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.

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.

The invention also provides an aqueous pharmaceutical formulation comprising an insulin analog selected from the group consisting of

(a) Gly(A21), Arg(B31), Arg(B32) human insulin, or a pharmacologically tolerable salt thereof, and

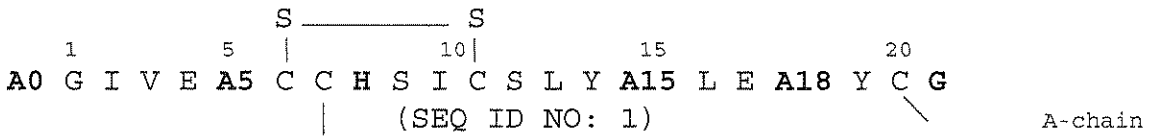
(b) Arg(A0), His(A8), Glu (A15), Asp(A18), Gly(A21), Arg(B31), Arg(B32) — NH_2 human insulin, or a pharmacologically tolerable salt thereof, and methionine,

said pharmaceutical formulation having a pH of 4.5 or less.

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

The invention further provides a pharmaceutical formulation as described above, the insulin being selected from a group containing human insulin, porcine insulin, and bovine insulin.

The invention further provides a pharmaceutical formulation as described above, the insulin analog being selected from the group containing Gly(A21), Arg(B31), Arg(B32) human insulin, Lys(B3), Glu(B29) human insulin, Asp(B28) human insulin, Lys(B28) Pro(B29) human insulin, Des(B30) human insulin and an insulin analog of the formula I



What is claimed is:

1. An aqueous pharmaceutical formulation comprising an insulin analog 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, and methionine, said pharmaceutical formulation having a pH of 4.5 or less.

2. The pharmaceutical formulation as claimed in claim 1, having a pH in the range of pH 2.5-4.5.

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

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

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

6. The pharmaceutical formulation as claimed in in any one of claims 1 to 5, 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.

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

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

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

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

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

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

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

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

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

16. The pharmaceutical formulation as claimed in any one of claims 1 to 14, further comprising H-desPro^{36}-exendin-4-Lys$_6$-NH$_2$, or a pharmaceutically acceptable salt thereof.

17. The pharmaceutical formulation as claimed in any one of claims 1 to 14, further comprising Arg^{34}, Lys^{26}(N^{ε}(y-glutamyl(N^{α}-hexadecanoy1))) GLP-1 (7-37) [liraglutide] or a pharmacologically tolerable salt thereof.

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

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

20. A process for preparing a formulation as claimed in any one of claims 1 to 19, which comprises
(a) introducing the components into an aqueous solution, and
(b) adjusting the pH.

21. Use of a formulation as claimed in any one of the claims 1 to 19 in the manufacture of a medicament for treating diabetes mellitus.

22. A medicament for treating diabetes mellitus, composed of a formulation as claimed in one or more of claims 1 to 19.