Title: METHODS AND COMPOSITIONS FOR RECTAL ADMINISTRATION OF INSULIN

Abstract: This invention provides compositions comprising insulin and an absorption enhancer, methods for treating diabetes mellitus, comprising administering same, and methods for rectal administration of insulin.

FIGURE 1

Glucose mg%
METHODS AND COMPOSITIONS FOR RECTAL ADMINISTRATION OF
INSULIN

FIELD OF INVENTION

[001] This invention provides compositions comprising insulin and a chelating agent, and a
method for administering same.

BACKGROUND OF THE INVENTION

[002] Due to improved biotechnology, the accessibility of biologically active peptides to the
pharmaceutical industry has increased considerably. However, a limiting factor in the
development of peptide drugs is the relative ineffectiveness when given rectally. Almost all
peptide drugs are parenterally administered, although parenterally administered peptide drugs are
often connected with low patient compliance.

[003] There is no known cure for diabetes. Treatment of the disease requires constant care and
monitoring, along with some form of insulin or drug therapy coupled with diet and exercise. In
spite of the above, the DCCT (Diabetes Control and Complications Trial) of Type I, as well as the
UKPDS (United Kingdom Prospective Diabetes Study), demonstrated that tight control of both
Type I and Type II diabetes can prevent complications associated with diabetes. Insulin is a
medicament used to treat patients suffering from diabetes, and is the only treatment for insulin-
dependent diabetes mellitus. Diabetes Mellitus is characterized by a pathological condition of
absolute or relative insulin deficiency, leading to hyperglycemia, and is another of the main
threats to human health in the 21st century. The condition formally termed diabetes mellitus is a
hormone disorder signified by the cells' inability to absorb glucose from the blood. This can occur
either when there is not enough insulin in the blood, or when the body's cells fail to respond
normally to the insulin that is present. In either case, the negative results are manifold: First, the
blood becomes flooded by an overabundance of sugar, sending glucose concentrations in the
blood shooting up to dangerous levels. Second, without insulin, muscle and liver cells cannot
absorb glucose from the blood, so these cells lack sufficient sugar and are therefore starved for
energy. As a result, the body's supply of fats and proteins must be consumed for "fuel" to keep
normal physiologically processes going, simultaneously both depleting the body's energy storages
and disrupting normal metabolic regulation of fats and proteins.
The global figure of people with diabetes is set to rise to 220 million in 2010, and 300 million in 2025. Type I diabetes is caused primarily by the failure of the pancreas to produce insulin. Type II diabetes, involves a lack of responsiveness of the body to the action of insulin.

Approximately 20%-30% of all diabetics use daily insulin injections to maintain their glucose levels. An estimated 10% of all diabetics are totally dependent on insulin injections.

Currently, the only route of insulin administration is injection. Daily injection of insulin causes considerable suffering for patients. Side effects such as lipodystrophy at the site of the injection, lipatrophy, lilpohypertrophy, and occasional hypoglycemia are known to occur. In addition, subcutaneous administration of insulin does not typically provide the fine continuous regulation of metabolism that occurs normally with insulin secreted from the pancreas directly into the liver via the portal vein.

The present invention addresses the need for an alternate solution for administration of insulin. Rectal application of insulin would free patients of the pain and inconvenience of injections while providing some more physiologically advantageous route of administration.

**SUMMARY OF THE INVENTION**

This invention provides, in another embodiment, a composition comprising insulin and an absorption enhancer.

In one embodiment, the present invention provides a method for rectal administration of insulin to a subject, whereby a substantial fraction of the insulin retains its activity after absorption, through a rectal mucosal barrier of a subject, comprising administering rectally to a subject a pharmaceutical composition comprising said insulin and an absorption enhancer.

In another embodiment, the present invention provides a method for treating diabetes mellitus in a subject, comprising administering rectally to a subject a pharmaceutical composition comprising insulin and an absorption enhancer, thereby treating diabetes mellitus.

**BRIEF DESCRIPTION OF THE FIGURES**

Figure 1 is a graph demonstrating the Glucose lowering effect of the intra-rectal insulin preparation of the present invention.
DETAILED DESCRIPTION OF THE INVENTION

[0012] This invention provides compositions and methods comprising insulin and a chelating agent. In another embodiment, the present invention further provides an enhancer which enhances absorption through a rectal mucosal barrier of a subject. In one embodiment, as provided herein composition comprising insulin and a chelating agent has utility in the rectal administration of insulin, whereby the insulin is absorbed by the rectal mucosa into the bloodstream in an active form.

[0013] In another embodiment, the methods and compositions of the present invention comprise human insulin. In another embodiment, the insulin is recombinant insulin. In another embodiment, the insulin is recombinant human insulin. In another embodiment, the insulin is bovine insulin. In another embodiment, the insulin is porcine insulin. In another embodiment, the insulin is whale insulin. In another embodiment, the insulin is a metal complex of insulin (e.g. a zinc complex of insulin, protamine zinc insulin, or globin zinc).

