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(54) **Title**: COMPOSITION OF THIOSULFATE SALT FOR ORAL ADMINISTRATION

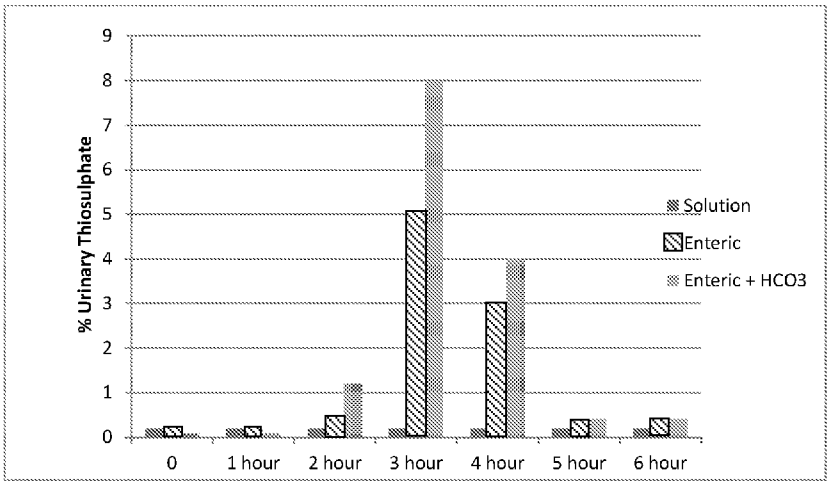

Figure 2

(57) **Abstract**: The present invention concerns coated or encapsulated, thiosulfate salts which can be administered orally and without the side-effects commonly associated with orally administered formulations. It has been established that by delaying the release of a thiosulphate salt from a composition until the composition reaches the small intestine and lower regions of the GI tact (in other words by delaying contact between the thiosulfate salt of a composition and the small intestine and lower regions of the GI tract), a marked improvement in bioavailability following oral administration is achieved and the incidence of GI side effects such as catharsis and irritation are reduced.

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COMPOSITION OF THIOSULFATE SALT FOR ORAL ADMINISTRATION

FIELD OF THE INVENTION

The present invention provides oral formulations of thiosulfate salts.

BACKGROUND OF THE INVENTION

Thiosulfate salts occur naturally and can be produced by certain biochemical processes. Thiosulphate salts rapidly dechlorinate water and are notable for their use to halt bleaching in the paper-making industry. Thiosulfate is also useful in smelting silver ore, in producing leather goods and to set dyes in textiles. Sodium thiosulfate, commonly called *hypo* ("Hyposulfite"), was widely used in photography to fix black and white negatives and prints after the developing stage. However, modern rapid fixers use ammonium thiosulfate as a fixing salt because it acts three to four times faster.

In addition to industrial uses, thiosulphate salts have been used medicinally to treat a variety of conditions. For example thiosulphate salts, by virtue of the ability of the anion to react with the cyanide group (producing thiocyanate anions), have been used as an antidote to cyanide poisoning. The reaction of the thiosulfate anion with cyanide is facilitated by the action of the mitochondrial enzyme Rhodanese. Thiosulphate has also been used in oncology therapy to prevent cisplatin nephrotoxicity and as an antidote for extravasation of various chemotherapy agents. The mechanism by which thiosulphate the anion reduces nephrotoxicity and ototoxicity is not fully understood but may involve free radical scavenging and/or covalent binding to inactivate the platinum compound. Sodium thiosulfate (STS) reacts irreversibly with cisplatin to form $Pt(S_2O_3)_4$. Thiosulphate in the form of

sodium thiosulphate has also recently been used to treat Calciphylaxis and disorders of soft tissue calcification in end stage renal disease. Thiosulphate has also been used topically to treat superficial fungal infections of the skin.

In all the systemic medical applications of thiosulphate, the drug has to be administered parenterally - usually by slow intravenous infusion. The reason for this is that orally administered thiosulphate salts are generally recognised as being poorly bioavailable. In view of low and variable bioavailability of oral administered STS, the current recommendation is that only intravenous STS should be prescribed.

