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(54) **ACIDIC INSULIN PREPARATIONS HAVING IMPROVED STABILITY**

(75) Inventors: **Anette Brunner-Schwarz**, Frankfurt (DE); **Norbert Lill**, Kronberg (DE)

(73) Assignee: **Sanofi-Aventis Deutschland GmbH**, Frankfurt (DE)

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Primary Examiner—Jeffrey E Russel
(74) *Attorney, Agent, or Firm*—Balaram Gupta

(57) **ABSTRACT**

The invention relates to a pharmaceutical formulation comprising a polypeptide selected from the group consisting of insulin, an insulin metabolite, an insulin analog, an insulin derivative and combinations thereof; a surfactant or combinations of two or more surfactants; optionally a preservative or combinations of two or more preservatives; and optionally an isotonicizing agent, buffers or further excipients or combinations thereof, the pharmaceutical formulation having a pH in the acidic range.

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ACIDIC INSULIN PREPARATIONS HAVING IMPROVED STABILITY

This application is entitled to the benefit of U.S. Provisional Application 60/409,338, filed Sep. 9, 2002, and Federal Republic of Germany Application 10227232.8-41, filed Jun. 18, 2002.

SUMMARY OF THE INVENTION

The invention relates to a pharmaceutical formulation comprising a polypeptide selected from the group consisting of insulin, an insulin metabolite, an insulin analog, an insulin derivative or combinations thereof; a surfactant or combinations of two or more surfactants; optionally a preservative or combinations of two or more preservatives; and optionally an isotonicizing agent, buffers or further excipients or combinations thereof, the pharmaceutical formulation having a pH in the acidic range. These formulations can be employed for the treatment of diabetes, and are particularly suitable for preparations in which a high stability to thermal and/or physico-mechanical stress is necessary. The invention likewise relates to parenteral preparations which contain such formulations and can be used in diabetes and to methods for producing the preparations and for improving the stability of insulin preparations.

BACKGROUND OF THE INVENTION

Worldwide, approximately 120 million people suffer from diabetes mellitus. Among these, approximately 12 million are type I diabetics, for whom the substitution of the lacking endocrine insulin secretion is the only currently possible therapy. The affected persons are dependent lifelong on insulin injections, as a rule a number of times daily. In contrast to type I diabetes, there is not basically a deficiency of insulin in type II diabetes, but in a large number of cases, especially in the advanced stage, treatment with insulin, optionally in combination with an oral antidiabetic, is regarded as the most favorable form of therapy.

In the healthy person, the release of insulin by the pancreas is strictly coupled to the concentration of blood glucose. Elevated blood glucose levels, such as occur after meals, are rapidly compensated by a corresponding increase in insulin secretion. In the fasting state, the plasma insulin level falls to a basal value which is adequate to guarantee a continuous supply of insulin-sensitive organs and tissue with glucose and to keep hepatic glucose production low at night. The replacement of endogenous insulin secretion by exogenous, mostly subcutaneous administration of insulin, as a rule does not approximate the quality of the physiological regulation of the blood glucose described above. Often, deviations of blood glucose upward or downward occur, which in their severest forms can be life-threatening. In addition, however, blood glucose levels which are increased for years without initial symptoms are a considerable health risk. The large-scale DCCT study in the USA (The Diabetes Control and Complications Trial Research Group (1993) *N. Engl. J. Med.* 329, 977-986) demonstrated clearly that chronically elevated blood glucose levels are essentially responsible for the development of diabetic late damage. Diabetic late damage is microvascular and macrovascular damage which is manifested, under certain circumstances, as retinopathy, nephropathy or neuropathy and leads to loss of sight, kidney failure and the loss of extremities and is moreover accompanied by

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the blood glucose as closely as possible in the physiological range. According to the concept of intensified insulin therapy, this should be achieved by repeated daily injections of rapid- and slow-acting insulin preparations. Rapid-acting formulations are given at meals in order to level out the postprandial increase in the blood glucose. Slow-acting basal insulins should ensure the basic supply with insulin, in particular during the night, without leading to hypoglycemia.

Insulin is a polypeptide of 51 amino acids, which are divided into 2 amino acid chains: the A chain having 21 amino acids and the B chain having 30 amino acids. The chains are connected to one another by means of 2 disulfide bridges. Insulin preparations have been employed for diabetes therapy for many years. Not only are naturally occurring insulins used, but recently also insulin derivatives and analogs.

