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(54) **Title**: SOLUTION COMPRISING GLYCEROPHOSPHORIC ACID AND MAGNESIUM SALT THEREOF

(57) **Abstract**: An aqueous solution comprising magnesium glycerophosphate, a polyol such as glycerol and glycerophosphoric acid.

SOLUTION COMPRISING GLYCEROPHOSPHORIC ACID AND MAGNESIUM SALT THEREOF

This invention relates to magnesium glycerophosphate oral solutions, in particular to aqueous solutions comprising magnesium glycerophosphate, a polyol such as glycerol and glycerophosphoric acid.

By combining these three materials in an aqueous solution, a stable and efficacious product can be formed suitable for delivering Mg to a patient suffering from hypomagnesaemia without forming precipitates characteristic of current commercial products.

Background

Magnesium glycerophosphate is a white, odourless, amorphous powder with a somewhat bitter taste and sparing water solubility. Magnesium glycerophosphate is a preparation used to treat conditions such as hypomagnesaemia. In particular, it is used to prevent recurrence of magnesium hypomagnesaemia in people who have already been treated for this condition.

Hypomagnesaemia is the presence of abnormally low levels of serum magnesium. It is relatively common, being estimated to affect 2.5% to 15% of the general population and up to 65% of patients in intensive care settings. However, most patients with hypomagnesaemia are asymptomatic; symptoms are not usually seen until serum magnesium concentration falls below 0.5 mmol/litre.

Causes of hypomagnesaemia include inadequate dietary intake, reduced intestinal absorption and increased renal excretion. Magnesium salts are not well absorbed from the gastrointestinal tract, with most being absorbed in the small intestine. Excessive losses in diarrhoea, stomata or fistulae are reportedly the most common causes of hypomagnesaemia. Small bowel bypass surgery and diseases that cause malabsorption can also lead to hypomagnesaemia.

Magnesium is primarily excreted by the kidneys. Inherited renal tubular reabsorption defects that result in increased excretion of magnesium, such as Gitelman's syndrome, are associated with hypomagnesaemia. Other conditions associated with hypomagnesaemia include malnutrition, anorexia nervosa, chronic

alcoholism, total parenteral nutrition, acute pancreatitis, diabetic ketoacidosis, hypersecretion of aldosterone and lactation.

Certain drug treatments including diuretics, antibiotics (such as amphotericin B and aminoglycosides), immunosuppressants and chemotherapy drugs (particularly cisplatin) have been associated with hypomagnesaemia. The number of cases of hypomagnesaemia associated with proton pump inhibitors reported in the literature is increasing.

The signs and symptoms of hypomagnesaemia include neuromuscular, cardiovascular and metabolic features. Neuromuscular effects include muscle weakness, ataxia, tremor and spasms of the feet and hands. Severe hypomagnesaemia can cause seizures (especially in children) and coma. Cardiovascular effects include arrhythmias and electrocardiogram (ECG) abnormalities.

Hypomagnesaemia is often associated with other biochemical and electrolyte abnormalities, such as hypocalcaemia, hypokalaemia, hyponatraemia and metabolic acidosis. Some of the symptoms seen in hypomagnesaemia may relate to these associated abnormalities.

For symptomatic hypomagnesaemia, intravenous infusion of magnesium sulfate is initially used and oral magnesium supplements can be given subsequently to prevent recurrence. Intramuscular injection of magnesium sulfate is another option for initial treatment but is painful. Other sources advise that oral magnesium may be used as first-line treatment, the selection of route of administration being influenced by severity and oral tolerability,

The present invention relates to oral magnesium preparations, in particular those in solution form. In order to introduce Mg into the diet of patients with hypomagnesaemia Mg can be administered orally via a tablet or solution. However, the fact that magnesium glycerophosphate is essentially insoluble in water is a problem for any liquid solution, in particular aqueous solution. It also affects bioavailability.

In order to improve the solubility of the magnesium glycerophosphate in water, it is often formulated with glycerophosphoric acid, citric acid or an alkali citrate. However, on standing a solution containing these ingredients forms a

precipitate. After storage therefore, current magnesium glycerophosphate aqueous solutions contain unacceptable deposits and are unsuitable for oral administration. Without wishing to be limited by theory, it is suggested that the deposits are magnesium compounds.

The present inventors sought a way of producing solutions of magnesium glycerophosphate without the issue of deposits on storage. The inventors have surprisingly found that this problem can be solved by an aqueous solution as claimed in claim 1 in which the magnesium glycerophosphate is combined with a polyol such as glycerol and glycerophosphoric acid. In particular, the relative amounts of these components gives rise to a particularly advantageous solution in which deposits are avoided.

Summary of Invention

Thus viewed from one aspect the invention provides an aqueous solution comprising magnesium glycerophosphate, a polyol such as glycerol and glycerophosphoric acid.