The mechanism for the low bioavailability of orally administered thiosulfate salts is unknown. It might be at least partially explained by the degradation of thiosulphate anions in the acidic environment of the stomach. However, it might also be due to degradation by intestinal bacteria and/or different expression levels of a thiosulphate transporter in the gut mucosa.

There are other factors preventing the regular and routine oral administration of thiosulphate sulfate salts. For example, when administered orally, sodium thiosulphate acts as a saline cathartic; specifically, while ingestion of 12 g of sodium thiosulfate is non-toxic it produces violent catharsis. Ingestion of large doses of sodium thiosulphate may cause gastrointestinal irritation, gastrointestinal disturbances with nausea, vomiting, abdominal cramping and diarrhoea.

Additionally, Farese et al (2011) state that after oral application only 4% of orally administered STS was recovered in the urine of volunteers, reflecting a low

bioavailability of 7.6%. Indeed the authors conclude that thiosulfate salts should not be administered orally and that before suitable galenic formulations can be made the mechanisms of the low bioavailability or orally administered thiosulfate salts must be clarified.

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SUMMARY OF THE INVENTION

The present invention is based on the finding that when suitably coated or encapsulated, thiosulfate salts can be administered orally and without the side-effects commonly associated with orally administered formulations. Moreover, the inventors
10 have established that by delaying the release of a thiosulphate salt from a composition until the composition reaches the small intestine and lower regions of the GI tract (in other words by delaying contact between the thiosulfate salt of a composition and the small intestine and lower regions of the GI tract), a marked improvement in bioavailability following oral administration is achieved and the incidence of GI side
15 effects such as catharsis and irritation are reduced.

Specifically, the inventors have shown that problems associated with the bioavailability and side effects of orally administered thiosulphate salts can be (at least partly) addressed through the provision of coated or encapsulated thiosulfate
20 formulations.

Thus, a first aspect of this invention provides a coated thiosulfate salt composition.

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The coated thiosulfate salt compositions of this invention exhibit improved bioavailability when administered orally as compared to other (perhaps non-coated) oral formulations comprising thiosulfate salts. The invention provides coated thiosulfate composition, which composition exhibits improved bioavailability after oral administration as compared to other orally administered thiosulfate compositions, including those formulations which lack a coated thiosulfate component.

The compositions of this invention may be for oral administration – thus the invention provides oral (or orally administerable) thiosulphate salt compositions, which compositions comprise a coated thiosulphate salt.

The compositions of this invention may be pharmaceutical compositions further comprising, for example one or more excipient(s), carrier(s) and/or diluent(s). For example, the thiosulfate salt 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.

The compositions of this invention may comprise one or more thiosulfate salts. The one or more thiosulfate salts of the compositions of this invention may be individually coated. Additionally or alternatively, two or more thiosulfate salts may be combined and coated. Thus in a composition comprising a plurality of thiosulfate salts, the thiosulfate salts may be combined and coated as one.

The compositions of this invention may further comprise one or more other active agents (the thiosulfate salt component being an active agent itself). For example, the one or more thiosulfate salts of the compositions of this invention may be admixed and/or combined with one or more other active agents. For example, the one or more other active agents may be for treating or preventing one or more specific diseases, conditions and/or syndromes. By way of example, the other agents may comprise small organic molecule, protein, peptide, amino acid, nucleic acid and/or antibody based therapeutics. Other agents suitable for use in compositions of this invention may comprise, for example, chemotherapeutic, steroid, hormone, anti-cancer, antibiotic, antiviral, antifungal and/or anti-inflammatory type compounds.

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 cabonate) salt(s). Surprisingly, the inventors have discovered that thiosulfate compositions, in particular the coated compositions for oral administration described herein, 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 bicarbonate salt component (may neutralise stomach acid and prevent any premature degradation of the thiosulfate in the composition – this may be particularly important where the coating of the thiosulfate composition has been breached or is weak. However, it is also known that the putative thiosulphate transporter is trans-stimulated in the presence of bicarbonate ions – thus this may further account for the observed improved bioavailability of orally administered thiosulfate in a composition of this invention.