Insulin analogs are analogs of naturally occurring insulins, namely human insulin or animal insulins, which differ by substitution of at least one naturally occurring amino acid residue with other amino acids and/or addition/removal of at least one amino acid residue from the corresponding, otherwise identical, naturally occurring insulin. The amino acids can in this case also be those which do not occur naturally.

Insulin derivatives are derivatives of naturally occurring insulin or an insulin analog which are obtained by chemical modification. This chemical modification can consist, for example, of the addition of one or more specific chemical groups to one or more amino acids. As a rule, insulin derivatives and insulin analogs have a somewhat modified action compared with human insulin.

Insulin analogs having an accelerated onset of action are described in EP 0 214 826, EP 0 375 437 and EP 0 678 522. EP 0 124 826 relates, inter alia, to substitutions of B27 and B28. EP 0 678 522 describes insulin analogs which in position B29 have various amino acids, preferably proline, but not glutamic acid. EP 0 375 437 includes insulin analogs with lysine or arginine in B28, which can optionally be additionally modified in B3 and/or A21.

In EP 0 419 504, insulin analogs are disclosed which are protected against chemical modifications, in which asparagine in B3 and at least one further amino acid in the positions A5, A15, A18 or A21 are modified.

In WO 92/00321, insulin analogs are described in which at least one amino acid of the positions B1-B6 is replaced by lysine or arginine. According to WO 92/00321, insulins of this type have a prolonged action. The insulin analogs described in EP-A 0 368 187 also have a delayed action.

The insulin preparations of naturally occurring insulins on the market for insulin substitution differ in the origin of the insulin (e.g. bovine, porcine, human insulin), and also the composition, whereby the profile of action (onset of action and duration of action) can be influenced. By combination of various insulin preparations, very different profiles of action can be obtained and blood sugar values which are as physiological as possible can be established. Recombinant DNA technology today makes possible the preparation of such modified insulins. These include insulin glargine (Gly(A21)-Arg(B31)-Arg(B32)-human insulin) with a prolonged duration of action. Insulin glargine is injected as an acidic, clear solution and precipitates on account of its solution properties in the physiological pH range of the subcutaneous tissue as a stable hexamer associate. Insulin glargine is injected once daily and is distinguished compared with other long-acting insulins by its flat serum profile and the reduction of the danger of nightly hypoglycemia associated therewith (Schubert-Zsilavec et al., 2: 125-130(2001)).

to previously described preparations, by a clear solution having an acidic pH. Especially at acidic pH, insulins, however, show a decreased stability and an increased proneness to aggregation on thermal and physicochemical stress, which can make itself felt in the form of turbidity and precipitation (particle formation) (Brange et al., J. Ph. Sci 86:517-525 (1997)).

The proneness to aggregation can additionally be promoted by hydrophobic surfaces which are in contact with the solution (Sluzky et al., Proc. Natl. Acad. Sci. 88:9377-9381 (1991)). Surfaces which can be considered as hydrophobic are the glass vessels of the preparations, the stopper material of the sealing caps or the boundary surface of the solution with the air supernatant. In addition, very fine silicone oil droplets can function as additional hydrophobic aggregation nuclei in the taking of the daily insulin dose by means of customary, siliconized insulin syringes and accelerate the process.

WO 01/43762 describes aqueous, parenteral pharmaceutical preparations comprising a polypeptide and glycerol, in which the stabilization of the preparation is to be achieved by purifying off destabilizing constituents of the glycerol.

WO 00/23098 describes insulin preparations stabilized using polysorbate 20 or poloxamer 188 for pulmonary administration, but does not describe the stabilization in an acidic solution against aggregation nuclei.

Published International patent application WO 02/076495 describes zinc-free and low-zinc insulin preparations having improved stability at room and body temperature and to mechanical stress by the addition of surfactants, but does not describe the stabilization of acidic insulin preparations against hydrophobic aggregation nuclei.

The present invention was thus based on the object of finding preparations for acid-soluble insulins containing surfactants, which are distinguished by a high long-term stability to stress due to temperature or physicochemical stressing and tolerate a high stress with hydrophobic aggregation nuclei.

DETAILED DESCRIPTION OF THE INVENTION

It has now surprisingly been found that the addition of surfactants can greatly increase the stability of acidic insulin preparations and thus preparations can be produced which guarantee superior stability to hydrophobic aggregation nuclei for several months under temperature stress.

The pharmaceutical preparations of the present invention contain 60-6000 nmol/ml, preferably 240-3000 nmol/ml, of an insulin, an insulin metabolite, an insulin analog or an insulin derivative.