[0014] In another embodiment, the insulin is regular-acting insulin. In another embodiment, the insulin is fast-acting insulin. In another embodiment, the insulin is lente insulin. In another embodiment, the insulin is semilente insulin. In another embodiment, the insulin is Ultralente insulin. In another embodiment, the insulin is NPH insulin. In another embodiment, the insulin is glargine insulin. In another embodiment, the insulin is lispro insulin. In another embodiment, the insulin is aspart insulin. In another embodiment, the insulin is a combination of two or more of any of the above types of insulin. In another embodiment, the insulin is any other type of insulin known in the art. Each possibility represents a separate embodiment of the present invention.

[0015] In another embodiment, the insulin is crystalline insulin. In another embodiment, the duration of action of insulin is influenced by the physical state and size of the insulin particles. In another embodiment, bovine insulin is used for crystalline preparations. In another embodiment, porcine insulin is used for crystalline preparations. In another embodiment, recombinant human insulin produced in bacterial cells is used for crystalline preparations. In another embodiment, recombinant human insulin produced in Escherichia coli is used for crystalline preparations. In another embodiment, recombinant human insulin produced in yeast cells is used for crystalline preparations. In another embodiment, recombinant human insulin produced in Saccharomyces cerevisiae is used for crystalline preparations. In another embodiment, the crystalline insulin of the present invention is modified insulin synthesised by mutation of the genes used in E. coli or S.
cerevisiae. In another embodiment, recombinant human insulin produced in insect cells is used for crystalline preparations. In another embodiment, recombinant human insulin produced in a cell line is used for crystalline preparations: In another embodiment, recombinant human insulin produced in CHO cells is used for crystalline preparations.

[0016] In another embodiment, recombinant insulin is full length insulin. In another embodiment, recombinant insulin is an insulin fragment with enzymatic activity. In another embodiment, recombinant insulin is a human insulin homologue. In another embodiment, recombinant insulin is a sequence-modified human with enzymatic activity. In another embodiment, recombinant insulin of the present invention is modified by man. In another embodiment, recombinant insulin of the present invention is chemically protected. In another embodiment, recombinant insulin of the present invention is short-acting insulin. In another embodiment, recombinant insulin of the present invention is long-acting insulin. In another embodiment, recombinant insulin of the present invention is a mixture of long-acting and short-acting insulin.

[0017] In some embodiments, insulin of the present invention exists in rhombohedral crystals as hexamers. In another embodiment the crystalline insulin of the present invention is crystalline insulin-zinc. In another embodiment, crystalline insulin comprises insulin-protamine complexes, such as neutral protamine Hagedorn (NPH) insulin.

[0018] In another embodiment, crystalline insulin is over 99% pure as measured by rpHPLC. In another embodiment, crystalline human zinc insulin is over 99% pure as measured by rpHPLC.

[0019] In some embodiments, the compositions of the present invention comprise mixtures of crystalline and amorphous forms of insulin.

[0020] In some embodiments, crystalline dry powder insulin may be formed by grinding or jet milling of bulk crystalline insulin.

[0021] In another embodiment, the amount of insulin utilized in methods and compositions of the present invention is 0.5-3 units (u)/kg in humans. In another embodiment, the units used to measure insulin in methods and compositions of the present invention are USP Insulin Units. In another embodiment, the units used to measure insulin are milligrams. In another embodiment, another USP Insulin Unit is equivalent to 45.5 mg insulin.
[0022] In another embodiment, the amount of insulin is 0.1-1 u/kg. In another embodiment, the amount is 0.2-1 u/kg. In another embodiment, the amount is 0.3-1 u/kg. In another embodiment, the amount is 0.5-1 u/kg. In another embodiment, the amount is 0.1-2 u/kg. In another embodiment, the amount is 0.2-2 u/kg. In another embodiment, the amount is 0.3-2 u/kg. In another embodiment, the amount is 0.5-2 u/kg. In another embodiment, the amount is 0.7-2 u/kg. In another embodiment, the amount is 1-2 u/kg.

[0023] In another embodiment, the amount is 1.2-2 u/kg. In another embodiment, the amount is 1-1.2 u/kg. In another embodiment, the amount is 1-1.5 u/kg. In another embodiment, the amount is 1-2.5 u/kg. In another embodiment, the amount is 1-3 u/kg. In another embodiment, the amount is 2-3 u/kg. In another embodiment, the amount is 1-5 u/kg. In another embodiment, the amount is 2-5 u/kg. In another embodiment, the amount is 3-5 u/kg.

[0024] In another embodiment, the amount of insulin is 0.1 u/kg. In another embodiment, the amount is 0.2 u/kg. In another embodiment, the amount is 0.3 u/kg. In another embodiment, the amount is 0.4 u/kg. In another embodiment, the amount is 0.5 u/kg. In another embodiment, the amount is 0.6 u/kg. In another embodiment, the amount is 0.8 u/kg. In another embodiment, the amount is 1 u/kg. In another embodiment, the amount is 1.2 u/kg. In another embodiment, the amount is 1.4 u/kg. In another embodiment, the amount is 1.6 u/kg. In another embodiment, the amount is 1.8 u/kg. In another embodiment, the amount is 2 u/kg. In another embodiment, the amount is 2.2 u/kg. In another embodiment, the amount is 2.5 u/kg. In another embodiment, the amount is 3 u/kg.

