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(54) **POLYPEPTIDE COMPOSITIONS WITH IMPROVED STABILITY**

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See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides means to improve the chemical stability of aqueous, parenteral pharmaceutical compositions comprising a polypeptide and glycerin. Reactive aldehydes are identified in commercial glycerins, and means for reducing such are provided. Convenient means are provided to assay for reactive aldehydes in glycerin, and a strong linear correlation between the level of reactive aldehydes in glycerin and chemical stability of compositions comprising a polypeptide and glycerin is demonstrated. The invention includes aqueous compositions comprising a polypeptide and glycerin having improved chemical stability compared to compositions previously known.

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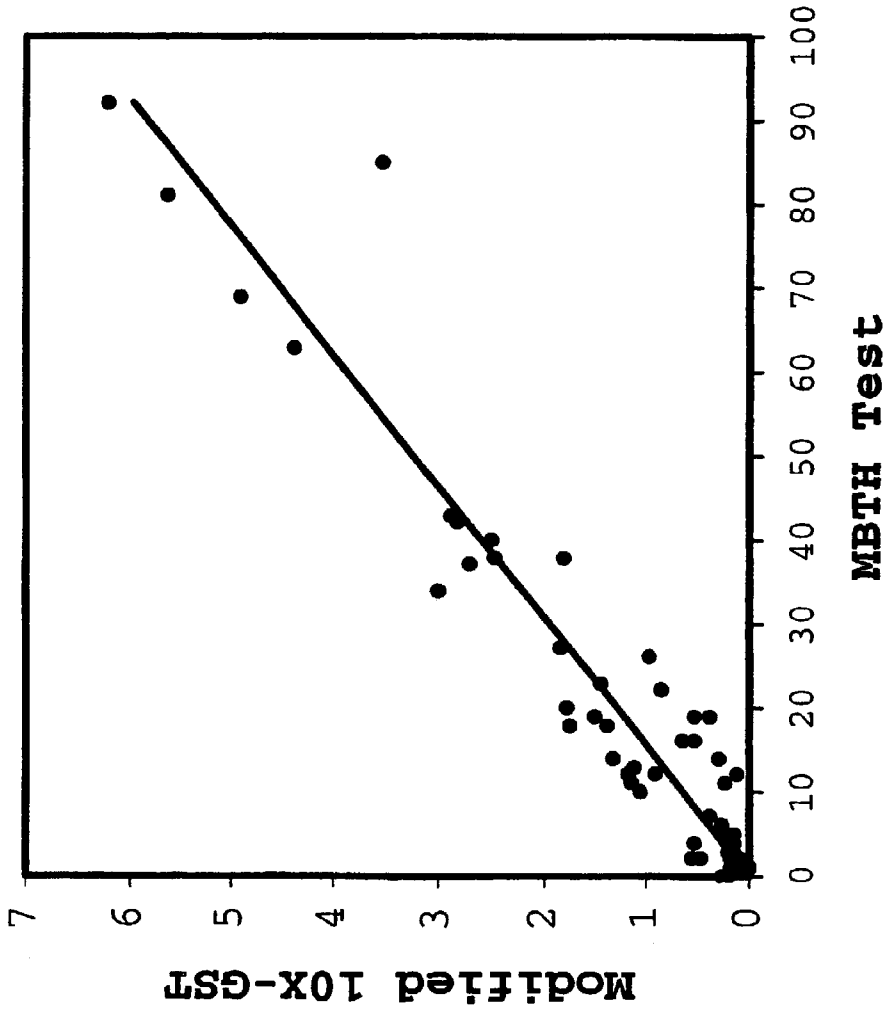

FIG. 1

POLYPEPTIDE COMPOSITIONS WITH IMPROVED STABILITY

This application is a United States national stage application filed under 35 U.S.C. §371 from International Application No. PCT/US00/32421, filed Dec. 5, 2000, which claims benefit of U.S. Provisional Application 60/171,135, filed Dec. 16, 1999, Japanese Patent Application 377208/99, filed Dec. 28, 1999, and U.S. Provisional Application 60/181,030, filed Feb. 8, 2000, each of which application is entirely incorporated herein by reference.