Viewed from another aspect the invention provides an aqueous solution comprising glycerophosphate, a polyol such as glycerol and glycerophosphoric acid for use in the treatment or prevention of hypomagnesaemia.

Viewed from another aspect the invention provides a method of treating or preventing hypomagnesaemia comprising administering to a patient in need therefor an effective amount of an aqueous solution of glycerophosphate, a polyol such as glycerol and glycerophosphoric acid.

Viewed from another aspect the invention provides use of an aqueous solution of glycerophosphate, a polyol such as glycerol and glycerophosphoric acid in the manufacture of a medicament for the treatment of hypomagnesaemia.

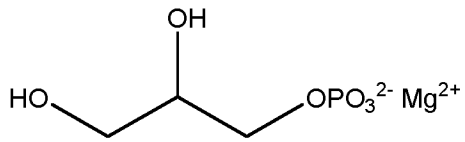
Viewed from another aspect the invention provides a process for the preparation of an aqueous solution as hereinbefore defined comprising dissolving magnesium glycerophosphate in glycerophosphoric acid in water to form a solution and subsequently adding a polyol such as glycerol.

Detailed description of the invention

The composition of the invention is an aqueous solution. The components of the solution therefore dissolve in the water present. The invention does not therefore relate to a suspension or emulsion. The solution is preferably clear. It may have a pH of 1.5 to 5, such as 2 to 4.

The aqueous solution is suitable for pharmaceutical administration. Along with water, the solution of the invention comprises a minimum of three components. In some embodiment the composition of the invention consists of the three components recited above as well as water.

Magnesium glycerophosphate is a compound of formula (I)



The amount of magnesium glycerophosphate in the aqueous solution of the invention may be 5 to 50 wt%, preferbly 10 to 30 wt%, such as 12 to 25 wt%, especially 15 to 20 wt%, such as 16 to 18 wt%. In terms of dry weight (i.e. based on the components without water), magnesium glycerophosphate may form 25 to 50 wt% of the composition, such as 30 to 45 wt%, preferably 35 to 45 wt%.

The amount of magnesium glycerophosphate present is preferably adjusted to deliver between 100 and 150 mg of Mg per 5 ml of the solution, such as 110 to 140 mg/5 ml of solution. The magnesium glycerophosphate itself may contain 11 to 12.5wt% of Mg. Mg preferably forms around 11.5 wt% of the magnesium glycerophosphate.

In molar terms, a preferred amount is 2 to 10 mmol Mg/5 ml of solution, such as 5 mmol Mg/5ml.

In order to dissolve the magnesium glycerophosphate to create a solution, it is necessary to add glycerophosphoric acid. It is preferred if the glycerophosphoric acid is provided in an aqueous solution. The amount of glycerophosphoric acid in the solution can vary. Suitable concentrations include a 5 to 50 wt% solution of

glycerophosphoric acid in water, such as a 10 to 30 wt% solution, preferably a 15 to 25 wt% solution, e.g. 20 wt% solution.

The more important figure is the amount of glycerophosphoric acid relative to the amount of magnesium glycerophosphate. It is preferred if there is at least an equimolar molar amount of glycerophosphoric acid relative to magnesium glycerophosphate, i.e. the molar ratio is 1:1 or there is an excess of glycerophosphoric acid, e.g. a molar ratio of 1:1 to 1:2 such as 1:1 to 1.5, magnesium glycerophosphate to glycerophosphoric acid. Especially preferably, the molar ratio of magnesium glycerophosphate to glycerophosphoric acid is 1.0 to 1.0 such as 1.00:1.00 or 1.00:(1.00 to 1.05, such as 1.00 to 1.01).

Hence, the glycerophosphoric acid content in the solution of the invention might be 5 to 40 wt%, such as 6 to 30 wt%, ideally 7 to 20 wt%, such as 10 to 15 wt%. In terms of dry weight, the glycerophosphoric acid may form 20 to 40 wt% , such as 25 to 35 wt% of the composition.

Water preferably forms at least 40 wt% of the solution, such as at least 45 wt%, ideally at least 50 wt%, e.g. the balance of the solution. Water is preferably supplied only as part of the glycerophosphoric acid solution.

The use however of magnesium glycerophosphate and glycerophosphoric acid alone does not result in a solution that is free of deposits. The inventors have found that the addition of a polyol, in particular glycerol, gives rise to a composition that remains in solution on storage. It is the combination of the components that solves the problem. It is the presence of the polyol that appears to prevent deposits forming.