In addition and again without wishing to be bound by theory, the inventors have noted that coated thiosulfate compositions which further comprise a quantity of hydrogen carbonate or bicarbonate (HCO_3^-) may facilitate the prevention of metabolic acidosis which can be a side effect of an orally administered thiosulphate 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.

Thus, this invention provides a coated composition comprising a thiosulfate salt and bicarbonate, wherein the composition is for oral administration.

It should be understood that the thiosulfate salt component and the bicarbonate component of the composition of this invention may be separately coated or coated together.

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 thiosulfate salt composition (or bicarbonate supplement) of this invention.

A thiosulfate composition 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".

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 a thiosulphate salt 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 active compound with an inert liquid diluent.

A composition of this invention may comprise a core component comprising a thiosulfate salt and/or one or more other active agents, (carbonate) salts, carriers, diluents and/or excipients and one or more coating and/or encapsulating layers applied to or containing/encapsulating 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 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 barrier between the core component of a composition of this invention (containing thiosulfate salt, other compounds

(including other actives and/or salts) excipients and the like), and any enteric coat or capsule.

The seal coat may comprise one or more pharmaceutically acceptable film-forming polymers optionally in combination with one or more pharmaceutically acceptable excipients(s). By way of example, a seal coat may comprise a film forming polymeric materials, 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 core (and in particular the thiosulfate component thereof) to acidic conditions, improve stability of the thiosulfate salt component of the composition by minimizing, restricting or preventing interaction between the thiosulfate salt component of the core 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 palmitosterate and mixtures thereof.

A capsule may be prepared by filling a thiosulphate salt, either alone or in admixture with one or more accessory ingredients, into a capsule shell and then sealing them in the usual manner. Suitable capsules may comprise hard shell capsules and/or soft shell type capsules. Materials suitable for the formation of capsules include, for example gelling agents and proteins (for example gelatin), polysaccharides including carrageenans and modified forms of starch and cellulose (hypromellose).

One of skill will appreciate that an important objective of any delayed or controlled release dosage formulation is to provide a desired blood concentration versus time (pharmacokinetic, or PK) profile for the drug. Fundamentally, the PK profile for a drug (for example a thiosulfate salt) is dependent on the rate of absorption of the drug into the blood, and the rate of elimination of the drug from the blood. To be absorbed into the blood (circulatory system), the drug must first be dissolved in the gastrointestinal fluids. For those relatively rapidly absorbed drugs whose dissolution in the gastrointestinal fluids is the rate limiting step in drug absorption, controlling the rate of dissolution (i.e., drug release from the dosage form) allows the formulator to control the rate of drug absorption into the circulatory system of a patient.

A suitable PK profile may be achieved by a dosage form that delivers a delayed release dissolution profile, in which the release of one or more doses of drug from the dosage form is delayed for a pre-determined time after contacting of the dosage form by a liquid medium, such as for example, by the gastro-intestinal fluid after ingestion by the patient. The delay period ("lag time") can be followed either by prompt release of the active ingredient ("delayed burst"), or by sustained (prolonged, extended, or retarded) release of the active ingredient ("delayed then sustained"). U.S. Pat. No. 5,464,633 to Jagotec, for example, discloses delayed-release dosage forms consisting of a core containing an active substance and an external layer completely coating the core in which the external coating layer is applied by a compression coating process.

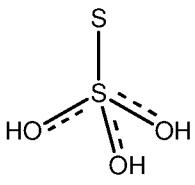
A further type of delayed release PK profile is a "pulsatile" release profile, in which for example, a first dose of a drug is delivered, followed by a delay period ("lag time") during which there is substantially no release of the drug from the dosage form,

followed by either prompt or sustained release of a subsequent dose of the same drug. In one type of pulsatile drug delivery system, the first dose is released essentially immediately upon contacting of the dosage form with a liquid medium and the delay period corresponds approximately to the time during which a therapeutic concentration of the first dose is maintained in the blood. Pulsatile delivery systems are particularly useful for applications where a continuous release of drug is not ideal. Examples of this are drugs exhibiting first pass metabolism by the liver, drugs that induce biological tolerance, i.e., the therapeutic effect decreases with continuous presence of the drug at the site of action, and drugs whose efficacy is influenced by circadian rhythms of body functions or disease. One typical pulsatile dosage form design contains the first dose of drug in an exterior coating, or shell, while subsequent doses of drug are contained in underlying layers of sub-coatings, or a central core. Pulsatile dosage forms may deliver an active ingredient in a pH dependent or pH independent manner. pH dependent types of dosage form typically deliver the active ingredient through the addition of a pH dependent polymer, such as an enteric or reverse-enteric polymer.

