Atty. Dkt. No. 016777/0454

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Indu J. Isaacs

Title: GLP-2 FORMULATIONS

Appl. No.: Unknown

Filing Date: Herewith

Examiner: Unknown

Art Unit: Unknown

UTILITY PATENT APPLICATION TRANSMITTAL

Commissioner for Patents
Box PATENT APPLICATION
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Sir:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is the nonprovisional utility patent application of:

Indu J. Isaacs

Enclosed are:

[**X**] Specification, Claim(s), and Abstract (27 pages including a cover page).

[**X**] Informal drawings (6 sheets, Figures 1-6).

[**X**] Unexecuted Declaration and Power of Attorney (4 pages).

[ ] Assignment of the invention to NPS ALLELIX CORP..

[ ] Assignment Recordation Cover Sheet.

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Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

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U.S. PATENT APPLICATION FOR

GLP-2 FORMULATIONS

BY

Indu J. Isaacs

GLP-2 FORMULATIONS

FIELD OF INVENTION

The present invention provides formulations for GLP-2 peptides and analogs thereof. In particular, the invention provides formulations of GLP-2 peptides and GLP-2 analogs with improved stability.

BACKGROUND OF THE INVENTION

Administration of therapeutic peptides requires peptide formulations that remain stable during storage. In general, parenteral administration is used with peptides because of their increased size and subsequent difficulty in crossing biological membranes. Peptides can be particularly difficult to formulate because of their tendency to degrade over time and/or undergo aggregation and precipitation. Degradation, aggregation, and precipitation are all indicative of an unstable formulation. Such an unstable formulation is not commercially viable, as it cannot pass U.S. Food and Drug Administration approval.

Formulation variables which affect the degradation of peptides during storage include, but are not limited to, pH, the quantity of salts present, and the type and quantity of excipients. In addition, temperatures, pressures, and time for freezing and drying cycles can affect the stability of a lyophilized peptide formulation. The role of most of these variables has been studied; however, the synergistic effect of the variables is still poorly understood.

Glucagon-like peptide-2 (GLP-2) is a 33 amino acid peptide having therapeutic applications in the treatment of diseases of the gastrointestinal tract . In particular, it has been determined that GLP-2 and analogs thereof act as trophic agents to enhance and maintain the functioning of the gastrointestinal tract and to promote growth of intestinal tissue. *See e.g.,* U.S. Patent Nos. 5,834,428; 5,789,379; and 5,990,077; and International Publication No. WO 98/52600.

Commercial exploitation of GLP-2 or an analog thereof requires a stable GLP-2 formulation that can be readily prepared using a commercially acceptable process. Because GLP-2 is a protein, and thus far more labile than traditional small molecular weight drugs, the formulation of GLP-2 or an analog thereof presents challenges not commonly encountered by the pharmaceutical industry. For example, methionine oxidation at position 10 and aspargine deamination at position 11, 16, and/or 24 of GLP-2 are potential routes of degradation.

Furthermore, GLP-2 or an analog thereof may also be adsorbed to surfaces to form aggregates and/or precipitate, which would then render the formulation unstable.

There is a need in the art for stable formulations of GLP-2 peptides and analogs thereof which can be prepared using a commercially acceptable process. The present invention satisfies these needs.

SUMMARY OF THE INVENTION

The present invention provides stable formulations of GLP-2 and analogs thereof, which can be prepared using a commercially acceptable process.

It has been discovered that relatively high concentrations of GLP-2 can be used in pharmaceutically acceptable formulations. Moreover, it has been discovered that a pH of greater than about 5.5, more preferably greater than about 6, even more preferably from about 6.9 to about 7.9, and most preferably about 7.3 to about 7.4, is suitable for a stable formulation.

It has also been discovered that the GLP-2 analog h[Gly2]GLP-2 undergoes a phase transition between 40-55°C, depending upon the salt concentration, and becomes hydrophobic in the presence of salt. It has also been discovered that Tween 80®, salt, and arginine are not suitable materials for producing a stable formulation for h[Gly2]GLP-2.

According to one aspect of the present invention, there is provided a GLP-2 formulation comprising: (1) a medically useful amount of GLP-2; (2) a phosphate buffer sufficient to adjust the pH of the formulation to a pharmaceutically acceptable level, and in particular above about 6.0; (3) a stabilizing amount of the amino acid L-histidine; and (4) a bulking agent selected from sucrose and mannitol.

More particularly, there is provided a GLP-2 formulation comprising: (1) a medically useful amount of GLP-2 comprising from about 0.1 to about 50 mg/ml of GLP-2, preferably about 5 to about 40 mg/ml, more preferably about 7 to about 30 mg/ml, even more preferably about 10 to about 20 mg/ml, and most preferably about 20 mg/ml; (2) a phosphate buffer to maintain the pH at a physiologically tolerable level, i.e., above 6; (3) a stabilizing amino acid, particularly L-Histidine; and (4) a bulking agent, particularly mannitol. All percentages described herein (except for percentages for water) are weight/volume of formulated product prior to lyophilization in gms/ml (x100). Percentages for water content are weight/weight of lyophilized product (x100).

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