Moreover, the use of glycerol in the aqueous solution of the invention is advantageous because glycerol acts as a preservative and therefore the addition of other preservative agents can be avoided. Moreover, the composition of the invention is administered orally. The presence of a polyol provides the composition with a sweet taste. This means that taste masking agents or flavors that might otherwise be needed to make an oral solution palatable can also be avoided. As a further benefit, glycerol is a liquid and can itself act to dissolve the active ingredients present. This makes formulation of the product easier relative to adding other polyols which are often powders.

For the reasons above, the amount of polyol present can vary. Once sufficient polyol is present to allow a solution to be formed (and hence to prevent deposits forming in the solution), any excess polyol acts as a preservative and sweetener for the formulation.

The amount of a polyol such as glycerol present is preferably 5 to 40 wt% of the solution, such as 7 to 30 wt%, preferably 8 to 20 wt%, ideally 10 to 18 wt%. In terms of dry weight, polyols may form 20 to 40 wt%, such as 25 to 35 wt% of the composition. Ideally there is more magnesium glycerophosphate than polyol in terms of wt%.

Polyols of use in the solution are compounds comprising 10 carbon atoms or less and at least two hydroxyl groups such as glycerol. Preferably the polyol is a liquid at standard ambient temperature (25 °C). Preferred polyols contain C, H and O atoms only. Preferably the polyol comprises 2 to 6 C atoms, such as 3 to 5 C atoms. Preferred polyols have 2 to 4 OH groups such as 3 OH groups. Mixtures of polyols may also be used.

Advantageously, the solution of the invention does not give rise to any deposits upon standing, e.g. at 23°C for 3 months.

The solution of the invention can be prepared simply by mixing the components in water. In one embodiment, the glycerophosphoric acid solution is added to magnesium glycerophosphate before the glycerol is added.

In more detail however, it is important to know how much magnesium glycerophosphate is present so that enough glycerophosphoric acid is added to ensure the formation of a solution. Thus, as a first step an assay of magnesium glycerophosphate can be carried out. Using the result of that assay, a suitable amount of magnesium glycerophosphate can be added to the glycerophosphoric acid solution (such as a 20 wt% solution in water) to ensure that there is a 1:1 ratio of these components or to ensure that there is an excess of the acid. It may be necessary to assay the glycerophosphoric acid solution to make sure the glycerophosphoric acid content of the solution is known accurately.

Once the dissolution process has been carried out and a clear solution obtained, the polyol such as glycerol can be added. Polyol is typically added to ensure a desired final concentration of Mg in the solution, such as 25 mg of Mg/ml.

Viewed from another aspect the inventino provides an aqueous solution comprising:

(i) 5 to 40 wt%, preferably 7 to 20 wt%, such as 10 to 15 wt% glycerophosphoric acid;

(ii) 5 to 50 wt%, preferably 10 to 30 wt%, especially 15 to 20 wt% magnesium glycerophosphate

(iii) at least 40 wt% water; and

(iv) 5 to 40 wt%, preferably 8 to 20 wt%, preferably 10 to 18 wt% polyol.

The solution is preferably stored in an airtight container ready for administration orally when a patient needs it. It can be stored in a refrigerator and may be stored in the dark.

It will be appreciated that the amount of Mg in the solution can be readily adjusted by changing the amount of the active ingredient present so that different dosage solutions can be designed.

Dosages of the solution to be given to a patient will be determined by a physician assessing the patient in question. To prevent recurrence of hypomagnesaemia in adults for example, oral magnesium may be given in a dose of 300 to 600 mg/day. A typical dose might be 24 mmol Mg^{2+} daily.

The solutions of the invention may contain small amounts (e.g. less than 2 wt%) of standard additives but preferably the solution of the invention consists of water, polyols, glycerophosphoric acid and magnesium glycerophosphate.

The solution is suitable for treating or preventing hypomagnesaemia. Thus, the solution may be given to a patient at risk of developing hypomagnesaemia or to a patient with hypomagnesaemia. The solution is ideally for oral administration.

The invention will now be described with reference to the following non-limiting examples.

Example 1

A composition is prepared comprising the following:

Per 100ml:

Component	Per 100 ml batch	g
		g
Magn. Glycerophosphate (MGP)	21,13 (0.1 mol)	g
Glycerophosphoric acid 20 wt% in water	86,01 (0.1 mol)	g
Glycerol	17,00	g

Commercially supplied, MGP contains between 11 and 12.5 wt%, such as 11.5 wt% Magnesium(Mg). For MGP containing 11.5 wt%, Mg, 243 mg Mg/10ml means (243/11,5)*100=2113 mg MGP per 10 ml.

According to the literature, the solubility of MGP in water (20°C) is 8.0 gram/100mL. As will immediately be clear, the solution of the invention contains 21.13 g of MGP per 100ml and hence contains almost three times the active content than the conventional solubility of MGP in water. Solubility of MGP is hence markedly enhanced by dissolving MGP in the acid and glycerol.