These and other PK profiles may be provided by the compositions of this invention, which coated or encapsulated compositions may be delayed and/or controlled release type compositions. That is to say, the coating(s) and/or capsule(s) which contain a thiosulfate salt, may be formulated to release their contents following contact with a liquid. For example, the coating may comprise a delayed release means. The delayed release means may comprise a capsule and/or seal and/or enteric coating(s).

The speed at which the coating and/or capsule degrades or breaks down may vary and will depend upon the precise nature or formulation of the coating(s) or capsule. In the present case, a coating or capsule of the composition may be formulated to breakdown or degrade following contact with gastrointestinal fluids. Moreover, the speed at which the coating and/or capsule degrades or breaks down may be timed such that the thiosulfate salt component is released in the small intestine and lower regions of the GI tract. The coating may be formulated such that it releases the thiosulfate salt at a site selected from the group consisting of the duodenum, jejunum, ileum and/or ascending colon. The coating may be formed and adapted to achieve the controlled/sustained release of the thiosulfate during passage of the composition through the duodenum, jejunum, ileum and/or ascending colon.

One of skill will appreciate that the term "thiosulfate" refers to the oxyanion of sulfur ($S_2O_3^{2-}$) having the general formula:



Formula I: thiosulfate anion

The prefix thio- indicates that the thiosulfate ion is a sulfate ion with one oxygen replaced by sulfur. The thiosulfate anion is tetrahedral in shape and is notionally derived by replacing one of the oxygen atoms by a sulfur atom in a sulfate anion. The S-S distance indicates a single bond, implying that the sulfur bears significant negative charge and the S-O interactions have more double bond character. Thus the first protonation of thiosulfate occurs at sulfur.

The term "thiosulfate salt" includes any naturally occurring or synthetically produced salt. For example, the invention encompasses coated compositions comprising, for example (but not limited to) sodium thiosulfate and lanthanum thiosulfate. Moreover, the invention provides encapsulated and/or seal and/or enterically coated sodium thiosulfate and/or lanthanum thiosulfate compositions, which compositions are suitable for oral administration.

In a second aspect, the invention provides a coated thiosulfate salt composition for use in medicine or for use as a medicament. For the avoidance of doubt, it should be understood that the term "composition" as used in this second aspect of the invention encompasses the coated (encapsulated and/or seal/enterically coated) compositions described above and with reference to the first aspect of this invention. The second aspect of this invention may encompass medicaments which find application in methods which comprise the administration of coated thiosulfate compositions as described herein for the purpose of treating and/or preventing medical conditions.

The compositions, medicaments and methods of this invention may be applied to, for example, the treatment or prevention of instances of poisoning (including cyanide poisoning); calciphylaxis (as might occur in haemodialysis; fungal infections (including ringworm). Moreover, the compositions of this invention may find application in methods of managing extravasations during chemotherapy.

In a third aspect, the invention provides a method of treating a disease or conditions, said method comprising administering to a subject in need thereof a therapeutically effective amount of a coated thiosulfate salt composition of this invention. Again and

for the avoidance of doubt, it should be understood that the term "composition" as used in this third aspect of the invention encompasses the coated (encapsulated and/or seal/enterically coated) compositions described above and with reference to the first aspect of this invention and/or the medicaments of the second aspect of this invention. By way of example, the third aspect of this invention encompasses methods which comprise the administration of coated sodium thiosulfate compositions – such compositions optionally further comprising other active agents, carbonate salts, excipients, diluents and the like. The medical methods of this invention may be applied to, for example, the treatment or prevention of instances of poisoning (including cyanide poisoning); calciphylaxis (as might occur in haemodialysis; fungal infections (including ringworm). Moreover, the compositions of this invention may find application in methods of managing extravasations during chemotherapy.

