession to be present.

Therefore, it is at least one object of the present invention to provide a composition comprising both a calcium binder and a phosphate binder, and methods of preparation of the same.

Furthermore, lanthanum thiosulfate, one compound that comprises both a phosphate binder (lanthanum ion) and a calcium binder (thiosulfate ion), has not as yet been made in a stable form that could be administered to patients.

Therefore, it is a further object of the invention to provide a method of preparation of lanthanum thiosulfate in which the compound produced is in a form which is suitable for therapeutic application.

Statements of the Invention

According to a first aspect of the invention, there is provided a method of preparing lanthanum thiosulfate comprising the steps:

- 5 (a) mixing barium thiosulfate and lanthanum sulfate in water to produce a mixture of barium sulfate and lanthanum thiosulfate in water;
- (b) removal of barium sulfate sediment from the mixture to give an aqueous solution of lanthanum thiosulfate; and
- (c) freeze-drying the aqueous solution to obtain solid lanthanum
10 thiosulfate.

Typically, the barium thiosulfate and lanthanum sulfate react in a double decomposition to produce the barium sulfate and lanthanum thiosulfate mixture. The skilled person in the art will appreciate that the term “double decomposition reaction” refers to the reaction between
15 two compounds, typically metal salts, in which parts of each species is interchanged to form two new compounds, such as the double decomposition of AB and XY producing the products AY and XB, for example.

Preferably, the method comprises the additional step of (d) concentrating the aqueous
20 solution of lanthanum thiosulfate obtained in step (b) under vacuum to give a concentrated solution before the concentrated solution is freeze-dried in step (c). Preferably, the concentrated solution is freeze-dried to obtain lanthanum thiosulfate.

“Concentrating the solution” typically refers to removal of solvent (in this case water) from
25 the solution to increase the concentration of the product (in this case lanthanum thiosulfate) within the solution.

The step of concentrating the solution typically increases the efficiency of step (c).

30 Typically, attempts to synthesise lanthanum thiosulfate reported in the art, (for example, Dutt, Jour. Indian Chem. Soc., Vol.26, No.9, 1949, and Pinto et al. Rev. Port. Quim., **15**, 96, 1973) use the step of adding an alcohol to the reactant mixture to induce precipitation of the product from solution. However, alcohol precipitation has been observed to result in at least partial decomposition of the thiosulfate ion into a mixture of free sulfur (S(s)) and sulfite ions
35 (SO_3^{2-}), thereby rendering the product unsuitable for a therapeutic application.

Accordingly, there has been a long-felt need that, despite great interest in the compound, no one has yet been able to satisfy.

Surprisingly, the inventors have found that using the present method for preparation of lanthanum thiosulfate from barium thiosulfate allows the extraction of the desired product from the reactant mixture without the use of alcohol induced precipitation. The inventors have found that, due to the insolubility of the barium sulfate side product in water, the barium sulfate precipitates out of solution as it is formed, and therefore, may be removed from the reactant mixture using physical methods, such as filtration or centrifugation, rather than requiring the addition of an alcohol such as methanol or ethanol to precipitate the product from the solution. Therefore, the resultant product does not suffer from the decomposition of the thiosulfate ion as described in the attempts to synthesise lanthanum thiosulfate known in the art. Thus, the present method overcomes the shortcomings of the prior processes and for the first time produces a form of lanthanum thiosulfate that is suitable for use therapeutically.

Accordingly there is provided lanthanum thiosulfate in a form suitable for use in therapy, including as a calcium ion sequestering agent and/or as a phosphate ion sequestering agent, and/or as a calcium binder and as a phosphate binder in therapy such as in the treatment or prevention of end stage renal disease (ESRD), chronic kidney disease (CKD), and/or chronic renal insufficiency. According to a further aspect there is provided a process for the preparation of lanthanum thiosulfate in a form suitable for use in therapy, including as a calcium ion sequestering agent and/or as a phosphate ion sequestering agent, and/or as a calcium binder and as a phosphate binder in therapy, and for use of the so-produced lanthanum thiosulfate in such therapy.