[0025] In another embodiment, the amount of insulin is 1-10 u. In another embodiment, the amount is 2-10 u. In another embodiment, the amount is 3-10 u. In another embodiment, the amount is 5-10 u. In another embodiment, the amount is 1-20 u. In another embodiment, the amount is 2-20 u. In another embodiment, the amount is 3-20 u. In another embodiment, the amount is 5-20 u. In another embodiment, the amount is 7-20 u. In another embodiment, the amount is 10-20 u. In another embodiment, the amount is 12-20 u. In another embodiment, the amount is 10-12 u. In another embodiment, the amount is 10-15 u. In another embodiment, the amount is 10-25 u. In another embodiment, the amount is 10-30 u. In another embodiment, the amount is 20-30 u. In another embodiment, the amount is 10-50 u. In another embodiment, the amount is 20-50 u. In another embodiment, the amount is 30-50 u. In another embodiment, the amount is 20-100 u. In another embodiment, the amount is 30-100 u. In another embodiment, the
amount is 100-150 u. In another embodiment, the amount is 100-250 u. In another embodiment, the amount is 100-300 u. In another embodiment, the amount is 200-300 u. In another embodiment, the amount is 100-500 u. In another embodiment, the amount is 200-500 u. In another embodiment, the amount is 300-500 u. In another embodiment, the amount is 200-1000 u.

In another embodiment, the amount is 300-1000 u.

[0026] In another embodiment, the amount of insulin is 1 u. In another embodiment, the amount is 2 u. In another embodiment, the amount is 3 u. In another embodiment, the amount is 4 u. In another embodiment, the amount is 5 u. In another embodiment, the amount is 6 u. In another embodiment, the amount is 8 u. In another embodiment, the amount is 10 u. In another embodiment, the amount is 12 u. In another embodiment, the amount is 14 u. In another embodiment, the amount is 16 u. In another embodiment, the amount is 18 u. In another embodiment, the amount is 20 u. In another embodiment, the amount is 22 u. In another embodiment, the amount is 25 u. In another embodiment, the amount is 30 u. In another embodiment, the amount is 50 u. In another embodiment, the amount is 80 u. In another embodiment, the amount is 100 u. In another embodiment, the amount is 120 u. In another embodiment, the amount is 140 u. In another embodiment, the amount is 160 u. In another embodiment, the amount is 180 u. In another embodiment, the amount is 200 u. In another embodiment, the amount is 300 u. In another embodiment, the amount is 500 u.

[0027] In another embodiment, the use of sustained release dosage forms (e.g. sustained release microencapsulation) enables the treatment frequency to be reduced to once or twice a day. In another embodiment, the insulin dosage is increased correspondingly with decreasing frequency of administration.

[0028] Each amount of insulin represents a separate embodiment of the present invention.

[0029] Methods of measuring insulin levels are well known in the art. In another embodiment, levels of recombinant insulin are measuring using a human insulin radioimmunoassay (RIA) kit, e.g. the kit manufactured by Linco Research Inc, (St. Charles, Missouri). In another embodiment, levels of C peptide are measured as well, to determine the relative contributions of endogenous and exogenous insulin to observed rises in insulin levels. In another embodiment, insulin ELISA kits are used. In another embodiment, insulin levels are measured by any other method known in the art. Each possibility represents a separate embodiment of the present invention.
[0030] In another embodiment, the compositions of the present invention further comprise pharmaceutical excipients. In another embodiment, pharmaceutical excipients comprise chelating agents. In another embodiment, pharmaceutical excipients comprise a substance that enhances absorption of insulin through a rectal mucosal barrier. In another embodiment, a substance that enhances absorption of the insulin through a rectal mucosal barrier is a rectal absorption enhancer. In another embodiment, the terms "rectal absorption enhancer" and "absorption enhancer" are used interchangeably. In another embodiment, a substance that enhances absorption of the insulin through a rectal mucosal barrier is an insulin rectal absorption enhancer. In another embodiment, a substance that enhances absorption of recombinant insulin through a rectal mucosal barrier is a rectal absorption enhancer. In another embodiment, the absorption enhancer of the present invention is a chelating agent. In another embodiment, the absorption enhancer, when administered to the rectum in a composition comprising crystalline insulin, acts within the rectum in such a way as to induce absorption of crystalline insulin into the living body through the rectal mucous membrane.

[0031] In another embodiment, the compositions of the present invention further comprise a chelating agent. In another embodiment, a chelating agent enhances absorption of insulin. In another embodiment, as provided herein, enhancers, when used in a composition comprising insulin, enhance its ability to be absorbed in the blood.