FIELD OF THE INVENTION

This invention is in the field of human medicine. In particular, this invention is in the field of pharmaceutical compositions for treating various diseases, including diabetes and hyperglycemia.

BACKGROUND OF THE INVENTION

Many polypeptide pharmaceutical compositions are utilized for the treatment of diseases in humans and other mammals. Due to their high lability following oral delivery, polypeptide drugs must generally be delivered by parenteral routes. Chief among these routes are subcutaneous, intramuscular and intravenous.

Polypeptide drug products are traditionally supplied to pharmacies, hospitals and patients as solutions, suspensions, or lyophilized products. In liquid form, each polypeptide drug formulation requires a certain minimum level of chemical and physical stability for a defined length of time governed by treatment regimen, patient convenience, patient safety and regulatory guidelines.

To avoid pain or possible tissue damage, liquid polypeptide drug compositions are designed to provide tonicity or osmolarity close to that of the bodily fluids at or surrounding the site of administration. Excipients such as glycerin, dextrose, mannitol, lactose and salts such as sodium chloride are often used for this purpose. Examples of polypeptide drug products employing glycerin as an isotonicity agent include those comprising as active agent human insulin, insulin lispro, insulin aspart and glucagon.

Glycerin has also been used in pharmaceutical compositions as a solubilizer, wetting agent, emulsifier, solvent, bulking substance, antioxidant, chelating agent and preservative [Spiegel, A. J., et al., J. Pharm. Sci. 52:917–927 (1963); Wang, Y-C. J, et al., J. Parenteral Drug Assoc. 34:452–462 (1980); Remington's Pharmaceutical Sciences, Mack Publishing Company 18th Edition, p. 1316 (1990); Li, S., et al., J. Pharm. Sci. 85:868–872 (1996); Sieger, G. M., et al., U.S. Pat. No. 4,016,273, issued 5 Apr. 1977; Heinz, D. N., WIPO publication WO98/29131, 9 Jul. 1998].

For some polypeptide formulations, physical instability precludes the use of salts for isotonicity, a problem often solved by employing glycerin. Glycerin, however, is known to contribute to chemical instability in polypeptide products. In particular, impurities present in glycerin, such as aldehydes, are believed to initiate covalent crosslinking reactions leading to polypeptide dimers and polymers. See, for example, Bello, J., et al. [Arch. Biochem. Biophys. 172: 608–610 (1976)]. For insulin products, such dimers and polymers have been linked to antigenicity and cutaneous allergy as described in Robbins, D. C., et al. [Diabetes 36:838–841 (1987)]; Robbins, D. C., et al. [Diabetes

9:727–734 (1992)] concluded that covalent insulin dimers and polymers should be minimized to avoid these allergic reactions but no methods to achieve this goal were disclosed or suggested.

Three observations may be made about the problem of preparing reliably stable polypeptide compositions containing glycerin for parenteral administration. First, there has been a lack of a simple but accurate assay for determining the level of reactive aldehydes present in glycerin that lead to crosslinked polypeptide impurities. Second, there has been no teaching or suggestion in the prior art that commercial lots of glycerin manufactured from different sources should be evaluated to determine if certain sources are better than others in minimizing the polypeptide crosslinking reactions. Third, there has been no convenient, efficient way of lowering the reactive aldehyde content of glycerin to eliminate or minimize the aldehyde-induced crosslinking reactions in aqueous, pharmaceutical polypeptide compositions. Each of these three observations will now be described in more detail.

Measuring Reactive Aldehydes in Glycerin

The lack of a simple, reliable method of measuring the reactive aldehyde impurities in glycerin that lead to formation of crosslinked polypeptide impurities has hindered solution of the polypeptide crosslinking problem in formulations containing glycerin.