There are commercial formulations however, that claim MGP concentration of 1056.52 mg MGP/5mL. We tested this concentration of MGP in water and whilst initially clear MGP solutions were formed, the clear MGP test solutions demonstrated precipitation/crystallization of unknown, previously dissolved material after 2-3 days storage at room temperature.

The use therefore of water alone as a solvent was confirmed as inappropriate.

With reference to enhancement of MGP solubility in dilute acids, MGP aqueous solutions were acidified with a 20 wt% test concentration of citric acid, phosphoric acid and glycerophophoric acid. The molar ratio of MGP to acid was set at 1:1. The MGP content of the solutions was measured to give 2113 mg MGP per 10 ml.

On storage, all test formulations still showed precipitation/crystallization of unknown, previously dissolved material after 2-3 days storage at room temperature.

Glycerol was therefore selected as an additional medium to dilute MGP solutions.

Diluting 1:1 molar ratio MGP/glycerophosphoric acid solutions to 5.0 mmol Mg/5mL with glycerol was successful and resulted in a physically stable clear

aqueous MGP solutions. This solution was stored at room temperature for 2 months without the formation of deposits.

Results from a subsequently performed 3 months stability study confirmed that this formulation remains clear and stable (Mg assay, microbial), solutions were stored at ICH conditions 25°C and 5°C.

Viewed from another aspect, the invention provides an aqueous solution comprising magnesium glycerophosphate, a polyol such as glycerol and an acid selected from citric acid and phosphoric acid.

All discussion above, e.g. percentages of acid, presented in terms of glycerophosphoric acid, can be applied to the citric acid and phosphoric acid embodiment.

Claims

1. An aqueous solution comprising magnesium glycerophosphate, a polyol such as glycerol and glycerophosphoric acid.

2. An aqueous solution as claimed in any preceding claim in which the glycerophosphoric acid content in the solution is 7 to 20 wt%, such as 10 to 15 wt%.

3. An aqueous solution as claimed in any preceding claim in which the amount of magnesium glycerophosphate is 10 to 30 wt%, especially 15 to 20 wt%.

4. An aqueous solution as claimed in any preceding claim in which the solution comprises between 100 and 150 mg of Mg per 5 ml of the solution.

5. An aqueous solution as claimed in any preceding claim in which water forms at least 40 wt% of the solution, e.g. balance water.

6. An aqueous solution as claimed in any preceding claim in which the amount of polyol is 8 to 20 wt%, preferably 10 to 18 wt%.

7. An aqueous solution as claimed in any preceding claim in which the polyol is a liquid at standard ambient temperature.

8. An aqueous solution as claimed in any preceding claim in which the polyol comprises 2 to 6 C atoms, such as 3 to 5 C atoms.

9. An aqueous solution as claimed in any preceding claim in which the polyol has 2 to 4 OH groups, such as 3 OH groups.

10. An aqueous solution as claimed in any preceding claim in which the molar ratio of magnesium glycerophosphate to glycerophosphoric acid is 1:1 or in which there is an excess molar amount of glycerophosphoric acid.

11. An aqueous solution consisting of magnesium glycerophosphate, a polyol such as glycerol and glycerophosphoric acid.

12. An aqueous solution as claimed in any preceding claim comprising:

(i) 5 to 40 wt%, preferably 7 to 20 wt%, such as 10 to 15 wt% glycerophosphoric acid;
(ii) 5 to 50 wt%, preferably 10 to 30 wt%, especially 15 to 20 wt% magnesium glycerophosphate
(iii) at least 40 wt% water; and
(iv) 5 to 40 wt%, preferably 8 to 20 wt%, preferably 10 to 18 wt% polyol.

13. An aqueous solution as claimed in any preceding claim comprising: glycerophosphoric acid and magnesium glycerophosphate in a 1:1 molar ratio, at least 40 wt% water; and glycerol.

14. An aqueous solution comprising glycerophosphate, a polyol such as glycerol and glycerophosphoric acid for use in the treatment or prevention of hypomagnesaemia.

15. A method of treating or preventing hypomagnesaemia comprising administering to a patient in need therefor an effective amount of an aqueous solution of glycerophosphate, a polyol such as glycerol and glycerophosphoric acid.

16. Use of an aqueous solution of glycerophosphate, a polyol such as glycerol and glycerophosphoric acid in the manufacture of a medicament for the treatment of hypomagnesaemia.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/662 A61K47/10 A61P3/12
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 A61P

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, BIOSIS, EMBASE, 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	WO 2010/131994 A1 (OBSHCHESTVO S OGRANICHENNOJ OT [RU]; MANASHEROV TAMAZI OMAROVICH [RU];) 18 November 2010 (2010-11-18) examples 1,2	1-16
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
22 December 2016	09/01/2017

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/EP2016/078910

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