[0032] In another embodiment, the compositions of the present invention further comprise a polyunsaturated fatty acid (PUFA). In another embodiment, a PUFA of the present invention acts as an absorption enhancer. In another embodiment, the compositions of the present invention further comprise didecanoylphosphatidylcholine (DDPC). In another embodiment, the compositions of the present invention further comprise an aminopolycarboxylate. In another embodiment, the compositions of the present invention further comprise a chelating agent. In another embodiment, the absorption enhancer is a chelating agent. In another embodiment, the chelating agents of the present invention comprise ethylenediaminetetraacetic acid (EDTA) or egtazic acid EGTA. In another embodiment, the EDTA is sodium-EDTA. In another embodiment, the chelating agent is Sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC). In another embodiment, the chelating agent is diethylene triamine pentaacetic acid (DTPA). In another embodiment, the chelating agent is nitritoltriacetic acid (NTA). In another embodiment, NTA is combined with His-tags. In another embodiment, the chelating agent is a phosphonate. In another embodiment, the chelating agent is phosphonic acid. In another embodiment, the phosphonate is a bisphosphonate.
In another embodiment, the bisphosphonate is HEDP. In another embodiment, phosphonic acids of the invention comprise an amine group which, in some embodiments increases the metal binding abilities of the phosphonate.

[0033] In another embodiment, the compositions of the present invention further comprise tolmetin. In another embodiment, tolmetin acts as an absorption enhancer. In another embodiment, tolmetin of the present invention comprise tolmetin salt. In another embodiment, the compositions of the present invention further comprise sodium caprate. In another embodiment, sodium caprate acts as an absorption enhancer. In another embodiment, the compositions of the present invention further comprise salicylic acid. In another embodiment, salicylic acid acts as an absorption enhancer. In another embodiment, the compositions of the present invention further comprise oleic acid. In another embodiment, oleic acid acts as an absorption enhancer. In another embodiment, the compositions of the present invention further comprise linoleic acid. In another embodiment, linoleic acid acts as an absorption enhancer. In another embodiment, the compositions of the present invention further comprise linolenic acid. In another embodiment, linolenic acid acts as an absorption enhancer. In another embodiment, the compositions of the present invention further comprise eicosapentaenoic Acid (EPA). In another embodiment, EPA acts as an absorption enhancer. In another embodiment, the compositions of the present invention further comprise docahexaenoic Acid (DHA). In another embodiment, DHA acts as an absorption enhancer. In another embodiment, the compositions of the present invention further comprise benzilic acid. In another embodiment, benzilic acid acts as an absorption enhancer. In another embodiment, the compositions of the present invention further comprise lecithin. In another embodiment, lecithin acts as an absorption enhancer.

[0034] In some embodiments, the compositions of the present invention further comprise a nitric oxide (NO) donor. In some embodiments, the compositions of the present invention further comprise a bile acid, glycine-conjugated form of a bile acid, or an alkali metal salt. In another embodiment, the compositions of the present invention further comprise an ascorbic acid. In another embodiment, the ascorbic acid is sodium ascorbate or potassium ascorbate. In another embodiment, the compositions of the present invention further comprise a salicylic acid. In another embodiment, the compositions of the present invention further comprise sodium salicylate, potassium salicylate, acetyl-salicylic acid, salicylosaliclyc acid, aluminum acetylsalicylate, choline salicylate, salicylamide, or lysine acetylsalicylate. In another embodiment, the compositions of the present invention further comprise exalamide. In another
embodiment, the compositions of the present invention further comprise diflunisal. In another embodiment, the compositions of the present invention further comprise ethenzamide. In another embodiment, an NO donor, a bile acid, a glycine-conjugated form of a bile acid, an alkali metal salt, sodium ascorbate, potassium ascorbate, salicyclic acid, sodium salicylate, potassium salicylate, acetyl-salicylic acid, salicylosalicylic acid, aluminum acetylsalicylate, choline salicylate, salicylamide, lysine acetylsalicylate, exalamide, diflunisal, or ethenzamide act as an absorption enhancer.

[0035] In another embodiment, the absorption enhancer is characterized by being substantially nontoxic to living organisms. In another embodiment, the absorption enhancer contains in the molecule at least two hydrophilic groups selected from the class consisting of carboxyl groups, acidic hydroxyl groups, carboxyl groups in the form of pharmaceutically acceptable salts, acidic hydroxyl groups in the form of pharmaceutically acceptable salts, carboxyl groups in the form of amides and acidic hydroxyl groups in the form of esters. In another embodiment, the absorption enhancer contains at least two lipophilic groups.

[0036] In another embodiment, the absorption enhancer comprises an amino group, or acidic amino acids. In another embodiment, the compositions of the present invention further comprise glutamic acid. In another embodiment, the compositions of the present invention further comprise sodium glutamate. In another embodiment, the compositions of the present invention further comprise potassium glutamate. In another embodiment, the compositions of the present invention further comprise glutamine. In another embodiment, the compositions of the present invention further comprise pyroglutamic acid. In another embodiment, the compositions of the present invention further comprise sodium pyroglutamate. In another embodiment, the compositions of the present invention further comprise potassium pyroglutamate. In another embodiment, the compositions of the present invention further comprise pyroglutamic acid triethanolamine salt. In another embodiment, the compositions of the present invention further comprise aspartic acid. In another embodiment, the compositions of the present invention further comprise sodium aspartate. In another embodiment, the compositions of the present invention further comprise potassium aspartate. In another embodiment, the compositions of the present invention further comprise asparagine.