Preferably, the barium thiosulfate is prepared by a double decomposition reaction of a barium halide and an alkali metal thiosulfate. The barium halide may be chosen from barium chloride, barium bromide, or barium iodide, in any suitable form, such as anhydrous or hydrated forms thereof. Preferably, the barium halide is barium chloride in anhydrous or a hydrated form thereof, such as barium chloride dihydrate ($\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$). The alkali metal thiosulfate is preferably sodium thiosulfate, but may be potassium thiosulfate or lithium thiosulfate.

Preferably, step (b) comprises removing barium sulfate by filtration. Alternatively, step (b) may comprise removing barium sulfate by centrifugation.

In embodiments where barium sulfate is removed by filtration, the barium sulfate may be removed by gravity filtration, but preferably the barium sulfate is removed by vacuum filtration. The method may comprise a further filtration step to remove any residual barium sulfate. The step of further filtration may be carried out using an ultrafilter.

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Preferably, step (d) is carried out at or below 26°C. For example, step (d) may be carried out at a temperature of: 20°C; 15°C; 10°C; or 5°C or at a temperature in the range of: between 1°C and 20°C; between 1°C and 15°C; between 1°C and 10°C; or between 1°C and 5°C. Preferably, step (d) is carried out a temperature in the range of between 1°C and 10°C, and more preferably, between 2°C and 5°C.

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It has been suggested in the art (Pinto et al. Rev. Port. Quim., **15**, 96, 1973) that decomposition of the thiosulfate ion increases with increasing temperature, but in all experimental conditions tested (including varying temperature from 0°C to 50°C) the final product always comprised a mixture of thiosulfate decomposition products, namely free sulfur and thiosulfate.

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The inventors have surprisingly found that the combination of producing the lanthanum thiosulfate from barium thiosulfate, with subsequent concentration and isolation of the lanthanum thiosulfate at a low temperature, such as at or below ambient temperature, the decomposition of thiosulfate is prevented or substantially inhibited, to allow pure, or substantially pure, solid lanthanum thiosulfate to be obtained that is suitable for therapeutic application.

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Preferably, step (c) is carried out by rapidly chilling the aqueous solution or the concentrated solution to below 0°C before evaporating the remaining solvent from the concentrated solution at a temperature below 0°C. The aqueous solution or the concentrated solution may be rapidly chilled to: a temperature in the range of between -1°C and -20°C; and preferably to a temperature of less than -20°C, such as for example a temperature in the range of between -20°C and -30°C, a temperature of less than -30°C, a temperature in the range of between -30°C and -40°C, or a temperature of less than -40°C. More preferably, the aqueous solution or the concentrated solution is rapidly chilled to a temperature of less than -40°C, such as a temperature in the range of -40.5 to 45°C, or -41°C to -45°C, or to a temperature of -45°C or to a temperature of less than -45°C for example.

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The remaining solvent may be evaporated from the concentrated solution at a higher temperature than the temperature to which the concentrated solution is rapidly chilled.

For example, where the aqueous solution is chilled to a temperature of less than -20°C then the remaining solvent may be evaporated from the concentrated solution at a temperature in the range of: below -10°C ; below -15°C ; below -20°C ; at -20°C ; between -1°C and -20°C ; between -10°C and -20°C ; between -10°C and -15°C ; between -15°C and -20°C ; or a temperature between -11°C and -20°C . Preferably, the remaining solvent is evaporated from the concentrated solution at -20°C . Preferably, the remaining solvent is removed from the concentrated solution under vacuum.

According to an aspect step (a) is carried out at a temperature of from 0°C to room temperature, and preferably at a temperature in the range of from 5°C to room temperature, more preferably at about 10°C .

According to an aspect the aqueous solution obtained following step (b) is freeze-dried firstly with a rapid chill to about -45°C followed by evaporation of solvent (water) from the so-concentrated solution at -20°C , and preferably wherein such evaporation is carried out under vacuum.

The invention extends in a second aspect to the use of lanthanum thiosulfate as a calcium ion sequestering agent.

