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(57) Abstract

The present invention discloses a stable, soluble formulation comprising a medically useful peptide or protein, a hydrophobic preservative, and nicotinamide. Said storage–stable, soluble formulation is useful as a multi–use pharmaceutical product.

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PROTEIN FORMULATIONS

Field of Invention

The present invention is in the field of peptide and protein chemistry as it applies to human medicine. In particular, the invention relates to the preparation of soluble stabile peptide and protein formulations that include nicotinamide and hydrophobic preservatives.

Background of the Invention

Nicotinamide is not a widely-recognized excipient in pharmaceutical formulations. For example, it is not mentioned as an excipient in the *Handbook of Pharmaceutical Excipients*, 2nd ed., A. Wade & P. Weller, Eds. (1994). However, nicotinamide is known to increase the solubility of sparingly-soluble, non-protein, low molecular weight compounds, such as, certain piperazido and piperazino compounds [Fawzi, *et al.*, *J. Pharmaceut. Sci.* 69:104-106 (1980)], anti-cancer nucleoside analogs [Truelove, *et al.*, *Int. J. Pharmaceutics* 19:17-25 (1984)], paracetamol [Hamza, *et al.*, *Drug Dev. Industr. Pharmacy* 11:1577-1596 (1985)], diazepam, griseofulvin, progesterone, 17β-estradiol, and testosterone [Rasool, *et al.*, *J. Pharmaceut. Sci.* 80:387-393 (1991)], the phenothiazine derivative, moricizine [Hussain, *et al.*, *J. Pharmaceut. Sci.* 82:77-79 (1993)], and riboflavin [Coffman, *et al.*, *J. Pharmaceut. Sci.* 85:951-954 (1996)].

In the above cited formulations, nicotinamide apparently operates as a hydrotropic agent to increase the solubility of another solute when nicotinamide is added at a high concentration. This hydrotropic phenomenon is in direct opposition to normal solution behavior where addition of a second solute to a solution of a sparingly soluble substance will cause the less soluble substance to precipitate.

A combination of insulin and nicotinamide, optionally containing a preservative, was previously

described by Jorgensen in U.S. Patent No. 5,382,574. The formulation was reported to promote faster absorption of insulin from an injection site. Jorgensen does not discuss any effect of nicotinamide on formulation stability. Moreover, it is likely that the effect of nicotinamide was not observerd or appreciated because the specification specifically recommends that known stabilizing agents such as phospholipids be added to stabilize the formulations. Also, it fails to mention any effect on insulin stability produced by nicotinamide alone.

The molecular interactions in peptide and protein formulations are complex because a variety of factors such as choice of preservative, buffer, ionic strength, pH, temperature, and other excipients must be balanced to produce a relatively stable formulation suitable for manufacturing, shipping, and storage that meets regulatory requirement for such products. The role that each factor contributes to aggregation is uncertain in view of the complexity of the given peptide or protein molecule as well as the propensity for that peptide or protein to aggregate and precipitate in formulations containing preservatives. In view of this complexity and tendency to aggregate, the effect of nicotinamide on the stability of peptides and protein forumulations containing a hydrophobic preservative could not have been predicted from the art describing nicotinamide's effect as a hydrotropic agent for relatively small molecules, nor from its apparent ability to facilitate absorption of insulin from a subcutaneous injection.

Thus, the present invention provides conditions that increase the physical stability of medically useful peptides and proteins in the presence of hydrophobic preservatives and makes possible commercially-viable, multi-use soluble pharmaceutical products to treat a variety of human diseases.

Summary of the Invention

This invention provides a stable soluble formulation comprising a medically useful peptide or protein, a hydrophobic preservative, and nicotinamide.

The invention further provides a process for preparing said formulation which comprises combining a peptide or protein, a hydrophobic preservative, and nicotinamide to produce said formulation.

Detailed Description and Preferred Embodiments

For purposes of the present invention, as disclosed and claimed herein, the following terms and abbreviations are defined as follows:

Administering -- an act whose effect is to transfer a formulation of the present invention into the body of a mammal in need thereof. Administration may be via any route known to be effective by the physician of ordinary skill. Parenteral administration is commonly understood in the medical literature as the injection of a dosage form into the body by a sterile syringe or some other mechanical device such as an infusion pump. Peripheral parenteral routes of administration include, without limitation, intravenous, intramuscular, subcutaneous, and intraperitoneal routes of administration.

Alkylparaben -- refers to a C_1 to C_4 alkyl paraben, or mixtures thereof. Preferably, alkylparaben is methylparaben, ethylparaben, propylparaben, or butylparaben.

Cresol - refers to meta-cresol, ortho-cresol, para-cresol, chloro-cresol, or mixtures thereof.

Hydrophobic preservative -- refers to a hydrophobic compound that is added to a pharmaceutical formulation to act as an anti-microbial agent. A parenteral formulation must meet guidelines for preservative effectiveness to be a commercially viable multi-use product. Among hydrophobic preservatives known in the art as being effective and acceptable in parenteral formulations are the alkylparabens, the phenolic preservatives, benzyl alcohol,

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