[0037] In another embodiment, absorption enhancement is achieved through utilization of a combination of α-galactosidase and β-mannanase. In some embodiments, the compositions of the
present invention further comprise a fatty acid such as sodium caprate. In another embodiment, the compositions of the present invention further comprise sodium glycocholate. In another embodiment, the compositions of the present invention further comprise sodium salicylate. In another embodiment, the compositions of the present invention further comprise n-dodecyl-β-D-maltopyranoside. In some embodiments, surfactants serve as absorption enhancer. In another embodiment, the compositions of the present invention further comprise chitosan such as N,N,N-trimethyl chitosan chloride (TMC).

[0038] In another embodiment, NO donors of the present invention comprise 3-(2-Hydroxy-1-(1-methylethyl)-2-nitrosohydrazino)-1-propanamine, N-ethyl-2-(1-ethyl-hydroxy-2-nitrosohydrazino)-ethanamine, or S-Nitroso-N-acetylpenicillamine.

[0039] In another embodiment, the bile acid of the present invention is a cholic acid. In another embodiment, the bile acid of the present invention is a chenodeoxycholic acid. In another embodiment, the bile acid of the present invention is a taurocholic acid. In another embodiment, the bile acid of the present invention is a taurochenodeoxycholic acid. In another embodiment, the bile acid of the present invention is a glycocholic acid. In another embodiment, the bile acid of the present invention is a glycochenocholic acid. In another embodiment, the bile acid of the present invention is a 3 beta-monohydroxycholic acid. In another embodiment, the bile acid of the present invention is a lithocholic acid. In another embodiment, the bile acid of the present invention is a 5 beta-cholanic acid. In another embodiment, the bile acid of the present invention is a 3,12-diol-7-another-5 beta-cholanic acid. In another embodiment, the bile acid of the present invention is a 3 alpha-hydroxy-12-ketocholic acid. In another embodiment, the bile acid of the present invention is a 3 beta-hydroxy-12-ketocholic acid. In another embodiment, the bile acid of the present invention is a 12 alpha-3 beta-dihydrocholic acid. In another embodiment, the bile acid of the present invention is an ursodesoxycholic acid.

[0040] In another embodiment, pharmaceutical excipients of the present invention further comprise a nonionic surfactant. In another embodiment, the compositions of the present invention further comprise a nonionic surfactant. In another embodiment, the compositions of the present invention further comprise a nonionic polyoxyethylene ether surface active agent (e.g. another having an HLB value of 6 to 19, wherein the average number of polyoxyethylene units is 4 to 30). In another embodiment, the compositions of the present invention further comprise anionic surface active agents. In another embodiment, the compositions of the present invention further
comprise a cationic surface active agent. In another embodiment, the compositions of the present invention further comprise an ampholytic surface active agent. In another embodiment, zwitteruionic surfactants such as acylcarnitines serve as absorption enhancers.

[0041] In another embodiment, the amount of an absorption enhancer utilized in methods and compositions of the present invention is 0.1 mg/dosage unit. In another embodiment, the amount of enhancer is 0.2 mg/dosage unit. In another embodiment, the amount is 0.3 mg/dosage unit. In another embodiment, the amount is 0.4 mg/dosage unit. In another embodiment, the amount is 0.6 mg/dosage unit. In another embodiment, the amount is 0.8 mg/dosage unit. In another embodiment, the amount is 1 mg/dosage unit. In another embodiment, the amount is 1.5 mg/dosage unit. In another embodiment, the amount is 2 mg/dosage unit. In another embodiment, the amount is 2.5 mg/dosage unit. In another embodiment, the amount is 3 mg/dosage unit. In another embodiment, the amount is 5 mg/dosage unit. In another embodiment, the amount is 7 mg/dosage unit. In another embodiment, the amount is 10 mg/dosage unit. In another embodiment, the amount is 12 mg/dosage unit. In another embodiment, the amount is 15 mg/dosage unit. In another embodiment, the amount is 20 mg/dosage unit. In another embodiment, the amount is 30 mg/dosage unit. In another embodiment, the amount is 50 mg/dosage unit. In another embodiment, the amount is 70 mg/dosage unit. In another embodiment, the amount is 100 mg/dosage unit. In another embodiment, the absorption enhancer of the present invention is a chelating agent.