Preferably, the lanthanum thiosulfate in this second aspect is prepared using the method of the first aspect of the invention.

The invention extends in a third aspect to the use of lanthanum thiosulfate as a phosphate ion sequestering agent.

Preferably, the lanthanum thiosulfate in this third aspect is prepared using the method of the first aspect of the invention.

According to a fourth aspect of the invention, there is provided the use of lanthanum thiosulfate as both a calcium ion sequestering agent and a phosphate ion sequestering agent.

Preferably, the lanthanum thiosulfate in this fourth aspect is prepared using the method of the first aspect of the invention.

Therefore, a patient suffering from both phosphate and calcium enrichment of blood serum, such as ESRD and CKD patients, are only required to take a single drug to control the concentration of both the calcium and phosphate levels in their blood, potentially simplifying treatment, and reducing costs for the healthcare provider by allowing them to stock a single drug for both conditions.

There is additionally provided a method of treatment or prevention of diseases, such as end stage renal disease and/or chronic renal insufficiency, which method comprises administering to a mammal in need thereof, a therapeutically effective amount of lanthanum thiosulfate. Preferably, the lanthanum thiosulfate in this additional aspect is prepared using the method of the first aspect of the invention.

According to a fifth aspect of the invention, there is provided a pharmaceutical composition comprising lanthanum thiosulfate, and one or more excipients, carriers and/or diluents. For the avoidance of doubt the terms "pharmaceutical composition" and "composition" are used interchangeably and are intended to refer to the same entity.

Preferably, the lanthanum thiosulfate in this fifth aspect is prepared using the method of the first aspect of the invention.

For the avoidance of doubt, the optional and preferred features of the first aspect are optional and preferred features for the second, third, fourth and fifth aspects.

The lanthanum thiosulfate may be admixed or combined with one or more inert excipients (or carriers), fillers or extenders, binders, humectants, disintegrating agents, solution retarders, absorption accelerators, wetting agents, adsorbents, buffering agents and/or lubricants.

Preferably, the pharmaceutical composition is coated and the lanthanum thiosulfate of or within said composition is encapsulated by the coating. Accordingly, the lanthanum thiosulfate (the thiosulfate ion in particular) is protected from decomposition in the stomach, for example, and therefore, increases the bioavailability of the product. There is provided a pharmaceutical composition comprising lanthanum thiosulfate, and one or more excipients, carriers and/or diluents, wherein said composition is coated and the lanthanum thiosulfate of or within said composition is encapsulated by the coating.

The term "coat" or "coating" as used herein may encompass any form of layer/barrier or encapsulation technology. For example, a "coating" may apply to any protective or barrier layer applied to a pharmaceutical composition comprising lanthanum thiosulfate according to any aspect of this invention.

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Lanthanum thiosulfate of this invention that is suitable for oral administration may be provided in liquid or solid dosage form as a coated or encapsulated tablet, pill, granule or powder. An encapsulated composition may otherwise be known as a "capsule".

- 10 Typically, tablets for oral administration may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine lanthanum thiosulfate in a free-flowing form such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, lubricating agent, surface-active agent or dispersing agent. Moulded tablets may be made by moulding an
- 15 active compound with an inert liquid diluent.

- A composition of this invention may comprise a core component comprising lanthanum thiosulfate and/or one or more other active agents, salts, carriers, diluents and/or excipients and one or more coating and/or encapsulating layers applied to or containing/encapsulating
- 20 the core component. The core component of the compositions of this invention, may comprise a tablet prepared by compression or moulding as described above.

- The compositions of this invention may comprise seal coats and/or enteric coats. A seal coat and/or enteric coat may be applied directly to the core component of a composition of this
- 25 invention. One or more seal coats may be applied to the core component of a composition of this invention and one or more further or additional coats/capsules may be subsequently applied to or over the seal coat(s). For example, one or more enteric coats may be applied to the seal coat(s). Thus, a, or the, seal coat layer(s) may be disposed between the core component of the composition and a capsule or enteric coat(s). A seal coat may form a
- 30 barrier between the core component of a composition of this invention (containing lanthanum thiosulfate, other compounds (including other actives and/or salts) excipients and the like), and any enteric coat or capsule.