DETAILED DESCRIPTION

The present invention will now be described in detail with reference to the following figures which show: that delaying the intestinal release of orally administered thiosulphate markedly improves the oral bioavailability of the drug as estimated by the increased urinary excretion of thiosulphate. Moreover inclusion of sodium bicarbonate salt in the compounding formulation of enteric coated delayed release thiosulphate formulations further increases the bioavailability of thiosulphate.

EXAMPLE 1. Wax coated capsules.

Filling of capsules.

Anhydrous sodium thiosulphate (100g) was triturated in a mortar and pestle to a uniform degree of fineness. Commercially available hard gelatin capsules, size 000

(DRT&T HEALTH UK LTD) were then filled with the powder using the punch method (Judith E. Thompson in Contemporary Guide to Pharmacy Practice, 2009 3rd Ed. ISBN-10 0781783968). The term "capsules" means hard shell capsules each having telescopically engaged body and cap portions formed by a technique commonly known as the dip-molding technique (for example, see U.S. Pat. No. 3,173,840).

The triturated powder was placed on a clean glass plate. Using a spatula the powder was arranged into a compact, flat powder bed of uniform thickness on the glass plate. The depth of the powder cake was approximately one quarter the length of the capsule body. The capsule cap was removed and the empty capsule body held between thumb and forefinger and repeatedly punched downward into the powder cake until it was full. The cap was replaced and the filled capsule weighed using an empty capsule of the same size as a tare.

Coating of filled capsules.

The hot melt wax coating technique, defined as the application of fine layer of coating material in molten state over the capsule was used to coat the filled capsules. Edible paraffin wax was gently heated until liquid. Individual filled capsules were dipped into the liquid wax using tweezers and withdrawn when coated. The coated capsule was allowed to cool and the process repeated until a sufficient layer has been developed and the capsule was completely coated.

Measurement of thiosulphate oral bioavailability

Following oral administration of the 5.0 g of sodium thiosulphate salt as either a 50 ml solution or as a wax coated capsule, urine samples were collected on an hourly basis for 6 hours. Thiosulphate in the urine was determined by iodometric titrations.

As shown in Figure 1 following oral administration of sodium thiosulphate as a solution no detectable thiosulphate was recovered in the urine. In contrast, following administration of sodium thiosulphate in the form of a delayed release enteric wax coated capsule free thiosulphate was detectable in the urine at time periods of 3, 4 and 5 hours following administration. Enteric coated delayed release of sodium thiosulphate improved the oral bioavailability of thiosulphate.

EXAMPLE 2: Hypromellose enteric coated capsules.

Filling of capsules.

Anhydrous sodium thiosulphate (100g) was triturated in a mortar and pestle to a uniform degree of fineness. Additionally anhydrous sodium thiosulphate (90g) was triturated in a mortar and pestle with sodium bicarbonate (10g) to yield a formulation of sodium thiosulphate/sodium bicarbonate (90%/10% w/w).

Commercially available Clear Enteric coated capsules, filling size 00, (DRT&T HEALTH UK LTD) were then filled with each powder using the punch method (Judith E. Thompson in Contemporary Guide to Pharmacy Practice, 2009 3rd Ed. ISBN-10 0781783968).

Each triturated powder was placed on a clean glass plate. Using a spatula the powder was arranged into a compact, flat powder bed of uniform thickness on the glass plate.

The depth of the powder cake was approximately one quarter the length of the capsule body. The capsule cap was removed and the empty capsule body held between thumb and forefinger and repeatedly punched downward into the powder cake until it was full. The cap was replaced and the filled capsule weighed using an empty capsule of the same size as a tare.

Sodium thiosulphate was administered orally as either (i) a solution (ii) enteric capsule and (iii) enteric capsule plus 10% sodium bicarbonate. Following administration urine samples were collected on an hourly basis for 8 hours. Thiosulphate in the urine was determined by iodometric titrations. The results are shown in Figure 2.

Following oral administration of the 5.0 g of sodium thiosulphate salt as a 50 ml solution no detectable thiosulphate could be observed in the urine. Oral administration of the same dose as enteric coated capsules resulted in detectable levels of urinary thiosulphate being observed at 3, 4 and 5 hours following administration. When administered together with 10% w/w sodium bicarbonate as part of the formulation the urinary excretion of thiosulphate was markedly enhanced over the same time course suggesting an increased oral bioavailability of thiosulphate in the presence of bicarbonate salt.