Formaldehyde can initiate crosslinking of polypeptides by a reactive imine link [Schwendeman, S. P., et al., PNAS 92:11234–11238 (1995) and Fraenkel-Conrat, H., et al., JACS 70:2673–2684 (1948)]. Glyceraldehyde and glycolaldehyde react with amino groups in polypeptide solutions, forming crosslinked polypeptides as described in Acharya, A. S., et al. [PNAS 80:3590–3594 (1983)] and Acharya, A. S., et al. [Biochemistry 27:4522–4629 (1988)].

Aldehyde impurities in glycerol were speculated to be involved in formation of high molecular weight polymers in insulin formulations [Brange J., et al., Pharm. Res. 9:727–734 (1992); Brange, J., Stability of Insulin, Kluwer Academic Publishers, Boston, pp. 23–36 (1994); Brange, J., et al., Hormone Drugs, Published by the US Pharmacopoeial Convention, Rockville, Md., pp. 95–105 (1982)] but no methods to quantitate or remove the aldehyde impurities to improve chemical stability of the insulin formulations were disclosed.

There are many assays for aldehydes in the literature, but their applicability to measuring the reactive aldehyde content of glycerin as a predictor of polypeptide crosslinking in pharmaceutical formulations is questionable.

The European Pharmacopoeia Supplement 2000 [Council of Europe, Strasbourg, France, pp. 747–751 (1999)] describes an aldehyde test in its glycerol monograph. This test employs pararosaniline hydrochloride reagent and a 5 ppm formaldehyde standard solution as the comparator.

The British Pharmacopoeia 1999 [British Pharmacopoeia Commission, London, pp. 710–711 (1999)] discloses a test for aldehydes and reducing substances in glycerin using pararosaniline hydrochloride and visual comparison with a standard solution containing 5 ppm of formaldehyde.

The "Purpald" reagent, 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole [Dickinson, R. G., et al., Chem. Commun. p. 1719 (1970)] reacts with aldehydes and has been used for determination of formaldehyde in air, glycols,

Information Bulletin No. AL-145, Aldrich Chemical Co.; Hopps, H. B., Aldrichimica Acta 33:28–29 (2000)].

The reaction of formaldehyde with acetylacetone to form a colored product was described by Nash, T. [Biochem. J. 55:416–425 (1953)]. This reagent appeared to be fairly specific for formaldehyde, as interference from acetaldehyde was only 1% on a molar basis.

The glycerol monograph of The International Pharmacopoeia [Third Edition, WHO, 4:176–181 (1994)], described a test for aldehydes and reducing substances using fuchsin/sulfurous acid solution. Color intensity was compared to a 0.2 M solution of potassium permanganate.

In a promotional bulletin entitled "Discover the Origins of Some of the World's Most Consistently Pure Products; Synthetic Glycerine Products" by Dow Chemical Company (Freeport, Tex., USA), pp. 10–11, UV spectroscopy is used to compare OPTIM™ Glycerine 99.7% USP with less pure glycerin samples. No quantitative assessment of the level of aldehydes or other organic impurities is provided.

Glyceraldehyde reacts with 3-methyl-2-benzothiazolinone hydrazone hydrochloride (MBTH). In Sawicki, E., et al. [Anal. Chem. 33:93–96 (1961)] this reagent was shown to react with DL-glyceraldehyde, but only measurement of formaldehyde in auto exhaust fumes and polluted air was disclosed. Paz, M. A., et al. [Arch. Biochem. Biophys. 109:548–559 (1965)] showed that L-glyceraldehyde reacted with MBTH and disclosed an assay to detect trace quantities of aldehydes in the presence of ketones, keto acids and various types of pyranose carbohydrates during biochemical reactions. Eberhardt, M. A., et al. [Marine Chemistry 17:199–212 (1985)] disclosed the use of MBTH to measure aldehydes, especially formaldehyde, in seawater and bacterial cultures. MBTH is utilized in a commercial assay using glutaraldehyde, or 1,5-pentanedial [Glutaraldehyde Test Kit Model GT-1, Hach (Loveland, Colo., USA)] as a standard. This test uses a color wheel for measuring glutaraldehyde levels as low as 1 mg/L.