- There is provided a pharmaceutical composition comprising lanthanum thiosulfate, and one
- 35 or more excipients, carriers and/or diluents, wherein said composition is coated and the lanthanum thiosulfate of or within said composition is encapsulated by the coating and wherein said coating comprises one or more seal coats and/or one or more enteric coats.

The seal coat may comprise one or more pharmaceutically acceptable film-forming polymers optionally in combination with one or more pharmaceutically acceptable excipient(s). By way of example, a seal coat may comprise a film forming polymeric material, such as hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, methylcellulose, carboxymethylcellulose, hypromellose, acacia, gelatin to increase adherence and coherence of the seal coat.

The seal coat may prime the surface of the core component (by, for example, the provision of a smooth base) for the application of one or more enteric coats and/or a capsule.

In addition to any priming function, a seal coat may prolong the resistance of the thiosulfate ion to acidic conditions, improve stability of lanthanum thiosulfate by minimizing, restricting or preventing interaction between lanthanum thiosulfate and any enteric coating applied to the composition.

An enteric coating may comprise a layer or layers which are stable upon exposure to acid, including stomach acid, but which degrade or break down in more basic conditions. Suitable enteric coatings may comprise, for example, fatty acids, waxes, shellac, plastics, and/or plant fibers. Enteric coatings for use in this invention may comprise methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxy propyl methyl cellulose phthalate, hydroxy propyl methyl cellulose acetate succinate (hypromellose acetate succinate), polyvinyl acetate phthalate (PVAP), methyl methacrylate-methacrylic acid copolymers (for example such as, Eudragit L 30 D-55, Eudragit Li 00-55, Eudragit S 100, Eastacryl 30d, Kollicoat Mae 30 Dp, Kollicoat Mae 100 P), sodium alginate and stearic acid.

Enteric coats may further comprise, for example plasticizers, surfactants, pigments, anti-adherents, opacifying agents, colorants and the like -all of which are routinely used in the preparation of solutions and/or suspensions for use as coatings or enteric coatings.

Plasticizers for use in this invention may comprise polyethylene glycol, tributyl sebacate, acetylated monoglycerides, glycerin, triacetin, phthalate esters, castor oil, sorbitol, polysorbates such as sorbitan monolaurate (Span 20), sorbitan monopalmitate, sorbitan monostearate, sorbitan monoisostearate; citrate ester type plasticizers like triethyl citrate, citrate phthalate; propylene glycol, glycerin, polyethylene glycol (low & high molecular weight), dibutyl sebacate, tributyl sebacate; dibutyltartrate, dibutyl phthalate, glycerol palmitostearate and mixtures thereof.

The compositions of this invention may comprise one or more other salts, for example, carbonate salts. For example, the compositions may comprise a (or one or more) bicarbonate (hydrogen carbonate) salt(s).

5 Surprisingly, the inventors have discovered that thiosulfate-containing compositions, in particular the coated lanthanum thiosulfate compositions for oral administration described herein, when supplemented with bicarbonate salts (for example sodium bicarbonate/sodium hydrogen carbonate) exhibit improved bioavailability of thiosulfate following oral administration. Without wishing to be bound by theory, the inventors suggest that a
10 bicarbonate salt component may neutralise stomach acid and prevent any premature degradation of the thiosulfate in the composition. It is also suggested herein that this may be particularly important where the coating of the thiosulfate composition has been breached or is weak. In addition, it is also known that the putative thiosulfate transporter is trans-stimulated in the presence of bicarbonate ions - thus this may further account for the
15 observed improved bioavailability of orally administered thiosulfate in a composition in accordance with any aspect of this invention.

In addition and again without wishing to be bound by theory, the inventors have noted that coated thiosulfate compositions as described herein which further comprise a quantity of
20 hydrogen carbonate or bicarbonate (HCO_3^-) may facilitate the prevention of metabolic acidosis which can be a side effect of an orally administered thiosulfate salt. Moreover, it is suggested that compositions of this invention which are supplemented with a quantity of coated bicarbonate, will have the advantage of reducing the dose of the thiosulfate salt required.

