Common to all aqueous formulations of insulins, insulin analogs, and insulin derivatives is that the stated proteins are not entirely stable chemically, but instead, as a function of the time, storage temperature, and movement to which the formulation is subject, and many more, there are a range of molecular processes that may occur, affecting the insulins, insulin analogs and insulin derivatives, that are deleterious to the quality of the formulation. One substance which impairs the chemical stability of insulins, insulin analogs, and insulin derivatives is oxygen, whose contact with the formulations in question is unavoidable, owing to its presence in the air - particularly in the case of formulations in packs for multiple administration. It is assumed that, among other things, it is the oxidative potential of oxygen that brings about the impairments in chemical stability.

Summary of Invention

In one aspect, the present invention refers to an aqueous pharmaceutical formulation comprising an insulin analog and methionine, said pharmaceutical formulation having a pH within the range of pH 2.5-4.5, wherein the insultin analog is selected from the group consisting of (a) Gly(A21), Arg(B31), Arg(B32) human insulin, or a pharmacologically tolerable salt thereof, and Arg(A0), His(A8), Glu (A15), Asp(A18), Gly(A21), Arg(B31), Arg(B32) — NH_2 human insulin, or a pharmacologically tolerable salt thereof. In another aspect, the present invention refers to an aqueous pharmaceutical formulation comprising an insulin analog being Lys(B3), Glu(B29) human insulin, or a pharmacologically tolerable salt thereof, and methionine. In still another aspect, the present invention refers to a process for preparing a formulation of the present invention, which comprises (a) introducing the insulin analog and methionine of the pharmaceutical formulation as defined above into an aqueous solution, and (b) adjusting the pH. In yet another aspect, the present invention refers to the use of a formulation of the present invention in the manufacture of a medicament for treating diabetes mellitus. In another aspect, the present invention refers to a medicament for treating diabetes mellitus, composed of a formulation.

Detailed Description

It has now been found that, surprisingly, the addition of the amino acid methionine to formulations of insulins, insulin analogs, and insulin derivatives leads to an improved stability on the part of these proteins.

The invention accordingly provides an aqueous, pharmaceutical formulation comprising an insulin, insulin analog or insulin derivative, or a pharmacologically tolerable salt thereof, and methionine.

What is claimed is:

1. An aqueous pharmaceutical formulation comprising an insulin analog and methionine, said pharmaceutical formulation having a pH within the range of pH 2.5-4.5, wherein the insulin analog is selected from the group consisting of
   (a) Gly(A21), Arg(B31), Arg(B32) human insulin, or a pharmacologically tolerable salt thereof, and
   (b) Arg(A0), His(A8), Glu (A15), Asp(A18), Gly(A21), Arg(B31), Arg(B32) — NH_2 human insulin, or a pharmacologically tolerable salt thereof.

2. The pharmaceutical formulation as claimed in claim 1, having a pH in the range of pH 3.0-4.0.

3. The pharmaceutical formulation as claimed in any one of claims 1 to 2, having a pH of pH 3.75.

4. An aqueous pharmaceutical formulation comprising an insulin analog being Lys(B3), Glu(B29) human insulin, or a pharmacologically tolerable salt thereof, and methionine.

5. The pharmaceutical formulation as claimed in in any one of claims 1 to 4, comprising
   0.001 to 0.2 mg/ml of zinc,
   0.1 to 5.0 mg/ml of a preservative, and
   5.0 to 100 mg/ml of an isotonicity agent.

6. The pharmaceutical formulation as claimed in any one of claims 1 to 5, comprising a preservative selected from the group consisting of phenol, m-cresol, chlorocresol, benzyl alcohol, and parabens.

7. The pharmaceutical formulation as claimed in any one of claims 1 to 6, comprising an isotonicity agent selected from the group consisting of mannitol, sorbitol, lactose, dextrose, trehalose, sodium chloride, and glycerol.

8. The pharmaceutical formulation as claimed in any one of claims 1 to 7, wherein the insulin analog is present in a concentration of 240-3000 nmol/ml.

9. The pharmaceutical formulation as claimed in any one of claims 1 to 8, comprising glycerol at a concentration of 20 to 30 mg/ml.

10. The pharmaceutical formulation as claimed in any one of claims 1 to 9, comprising glycerol at a concentration of 25 mg/ml.

11. The pharmaceutical formulation as claimed in any one of claims 1 to 10, comprising m-cresol at a concentration of 1 to 3 mg/ml.

12. The pharmaceutical formulation as claimed in any one of claims 1 to 1, comprising m-cresol at a concentration of 2 mg/ml.

13. The pharmaceutical formulation as claimed in any one of claims 1 to 12, comprising zinc at a concentration of 0.01 or 0.03 or 0.08 mg/ml.

14. The pharmaceutical formulation as claimed in any one of claims 1 to 13, further comprising exendin-4, or a pharmaceutically acceptable salt thereof.

15. The pharmaceutical formulation as claimed in any one of claims 1 to 13, further comprising H-desPro^{36}-exendin-4-Lys$_6$-NH$_2$, or a pharmaceutically acceptable salt thereof.

16. The pharmaceutical formulation as claimed in any one of claims 1 to 13, further comprising Arg^{34}, Lys^{26}(N$^{\varepsilon}$(γ-glutamyl(N$^{\alpha}$-hexadecanoyl))) GLP-1 (7-37) [liraglutide] or a pharmacologically tolerable salt thereof.

17. The pharmaceutical formulation as claimed in any one of claims 1 to 16, comprising methionine in the concentration range of up to 10 mg/ml.

18. The pharmaceutical formulation as claimed in any one of claims 1 to 17, comprising methionine in the concentration range of up to 3 mg/ml.

19. A process for preparing a formulation as claimed in any one of claims 1 to 18, which comprises

(a) introducing the insulin analog and methionine of the pharmaceutical formulation as defined in claim 1 into an aqueous solution, and

(b) adjusting the pH.

20. Use of a formulation as claimed in any one of the claims 1 to 18 in the manufacture of a medicament for treating diabetes mellitus.

21. A medicament for treating diabetes mellitus, composed of a formulation as claimed in one or more of claims 1 to 18.

AQUEOUS INSULIN PREPARATIONS CONTAINING METHIONINE

ABSTRACT

The invention relates to an aqueous pharmaceutical formulation containing insulin, an insulin analog or an insulin derivative and methionine, and to the production thereof, the use thereof for treating diabetes mellitus, and to a medicament for treating diabetes mellitus.

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