Bailey, B. W., et al. [Anal. Chem. 43:782–784 (1971)] showed the reagent p-phenylenediamine reacted with formaldehyde, acetaldehyde and benzaldehyde but was highly selective for formaldehyde. It was used to measure low concentrations of formaldehyde in air.

We have surprisingly discovered a novel MBTH Test using glyceraldehyde as a standard that can be effectively used to accurately determine the level of reactive aldehydes present in glycerin samples. We have also discovered that the level of crosslinking in polypeptide formulations containing glycerin is strongly correlated in a linear relationship with the level of reactive aldehyde in the glycerin used to prepare the formulations as measured by the aforementioned assay. Thus, our novel MBTH Test may be used to readily predict the relative chemical stability of aqueous, parenteral polypeptide compositions comprising glycerin and may also be employed to select suitable lots of glycerin for use in preparing such compositions.

Glycerin Derived from Various Sources

Another hindrance to solving the polypeptide crosslinking problem in formulations containing glycerin has been the failure to recognize the importance of considering the source from which commercial glycerin is manufactured and the process by which the glycerin is manufactured. In particular, there has been no teaching or suggestion that commercial lots of glycerin manufactured from different sources should

Aldehydes in glycerin form by autocatalytic or thermal oxidation, as noted in Mohr, J., et al. [Canadian Patent Application 2,242,591, published 13 Jul. 1998]. As reported by Ziels, N. W. [J. Amer. Oil Chemists' Soc. 33:556–565 (1956)], the processes used to commercially manufacture and purify glycerin have a great impact on the final purity of the glycerin, regardless of the starting material. Glycerin has been manufactured from many sources, including animal fat, plants, fermentation, chemical synthesis from smaller organic molecules and from propylene. Methods of manufacturing glycerin from these and other sources are well known to those skilled in the art. However, what influence the source has on the level of reactive aldehydes found in lots of commercially manufactured glycerin and on the ultimate chemical stability of aqueous, parenteral polypeptide compositions comprising glycerin has not been explored or determined.

Rohde, T. D., et al. [Trans. Am. Soc. Artif. Intern. Organs, 33:316–318 (1987)] disclosed a new insulin formulation for use in implantable pumps containing about 80% glycerin in which the animal-rendered glycerin used in previous formulations was replaced with glycerin from an unspecified synthetic source that was further purified by the authors using a mixed bed ion exchange column. The new and previous formulations also differed in pH, a key factor influencing extent of crosslinking reactions in insulin formulations. In treating diabetic patients, a longer flow cycle and lower insulin usage with the new formulation suggested improved stability, which was attributed to the difference in pH and the synthetic glycerin's extra purification.

Using the MBTH Test described herein, we have most surprisingly discovered that commercial glycerin lots manufactured from non-animal sources contain lower levels of reactive aldehydes than animal-derived glycerin. This was demonstrated for glycerin derived from plants and propylene. Glycerin derived from propylene has particularly low levels of reactive aldehydes. We also discovered that commercially manufactured glycerin lots derived from plant and propylene sources have a much lower average reactive aldehyde content per month of age than glycerin lots derived from animal sources, which suggests the level of reactive aldehydes increases faster over time in animal derived glycerin than in plant and propylene derived glycerin.

Furthermore, we discovered that aqueous, parenteral pharmaceutical compositions of polypeptides comprising glycerin derived from propylene have improved chemical stability compared to similar compositions prepared with animal derived glycerin.

Lowering Reactive Aldehyde Levels in Glycerin

Finally, no simple, efficient method for lowering the level of reactive aldehydes in glycerin to improve the chemical stability of pharmaceutical polypeptide compositions comprising glycerin has been disclosed.

Bello, J. [Biochemistry 8:4535–4541 (1969)] and Bello, J., et al. [Arch. Biochem. Biophys. 172:608–610 (1976)] sought to prevent crosslinking in a protein solution containing glycerin by purifying the glycerin. The glycerin was first treated with the reducing agent sodium borohydride. The reduction step was followed by treating the glycerin with MB-3 resin to remove inorganic salts, and finally by distillation in vacuo. There was no indication of the level of reactive aldehydes before or after this treatment. The low-

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