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The invention extends in a sixth aspect to a kit of parts comprising a pharmaceutical composition comprising lanthanum thiosulfate and a pharmaceutical composition comprising a hydrogen carbonate or bicarbonate salt.

30 In accordance with a further aspect there is provided use of a pharmaceutical composition comprising lanthanum thiosulfate or a kit of parts as detailed hereinbefore, for the treatment of diseases such as end stage renal disease and/or chronic renal insufficiency.

Embodiments of the present invention will now be described, by way of non-limiting
35 example.

Specific Description of Embodiments of the Invention

While the making and using of various embodiments of the present invention are discussed in detail below, it should be appreciated that the present invention provides many applicable inventive concepts that can be embodied in a wide variety of specific contexts. The specific
5 embodiments discussed herein are merely illustrative of specific ways to make and use the invention and do not delimit the scope of the invention.

To facilitate the understanding of this invention, a number of terms are defined below. Terms defined herein have meanings as commonly understood by a person of ordinary skill in the
10 areas relevant to the present invention. Terms such as "a", "an" and "the" are not intended to refer to only a singular entity, but include the general class of which a specific example may be used for illustration. The terminology herein is used to describe specific embodiments of the invention, but their usage does not delimit the invention, except as outlined in the claims.

15 **Experimental Results and Details of Lanthanum Thiosulfate Preparation**

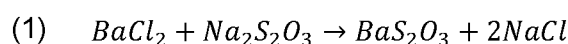
Introduction

Lanthanum thiosulfate is prepared using barium thiosulfate as an intermediate. Barium thiosulfate is only sparingly soluble in water and may be prepared by a double
20 decomposition reaction of barium chloride with sodium thiosulfate, both of which are readily soluble.

If required, the precipitated barium thiosulfate may be further purified by recrystallization from water, using standard methods.

Finally, a solution of the sparingly soluble barium thiosulfate is mixed with a solution of lanthanum sulfate and the precipitated barium sulfate is removed by filtration. Lanthanum thiosulfate is temperature sensitive in solution. It is also very soluble in water. The dilute solution of lanthanum thiosulfate is concentrated by evaporation at low temperature under
30 vacuum. Solid product is obtained by freeze drying of the concentrate.

1) Barium Thiosulfate Hydrate Preparation from Double Decomposition



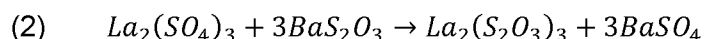
49 g of barium chloride dihydrate (which may be sourced from Sigma-Aldrich Company Ltd, UK) is dissolved in 306 ml of de-ionised water at ambient temperature. 31.8 g of sodium thiosulfate (which may be sourced from Sigma-Aldrich Company Ltd, UK) is dissolved in 90 ml water also at ambient temperature. The solutions are mixed and agitated for 2 hours at 30°C. Quantities may be scaled up as necessary.

The sodium thiosulfate may be either in the hydrated or anhydrous form.

The precipitated white crystals of barium thiosulfate hydrate are filtered, washed with de-ionised water and air or vacuum dried at ambient temperature.

This material may be recrystallized from de-ionised water by producing a saturated solution at 60°C (about 0.5%) and cooling to 5°C in an agitated flask. Crystals are then filtered, washed with de-ionised water and air or vacuum dried at ambient temperature.

2) Lanthanum Thiosulfate Preparation from Double Decomposition



1.05 g of barium thiosulfate hydrate prepared as described above are dissolved in 250 ml de-ionised water at 30°C. 1.1 g of lanthanum sulfate (which may be sourced from Sigma-Aldrich Company Ltd, UK) are dissolved in 100 ml of de-ionised water at ambient temperature. The solutions are mixed and agitated for 12 hours at 10°C. Quantities may be scaled up as necessary.