[0042] In another embodiment, the amount of an absorption enhancer is 0.1-1 mg/dosage unit. In another embodiment, the amount of enhancer is 0.2-1 mg/dosage unit. In another embodiment, the amount is 0.3-1 mg/dosage unit. In another embodiment, the amount is 0.5-1 mg/dosage unit. In another embodiment, the amount is 0.1-2 mg/dosage unit. In another embodiment, the amount is 0.2-2 mg/dosage unit. In another embodiment, the amount is 0.3-2 mg/dosage unit. In another embodiment, the amount is 0.5-2 mg/dosage unit. In another embodiment, the amount is 1-2 mg/dosage unit. In another embodiment, the amount is 1-10 mg/dosage unit. In another embodiment, the amount is 2-10 mg/dosage unit. In another embodiment, the amount is 3-10 mg/dosage unit. In another embodiment, the amount is 5-10 mg/dosage unit. In another embodiment, the amount is 1-20 mg/dosage unit. In another embodiment, the amount is 2-20 mg/dosage unit. In another embodiment, the amount is 3-20 mg/dosage unit. In another embodiment, the amount is 5-20 mg/dosage unit. In another embodiment, the amount is 10-20 mg/dosage unit. In another embodiment, the amount is 10-100 mg/dosage unit. In another
embodiment, the amount is 20-100 mg/dosage unit. In another embodiment, the amount is 30-100 mg/dosage unit. In another embodiment, the amount is 50-100 mg/dosage unit. In another embodiment, the amount is 10-200 mg/dosage unit. In another embodiment, the amount is 20-200 mg/dosage unit. In another embodiment, the amount is 30-200 mg/dosage unit. In another embodiment, the amount is 50-200 mg/dosage unit. In another embodiment, the amount is 100-200 mg/dosage unit. In another embodiment, the absorption enhancer of the present invention is a chelating agent.

[0043] In another embodiment, the amount of an absorption enhancer is 0.1-1000 mg/dosage unit. In another embodiment, the amount of enhancer is 1-1000 mg/dosage unit. In another embodiment, the amount is 10-1000 mg/dosage unit. In another embodiment, the amount is 100-1000 mg/dosage unit. In another embodiment, the amount is 200-1000 mg/dosage unit. In another embodiment, the amount is 300-1000 mg/dosage unit. In another embodiment, the amount is 500-1000 mg/dosage unit. In another embodiment, the amount is 300-900 mg/dosage unit. In another embodiment, the amount is 500-900 mg/dosage unit. In another embodiment, the amount is 600-900 mg/dosage unit. In another embodiment, the absorption enhancer of the present invention is a chelating agent.

[0044] In another embodiment, the amount EDTA 0.1-1000 mg/dosage unit. In another embodiment, the amount of EDTA is 1-1000 mg/dosage unit. In another embodiment, the amount is 10-1000 mg/dosage unit. In another embodiment, the amount is 100-1000 mg/dosage unit. In another embodiment, the amount is 200-1000 mg/dosage unit. In another embodiment, the amount is 300-1000 mg/dosage unit. In another embodiment, the amount is 500-100 mg/dosage unit. In another embodiment, the amount is 300-900 mg/dosage unit. In another embodiment, the amount is 500-900 mg/dosage unit. In another embodiment, the amount is 600-900 mg/dosage unit. In another embodiment, the amount is 750 mg/dosage unit. In another embodiment, the daily amount is 1.5 g.

[0045] In another embodiment, the composition of the present invention further comprises a surfactant. In another embodiment, the surfactant is sodium lauryl sulfate. In another embodiment, the surfactant is polyoxyethylene lauryl ether. In another embodiment, the surfactant is an antioxidant. In another embodiment, the antioxidant is butylhydroxytoluene. In another embodiment, the present invention further comprises preservatives. In another embodiment, the preservative is paraoxybenzoates.
Each type and amount of enhancer represents a separate embodiment of the present invention.

In another embodiment, the formulation of the present invention further comprises a base. In another embodiment, the base used in the pharmaceutical composition of this invention may be those which are known as bases of suppositories for intrarectal administration. In some embodiments, base include oils and fats comprising triglycerides as main companions or fats such as cacao butter, palm fat, palm kernel oil, coconut oil, fractionated coconut oil, lard and WITEPSOL RTM., waxes such as lanolin and reduced lanolin; hydrocarbons such as Vaseline, squalene, squalane and liquid paraffin; long to medium chain fatty acids such as caprylic acid, lauric acid, stearic acid and oleic acid; higher alcohols such as lauryl alcohol, cetanol and stearyl alcohol; fatty acid esters such as butyl stearate and dilauryl malonate; medium to long chain carboxylic acid esters of glycerin such as triolein and tristearin; glycerin-substituted carboxylic acid esters such as glycerin acetoacetate; and polyethylene glycols and its derivatives such as macrogols and cetomacrogol. They may be used either singly or in combination of two or more.

In some embodiments, the composition of this invention may further include a surface-active agent, preservative, and coloring agent, which are ordinarily used in suppositories.

In another embodiment, the unit dosage forms of the pharmaceutical composition of this invention include a solid suppository having as a base a solid fat which when administered to the rectum, becomes flowable within the rectum, such as cacao butter and WITEPSOL, a solid suppository having as a base a hydrophilic solid substance which becomes flowable in the rectum in the same way, such as macrogol, and a gelatin capsule suppository having a normally liquid substance (liquid at room temperature) such as neutral fatty acid triglycerides and vegetable oils as a base and coated with a gelatin film.