CLAIMS.

1. A composition comprising a coated thiosulfate salt.

2. A composition comprising a core and a coating, wherein the core comprises a thiosulfate salt and the coating is applied to the core.

3. The composition of claim 2, wherein the coating is applied to the outer surface of the core.

4. The composition of any preceding claim, wherein the composition is a pharmaceutical composition.

5. The composition of any one of claims 1 or 4, wherein the composition further comprises one or more excipients, carriers and/or diluents.

6. The composition of claims 2 or 3, wherein the core further comprises one or more excipients, carriers and/or diluents.

7. The composition of claims 1, 4 or 5, wherein the composition further comprises one or more bicarbonate salt(s).

8. The composition of claims 2, 3 or 6, wherein the core further comprises one or more bicarbonate salt(s).

9. The composition of any preceding claim, wherein the composition or core comprises sodium bicarbonate.

10. The composition of any preceding claim, wherein the thiosulfate salt or core is encapsulated.

11. The composition of any preceding claim, wherein the thiosulfate salt or core is seal and/or enterically coated.

12. The composition of any preceding claim, wherein the composition is for oral administration.

13. The composition of any preceding claim, wherein the composition exhibits improved bioavailability when administered orally as compared to a non-coated, orally administered thiosulfate composition.

14. The composition of any one of claims 1-13, for use in medicine or for use as a medicament.

15. The composition for use of claim 14, wherein the composition is to be administered orally or is for oral administration.

16. The composition for use of claims 14 or 15, wherein the composition exhibits improved bioavailability when administered orally as compared to a non-coated, orally administered thiosulfate composition.

17. A delayed and/or controlled release composition comprising a thiosulfate salt in combination with a delayed release means for releasing the thiosulfate salt in the lower gastrointestinal tract.

18. The delayed and/or controlled release composition of claim 17, wherein the delayed release means comprises a coating, a seal coating, an enteric coating and/or a capsule.

19. The delayed release and/or controlled release composition of claims 17 or 18 for use in medicine or for use as a medicament.

20. The composition of any one of claims 1-13 or 17-19, wherein the composition exhibits improved bioavailability when administered orally as compared to a non-coated, orally administered thiosulfate composition.

21. A method of treating a disease or condition, said method comprising administering a therapeutically effective amount of a composition according to any one of claims 1-13 or 17-19.