The solution is filtered using a Whatman grade 5 fine grade filter paper (laboratory scale), or a 0.5µm, 1.0µm or 2.0µm cartridge filter (continuous filtration) to remove the precipitated fine barium sulfate crystals. The filtrate containing the lanthanum thiosulfate obtained will be designated 'Solution P' in the following procedure.

Determining whether the reaction has reached completion

As will be appreciated by the skilled person, double decomposition reactions do not always run to completion, and therefore, it is necessary to test solution P to ensure that the reaction is complete.

50 ml test solutions are made up as follows:

Solution A - 1% barium chloride dihydrate in de-ionised water;

Solution B - 1% lanthanum sulfate in de-ionised water; and

Solution C - 0.1% barium thiosulfate monohydrate in de-ionised water.

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- *Test 1*

A 10 ml sample of solution P is taken from solution P and mixed with a 10 ml sample of solution A and agitated for 2 minutes. A cloudiness indicates an excess of sulfate in solution P.

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- *Test 2*

A 10 ml sample of solution P is taken from solution P and is mixed with a 10 ml sample of solution B and agitated for 2 minutes. A cloudiness indicates an excess of barium in solution P.

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Further samples of solution P are tested by mass spectroscopy for Ba, Cl, La, Na and S.

Small amounts of either solution B (lanthanum sulfate) or solution C (barium thiosulfate) are added to solution P to remove the excess, followed by agitation and filtration. Tests 1 and 2 are repeated on further samples of solution P until the slightest detectable excess of sulfate is present in solution P.

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Solution P is then concentrated by vacuum evaporation to about 10% w/w to produce a concentrated solution P. A Buchi or similar vacuum evaporator should be used with the flask temperature maintained at about 2°C to 5°C.

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The theoretical ratio of the weight of lanthanum and weight of sulfur in the product lanthanum thiosulfate is 1.44. Lanthanum sulfate and lanthanum sulfite both have ratios of 2.89. The inductively coupled plasma mass spectrometry (ICP-MS) analysis of the final concentrated solution gave a result of 1.38 close to the theoretical value for lanthanum thiosulfate.

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The concentrated solution P is then freeze dried – firstly with a rapid chill to about -45°C followed by evaporation of water under vacuum at about -20°C to furnish the desired product in freeze-dried form.

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All of the compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While this invention may be embodied in many different forms, there are described in detail herein specific preferred embodiments of the invention. The present disclosure is an exemplification of the principles of the invention and is not intended to limit the invention to the particular embodiments illustrated. In addition, unless expressly stated to the contrary, use of the term "a" is intended to include "at least one" or "one or more." For example, "a device" is intended to include "at least one device" or "one or more devices."

Any ranges given either in absolute terms or in approximate terms are intended to encompass both, and any definitions used herein are intended to be clarifying and not limiting. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Moreover, all ranges disclosed herein are to be understood to encompass any and all sub-ranges (including all fractional and whole values) subsumed therein.

Furthermore, the invention encompasses any and all possible combinations of some or all of the various embodiments described herein. It should also be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the invention and without diminishing its intended advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

CLAIMS

1. A method of preparing lanthanum thiosulfate comprising the steps:
 - (a) mixing barium thiosulfate and lanthanum sulfate in water to produce a mixture of barium sulfate and lanthanum thiosulfate in water;
 - 5 (b) removal of barium sulfate sediment from the mixture to give an aqueous solution of lanthanum thiosulfate; and
 - (c) freeze-drying the aqueous solution to obtain solid lanthanum thiosulfate.
- 10 2. The method according to Claim 1 wherein the mixing of the barium thiosulfate and lanthanum sulfate comprises a double decomposition reaction.
3. The method according to Claim 1 or 2 wherein step (c) is carried out by rapidly chilling the aqueous solution or the concentrated solution to below 0°C before
15 evaporating the remaining solvent from the concentrated solution at a temperature below 0°C.
4. The method according to any of the preceding Claims comprising the additional step of (d) concentrating the aqueous solution of lanthanum thiosulfate obtained in step
20 (b) under vacuum to give a concentrated solution before the concentrated solution is freeze-dried in step (c).
5. The method according to Claim 4 wherein the concentrated solution is freeze-dried to obtain lanthanum thiosulfate.
- 25 6. The method according to Claim 4 or 5 wherein step (d) is carried out at or below 26 °C.
7. The method according to any of Claims 4 to 6 wherein the aqueous solution or the concentrated solution in step (c) is rapidly chilled to a temperature of less than -20°C.
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8. The method according to any of Claims 4 to 7 wherein the aqueous solution or the concentrated solution in step (d) is rapidly chilled to a temperature of less than -40°C.
- 35 9. The method according to any of Claims 4 to 9 wherein the remaining solvent is evaporated from the concentrated solution at a temperature below -10°C, -15°C, or -20°C, preferably at -20°C.

