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(54) Titre : SOLUTIONS STABLES D'ELECTROLYTE DE TAUROLIDINE
 (54) Title: STABLE TAUROLIDINE ELECTROLYTE SOLUTIONS

(57) **Abrégé/Abstract:**

A taurolidine composition includes an aqueous solution containing about 1.5-3% by weight taurolidine, the solution containing a stability-enhancing effective amount of at least one physiologically acceptable electrolyte, such that the solution is substantially isotonic.



ABSTRACT

A taurolidine composition includes an aqueous solution containing about 1.5-3% by weight taurolidine, the solution containing a stability-enhancing effective amount of at least one physiologically acceptable electrolyte, such that the solution is substantially isotonic.

STABLE TAUROLIDINE ELECTROLYTE SOLUTIONS

FIELD OF THE INVENTION:

The present invention relates to taurolidine solutions.

DESCRIPTION OF THE BACKGROUND ART:

5 Although taurolidine 1% solutions have been prepared with electrolyte-containing solutions such as ringer solution, there previously has been no suggestion of taurolidine at concentrations greater than 1% in electrolyte solutions such as ringer solution.

10 Known taurolidine solutions at higher concentrations, e.g., known 2% taurolidine solutions, previously have sometimes had stability problems. For example, droplets clinging on the inside of bottles of 2% taurolidine solution sometimes dry and form crystals, resulting in undesirable particles in the solution. Prior methods for avoiding such problems include storing bottles horizontally on their sides so that droplets do not form in the bottles, and not storing the solutions under refrigeration. However, it is desirable to have bottles of solution which do not require special storage orientation, and which can be refrigerated to
15 extend the shelf-life.

There remains a need in the art for taurolidine solutions having greater stability.

SUMMARY OF THE INVENTION:

20 In accordance with the present invention, a taurolidine composition includes an aqueous solution containing about 1.5-3% by weight taurolidine, the solution containing a stability-enhancing effective amount of at least one physiologically acceptable electrolyte which is present at a concentration sufficient to render said solution substantially isotonic.

DESCRIPTION OF THE PREFERRED EMBODIMENTS:

25 The present invention solves the prior stability problems of higher concentration taurolidine solutions by providing stable aqueous solutions containing taurolidine at a concentration within the range of about 1.5 - 3% by weight. The solutions are rendered stable by including therein a stability-enhancing effective amount of at least one physiologically acceptable electrolyte so that the resulting solution is substantially isotonic. Suitable electrolyte(s) provide ions selected from the group consisting of Na⁺, K⁺, Mg⁺⁺, Cl⁻, H₂PO₄⁻, Acetate⁻, HCO₃⁻, and mixtures thereof. In preferred embodiments, the electrolyte(s)
30 are selected from the group consisting of NaCl, KCl, CaCl₂, NaHCO₃, and mixtures thereof.

In preferred embodiments, taurolidine is present in the solution within a range of about 1.5 - 2.5% by weight, more preferably within the range of about 1.7 - 2.3% by weight,

even more preferably within the range of about 1.8 - 2.2% by weight, still more preferably within the range of about 1.9 - 2.1% by weight, most preferably about 2% by weight.

For example, one composition in accordance with the present invention comprises an isotonic ringer solution including about 2% by weight taurolidine. An alternative to use
 5 of ringer solution is full electrolyte solution, which contains phosphates not present in ringer solution.

In particularly preferred embodiments, a composition in accordance with the present invention additionally includes sufficient physiologically acceptable colloidal material (colloid) so as to also effectively render the inventive solution iso-oncotic. The colloidal
 10 material can be polyvinylpyrrolidone (PVP), hydroxy ethyl starch (HES), or the like. Preferred colloidal materials include low molecular weight PVP, having an average molecular weight within the range of about 1,000 - 15,000, preferably within the range of about 1,000 - 13,000, more preferably about 9,000. A particularly preferred PVP for use in accordance with the present invention is Kollidon or Povidone. Preferred amounts of
 15 colloidal material in the solution are within the range of about 1 - 10% by weight, preferably about 3-7% by weight, most preferably about 5% by weight.