In another embodiment, a gelatin capsule shell of the present invention comprises 50-500 mg gelatin. In another embodiment, a gelatin capsule shell of the present invention comprises 100-300 mg gelatin. In another embodiment, a gelatin capsule shell of the present invention comprises 150-250 mg gelatin. In another embodiment, a gelatin capsule shell of the present invention comprises 100-200 mg gelatin. In another embodiment, a gelatin capsule shell of the present invention comprises 100-150 mg gelatin. In another embodiment, a gelatin capsule shell of the present invention comprises 150-200 mg gelatin.
[0051] In another embodiment, a gelatin capsule shell of the present invention comprises 20-300 mg glycerol. In another embodiment, a gelatin capsule shell of the present invention comprises 50-300 mg glycerol. In another embodiment, a gelatin capsule shell of the present invention comprises 50-200 mg glycerol. In another embodiment, a gelatin capsule shell of the present invention comprises 100-300 mg glycerol. In another embodiment, a gelatin capsule shell of the present invention comprises 80-200 mg glycerol. In another embodiment, a gelatin capsule shell of the present invention comprises 80-150 mg glycerol. In another embodiment, a gelatin capsule shell of the present invention comprises 80-120 mg glycerol.

[0052] In another embodiment, a gelatin capsule shell of the present invention comprises 10-100 ml purified water. In another embodiment, a gelatin capsule shell of the present invention comprises 10-50 ml purified water. In another embodiment, a gelatin capsule shell of the present invention comprises 20-100 ml purified water. In another embodiment, a gelatin capsule shell of the present invention comprises 50-100 ml purified water. In another embodiment, a gelatin capsule shell of the present invention comprises 20-80 ml purified water. In another embodiment, a gelatin capsule shell of the present invention comprises 30-60 ml purified water. In another embodiment, a gelatin capsule shell of the present invention comprises 30-50 ml purified water.

[0053] In another embodiment, a gelatin capsule shell of the present invention comprises 0.5-30 mg titanium oxide. In another embodiment, a gelatin capsule shell of the present invention comprises 0.5-10 mg titanium oxide. In another embodiment, a gelatin capsule shell of the present invention comprises 10-30 mg titanium oxide. In another embodiment, a gelatin capsule shell of the present invention comprises 15-30 mg titanium oxide. In another embodiment, a gelatin capsule shell of the present invention comprises 0.5-10 mg titanium oxide. In another embodiment, a gelatin capsule shell of the present invention comprises 1-10 mg titanium oxide. In another embodiment, a gelatin capsule shell of the present invention comprises 3-6 mg titanium oxide.

[0054] In another embodiment, a gelatin capsule shell of the present invention comprises 0.1-1.5 mg D&C yellow No. Quinoline Yellow. In another embodiment, a gelatin capsule shell of the present invention comprises 0.5-1.5 mg D&C yellow No. Quinoline Yellow. In another embodiment, a gelatin capsule shell of the present invention comprises 1-1.5 mg D&C yellow No. Quinoline Yellow. In another embodiment, a gelatin capsule shell of the present invention comprises 0.1-1 mg D&C yellow No. Quinoline Yellow. In another embodiment, a gelatin capsule shell of the present invention comprises 0.1-1 mg D&C yellow No. Quinoline Yellow. In another embodiment, a gelatin
capsule shell of the present invention comprises 0.2-1 mg D&C yellow No. Quinoline Yellow. In another embodiment, a gelatin capsule shell of the present invention comprises 0.1-0.6 mg D&C yellow No. Quinoline Yellow. In another embodiment, a gelatin capsule shell of the present invention comprises 0.2-0.6 mg D&C yellow No. Quinoline Yellow. In another embodiment, a gelatin capsule shell of the present invention comprises 0.3-0.6 mg D&C yellow No. Quinoline Yellow. In another embodiment, a gelatin capsule shell of the present invention comprises 0.4-0.5 mg D&C yellow No. Quinoline Yellow.

[0055] In another embodiment, the capsule fill comprises 50-5000 mg soybean oil. In another embodiment, the capsule fill comprises 500-5000 mg soybean oil. In another embodiment, the capsule fill comprises 50-500 mg soybean oil. In another embodiment, the capsule fill comprises 50-500 mg soybean oil. In another embodiment, the capsule fill comprises 500-3000 mg soybean oil. In another embodiment, the capsule fill comprises 50-5000 mg soybean oil. In another embodiment, the capsule fill comprises 500-2500 mg soybean oil. In another embodiment, the capsule fill comprises 1000-1500 mg soybean oil. In another embodiment, the capsule fill comprises 700-1200 mg soybean oil. In another embodiment, the capsule fill comprises 1000-1200 mg soybean oil. In another embodiment, the capsule fill comprises 700-1200 mg soybean oil. In another embodiment, the capsule fill comprises 600-900 mg soybean oil.