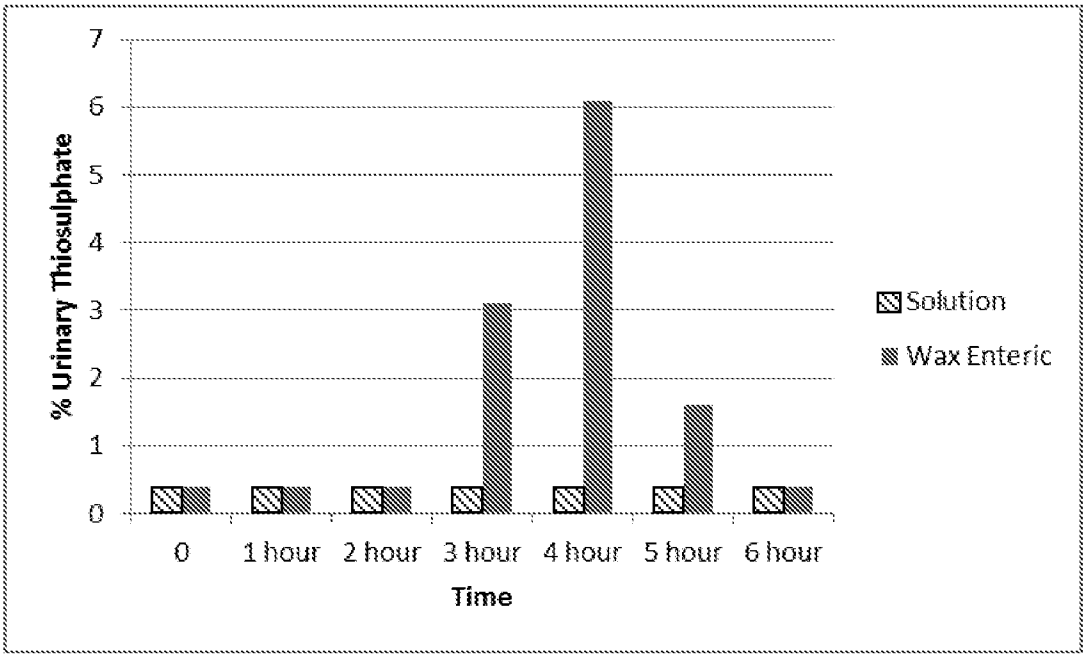

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Figure 1

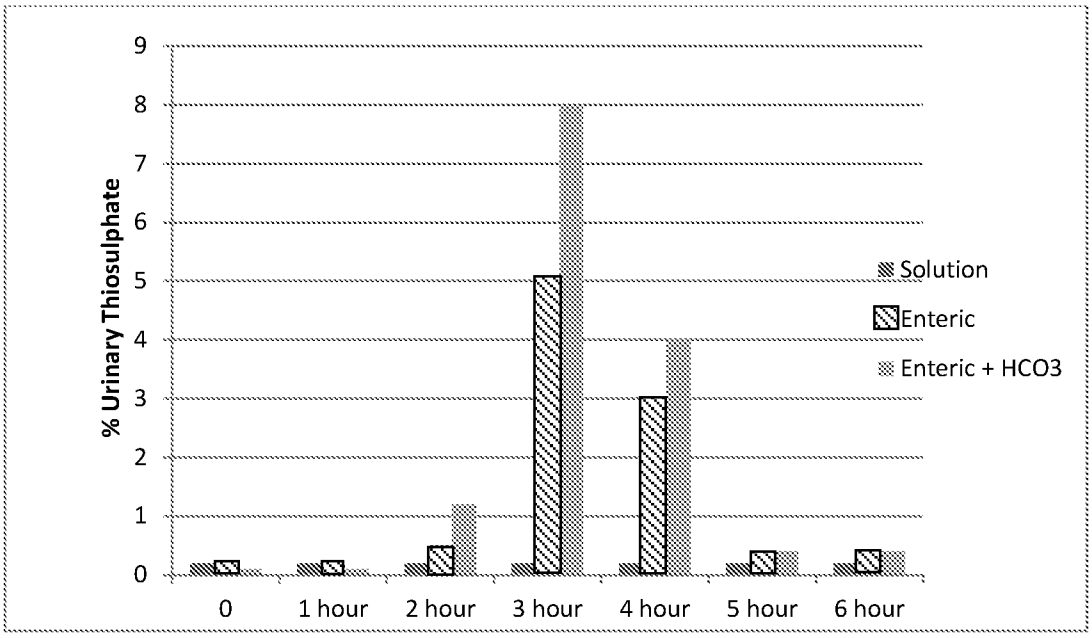
% Urinary Thiosulphate
9
8
7
6
5
4
3
2
1
0
0
1 hour
2 hour
3 hour
4 hour
5 hour
6 hour
Solution
Enteric
Enteric + HCO3

Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/053101

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/28 A61K9/50 A61K33/04
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)
A61K

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013/136725 A1 (GOJON-ROMANILLOS GABRIEL [MX]) 30 May 2013 (2013-05-30) paragraph [0002] - paragraph [0005] paragraph [0050] - paragraph [0064] paragraphs [0067], [0077], [0082], [0126] Formulation examples 2 and 4 claims 1, 2, 6, 8 -----	1-21
X	EP 2 151 241 A1 (TORAY INDUSTRIES [JP]; MARUHO KK [JP]) 10 February 2010 (2010-02-10) paragraph [0009] - paragraph [0011] paragraph [0068] - paragraph [0075]; examples 13-17 claims 1, 5, 6 ----- -/--	1-6, 10-21

[X] Further documents are listed in the continuation of Box C.

[X] 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 January 2015	13/01/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	González Ferreiro, M

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2014/053101

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