10. The method according to any of the preceding claims wherein the barium sulfate in step (b) is removed via filtration or centrifugation.

11. A method of preparing lanthanum thiosulfate in accordance with any of Claims 1 to 10 wherein the barium thiosulfate in step (a) is prepared by a double decomposition reaction of a barium halide and an alkali metal thiosulfate, such as barium chloride in anhydrous or a hydrated form thereof, such as barium chloride dihydrate ($\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$) and sodium thiosulfate.

12. Use of lanthanum thiosulfate as a calcium ion sequestering agent, and preferably wherein said lanthanum thiosulfate is prepared in accordance with the method of any of Claims 1 to 11.

13. Use of lanthanum thiosulfate as a phosphate ion sequestering agent, and preferably wherein said lanthanum thiosulfate is prepared in accordance with the method of any of Claims 1 to 11.

14. Use of lanthanum thiosulfate as both a calcium ion sequestering agent and as a phosphate ion sequestering agent, and preferably wherein said lanthanum thiosulfate is prepared in accordance with the method of any of Claims 1 to 11.

15. Lanthanum thiosulfate for use in therapy as a calcium ion sequestering agent and as a phosphate ion sequestering agent, and preferably wherein said lanthanum thiosulfate is prepared in accordance with the method of any of Claims 1 to 11.

16. Lanthanum thiosulfate for use in the treatment or prevention of end stage renal disease or chronic renal insufficiency, and preferably wherein said lanthanum thiosulfate is prepared in accordance with the method of any of Claims 1 to 11.

17. Use of lanthanum thiosulfate as a calcium binder and as a phosphate binder in therapy, such as for use in the treatment or prevention of end stage renal disease, chronic kidney disease, and/or chronic renal insufficiency, and preferably wherein said lanthanum thiosulfate is prepared in accordance with the method of any of Claims 1 to 11.

18. A method of treatment or prevention of diseases, such as end stage renal disease, chronic kidney disease, and/or chronic renal insufficiency, which method comprises administering to a mammal in need thereof, a therapeutically effective amount of lanthanum thiosulfate, preferably wherein said lanthanum thiosulfate is prepared in accordance with the method of any of Claims 1 to 11.
19. A pharmaceutical composition comprising lanthanum thiosulfate, and one or more excipients, carriers and/or diluents wherein said lanthanum thiosulfate is suitable for use as a calcium ion sequestering agent and/or as a phosphate ion sequestering agent, and preferably wherein said lanthanum thiosulfate is prepared in accordance with the method of any of Claims 1 to 11.
20. A kit of parts comprising a pharmaceutical composition comprising lanthanum thiosulfate and a pharmaceutical composition comprising a hydrogen carbonate or bicarbonate salt, and preferably wherein said lanthanum thiosulfate is prepared in accordance with the method of any of Claims 1 to 11.
21. Use of a pharmaceutical composition comprising lanthanum thiosulfate in accordance with Claim 19 or a kit of parts in accordance with Claim 20, for the treatment of diseases such as end stage renal disease, chronic kidney disease and/or chronic renal insufficiency.

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2016/050133

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K33/24 C01B17/64
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C01B A61K C01F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

11 April 2016

Date of mailing of the international search report

21/04/2016

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INTERNATIONAL SEARCH REPORT

International application No
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International application No

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