One preferred solution in accordance with the present invention includes the following in percentages by weight in water for injection:

20 2% taurolidine
 5% Kollidon
 0.4% NaCl
 0.005% KCl
 0.0066% CaCl₂
 0.005% NaHCO₃

25 Isotonic taurolidine solutions in accordance with the present invention also can be prepared so as to include at least one amino acid, wherein the amounts of other electrolytes added to the solution are reduced in proportion to the amount of the one or more amino acid(s) added, so as to maintain isotonicity. Preferred amounts of amino acid(s) in the solution are within the range of about 0.1 - 3% by weight, more preferably
 30 within the range of about 0.2 - 2% by weight, still more preferably within the range of about 0.3 - 1% by weight, even more preferably within the range of about 0.4 - 0.6% by weight, most preferably about 0.5% by weight. Taurine is particularly preferred. One exemplary composition in accordance with this embodiment, in water for injection, is as follows in percentages by weight:

2% taurolidine

5% Kollidon

0.5% taurine

0.26% NaCl

5 0.0033% KCl

0.004% CaCl₂

0.003% NaHCO₃

10 Solutions in accordance with the invention have a pH within the range of about 7.1 - 7.9. The above solution before sterilization has a pH of about 7.8, and after sterilization has a pH of about 7.2 - 7.38. Ideally, a solution in accordance with the present invention has a pH of about 7.4.

15 In yet another embodiment, taurultam is substituted for amino acid(s) such as taurine in isotonic taurolidine solutions according to the invention. For example, about 0.1 - 1% by weight taurultam may be substituted for amino acid(s) such as taurine in isotonic 1.5-3% taurolidine solutions, preferably about 0.2 - 0.5% by weight taurultam.

20 The present invention also is applicable to methods for preparing the compositions as described above. For example, the invention includes methods for stabilizing solutions of taurolidine within the range of about 1.5 - 3% by weight, comprising preparing a solution containing about 1.5 - 3% taurolidine and a substantially isotonic solution-forming amount of at least one physiologically acceptable electrolyte so as to form a substantially isotonic solution. In preferred embodiments, a physiologically acceptable colloidal material is added to the solution so as to render the solution substantially iso-oncotic.

CLAIMS:

1. A stabilized taurolidine composition comprising an aqueous solution containing about 1.5% to about 3% by weight taurolidine, about 0.1% to about 3% by weight of taurine, about 1% to about 10% weight colloidal material, NaCl, KCl, CaCl₂, and NaHCO₃, wherein said composition is substantially isotonic and substantially iso-oncotic.
2. The composition of claim 1 wherein said composition further contains ions selected from the group consisting of Mg⁺⁺, H₂PO₄⁻, Acetate⁻, and mixtures thereof.
3. The method of claim 1 wherein said solution contains about 1.7% to about 2.3% by weight taurolidine.
4. The composition of claim 1 wherein said solution contains about 1.8% to about 2.2% by weight taurolidine.
5. The composition of claim 1 wherein said solution contains about 1.9% to about 2.1% by weight taurolidine.
6. The composition of claim 1 wherein said solution contains about 2% by weight taurolidine.
7. The composition of claim 1 wherein said solution contains about 3% to about 7% by weight colloidal material.
8. The composition of claim 1 wherein said colloidal material is PVP having an average molecular weight of about 1000 to about 15000.
9. The composition of claim 1 wherein said colloidal material is PVP having an average molecular weight of about 9000.
10. The composition of claim 1, wherein said solution contains about 0.3% to about 1% by weight taurine.

11. The composition of claim 1, wherein said solution contains about 0.4% to about 0.6% by weight taurine.
12. The composition of claim 1, wherein said solution contains about 0.5% by weight taurine.
13. The composition of claim 1 wherein said solution further comprises about 0.1% to about 1% by weight taurultam.
14. The composition of claim 13, wherein said solution contains about 0.2% to about 0.5% by weight taurultam.
15. The composition of claim 1 which comprises:
 - 2% taurolidine;
 - 5% polyvinylpyrrolidone;
 - 0.5% taurine;
 - 0.26% NaCl;
 - 0.0033% KCl;
 - 0.004% CaCl₂; and
 - 0.003% NaHCO₃,in water.