The surfactants which can be used are, inter alia, nonionic surfactants. In particular, pharmaceutically customary surfactants are preferred, such as, for example: partial and fatty acid esters and ethers of polyhydric alcohols such as of glycerol, sorbitol and the like (Span®, Tween®, in particular Tween® 20 and Tween® 80, Myrj®, Brij®), Cremophor® or poloxamers. The surfactants are present in the pharmaceutical composition in a concentration of 5-200 µg/ml, preferably of 5-120 µg/ml and particularly preferably of 20-75 µg/ml.

The preparation can additionally optionally contain preservatives (e.g. phenol, cresol, parabens), isotonicizing agents (e.g. mannitol, sorbitol, lactose, dextrose, trehalose, sodium chloride, glycerol), buffer substances, salts, acids and alkalis and also further excipients. These substances can in each case be present individually or alternatively as mixtures.

Glycerol, dextrose, lactose, sorbitol and mannitol are cus-

150 mM. Buffer substances, such as, for example, phosphate, acetate, citrate, arginine, glycylglycine or TRIS (i.e. 2-amino-2-hydroxymethyl-1,3-propanediol) buffer and corresponding salts, are present in a concentration of 5-250 mM, preferably 10-100 mM. Further excipients can be, inter alia, salts or arginine.

The invention therefore relates to a pharmaceutical formulation comprising a polypeptide selected from the group consisting of insulin, an insulin analog, an insulin derivative, an active insulin metabolite and combinations thereof; a surfactant or combinations of two or more surfactants; optionally a preservative or combinations of two or more preservatives; and optionally an isotonicizing agent, buffer substances and/or further excipients or combinations thereof, the pharmaceutical formulation being a clear solution which has a pH in the acidic range (pH 1-6.8), preferably pH 3.5-6.8, very particularly preferably 3.5-4.5.

Preferred pharmaceutical formulations of the present invention are those wherein the surfactant is selected from the group consisting of partial and fatty acid esters and ethers of polyhydric alcohols such as of glycerol and sorbitol, and polyols; the partial and fatty acid esters and ethers of glycerol and sorbitol being selected from the group consisting of Span®, Tween®, Myrj®, Brij®, Cremophor®; the polyols being selected from the group consisting of polypropylene glycols, polyethylene glycols, poloxamers, Pluronic®, and Tetronics®; the preservative being selected from the group consisting of phenol, cresol, and parabens; the isotonicizing agent being selected from the group consisting of mannitol, sorbitol, sodium chloride, and glycerol; the excipients being selected from the group consisting of buffer substances, acids, and alkalis; the insulin analog being selected from the group consisting of Gly(A21)-Arg(B31)-Arg(B32)-human insulin; Lys(B3)-Glu(B29)-human insulin; Lys^{B28}Pro^{B29} human insulin, B28 Asp-human insulin, human insulin in which proline in position B28 has been substituted by Asp, Lys, Leu, Val or Ala and where in position B29 Lys can be substituted by Pro; AlaB26-human insulin; des(B28-B30)-human insulin; des(B27)-human insulin and des(B30)-human insulin; the insulin derivative being selected from the group consisting of B29-N-myristoyl-des(B30) human insulin, B29-N-palmitoyl-des(B30) human insulin, B29-N-myristoyl human insulin, B29-N-palmitoyl human insulin, B28-N-myristoyl Lys^{B28}Pro^{B29} human insulin, B28-N-palmitoyl-Lys^{B28}Pro^{B29} human insulin, B30-N-myristoyl-Thr^{B29}Lys^{B30} human insulin, B30-N-palmitoyl-Thr^{B29}Lys^{B30} human insulin, B29-N-(N-palmitoyl-γ-glutamyl)-des(B30) human insulin, B29-N-(N-lithocholy-γ-glutamyl)-des(B30) human insulin, B29-N-(ω-carboxyheptadecanoyl)-des(B30) human insulin and B29-N-(ω-carboxyheptadecanoyl) human insulin.

A further subject of the invention is a pharmaceutical formulation such as described above, in which the insulin, the insulin analog, the active insulin metabolite and/or the insulin derivative is present in a concentration of 60-6000 nmol/ml, preferably in a concentration of 240-3000 nmol/ml (this corresponds approximately to a concentration of 1.4-35 mg/ml or 40-500 units/ml);

in which the surfactant is present in a concentration of 5-200 µg/ml, preferably of 5-120 µg/ml and particularly preferably of 20-75 µg/ml.

A further subject of the invention is a pharmaceutical formulation such as mentioned above, in which glycerol and/or mannitol is present in a concentration of 100-250 mM, and/or

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