[0056] In another embodiment, the capsule fill comprises 10-1000 mg SNAC. In another embodiment, the capsule fill comprises 300-1000 mg SNAC. In another embodiment, the capsule fill comprises 10-1000 mg SNAC. In another embodiment, the capsule fill comprises 10-1000 mg SNAC. In another embodiment, the capsule fill comprises 10-500 mg SNAC. In another embodiment, the capsule fill comprises 10-300 mg SNAC. In another embodiment, the capsule fill comprises 50-250 mg SNAC. In another embodiment, the capsule fill comprises 50-150 mg SNAC. In another embodiment, the capsule fill comprises 80-120 mg SNAC.

[0057] In another embodiment, the capsule fill comprises 10-1000 mg EDTA. In another embodiment, the capsule fill comprises 300-1000 mg EDTA. In another embodiment, the capsule fill comprises 500-1000 mg EDTA. In another embodiment, the capsule fill comprises 10-1000 mg EDTA. In another embodiment, the capsule fill comprises 10-500 mg SNAC. In another embodiment, the capsule fill comprises 10-300 mg SNAC. In another embodiment, the capsule fill comprises 50-250 mg EDTA. In another embodiment, the capsule fill comprises 10-1000 mg SNAC. In another embodiment, the capsule fill comprises 100-250 mg EDTA.
embodiment, the capsule fill comprises 100-200 mg EDTA.

[0058] In another embodiment, the capsule fill comprises 1-50 mg RD-T recombinant human insulin. In another embodiment, the capsule fill comprises 10-50 mg RD-T recombinant human insulin. In another embodiment, the capsule fill comprises 15-50 mg RD-T recombinant human insulin. In another embodiment, the capsule fill comprises 30-50 mg RD-T recombinant human insulin. In another embodiment, the capsule fill comprises 1-30 mg RD-T recombinant human insulin. In another embodiment, the capsule fill comprises 10-30 mg RD-T recombinant human insulin. In another embodiment, the capsule fill comprises 1-20 mg RD-T recombinant human insulin. In another embodiment, the capsule fill comprises 2-15 mg RD-T recombinant human insulin. In another embodiment, the capsule fill comprises 2-10 mg RD-T recombinant human insulin. In another embodiment, the capsule fill comprises 3-5 mg RD-T recombinant human insulin.

[0059] In another embodiment, suppositories of the present invention are prepared by mixing crystalline insulin with a wax-like substance to form a semi-solid, bullet-shaped form that will melt after insertion into the rectum.

[0060] In another embodiment, composition of the present invention is formulated into insertable liquids for use as retention enemas.

[0061] In another embodiment, the present invention comprises capsules of gelatin comprising the composition of the present invention. In another embodiment, gelatin capsules comprising the composition of the present invention are for pediatric use.

[0062] In another embodiment, the present invention comprises rectal ointments that incorporate the composition of the present invention. In another embodiment, the present invention comprises rectal creams that incorporate the composition of the present invention. In some embodiments, ointments and creams of the invention further comprise rectal insertion and delivery tips.

[0063] In another embodiment, administration of internal rectal medicated cream or ointment requires placement of the applicator's lubricated tip at the rectal opening. In another embodiment, the correct dosage of the composition of the present invention is squeezed into the rectum.
In another embodiment, the present invention comprises rectal aerosol foams (oil-in-water emulsions resembling light creams, non-greasy) that incorporate the composition of the present invention. In another embodiment, the present invention comprises rectal coherent gel matrix that incorporate the composition of the present invention.

In another embodiment, the present invention comprises a non-dissolving, non-disintegrating slow-release suppository base consisting essentially of a linear polymer, such as methyl cellulose, and water in an amount of more than 35 parts by weight and less than 65 parts by weight of linear polymer.

In another embodiment, the present invention comprises a non-dissolving, non-disintegrating, slow-release, shaped suppository consisting essentially of polyvinyl pyrrolidone and water, wherein the water is present in an amount of more than 35 parts by weight wherein the suppository has flexibility and becomes slippery when moistened.

In another embodiment, the present invention comprises a suppository applicator which is a another-piece injection molded suppository applicator for ejecting medicament such as insulin into a body cavity comprising a cylindrical main body portion having a distal end and a proximal end. In another embodiment, the main body portion further comprises: an integral flexible chamber means at the distal end; a flexible junction means adjacent, integral to and at least partially the flexible chamber means; a plunger means adjacent and integral to the flexible chamber means; and a barrel stem; wherein the flexible junction means integrally joins the plunger means and flexible chamber means within the barrel stem.

In another embodiment, the present invention comprises a urethral suppository. In another embodiment, a urethral suppository comprises i) a relatively long, relatively small diameter shaft, ii) a bulbous head extending from a rounded nose through a relatively gradually outwardly curving insertion surface having an axial length equaling about two thirds of the overall length of the head and a relatively sharply curving retention surface extending from the intersection with the insertion surface which is the maximum diameter of the head to an intersection with the shaft, the intersection between the retention surface and the insertion surface not comprising a sharp edge or corner, and iii) a conical tail including an outwardly tapered retaining surface extending from the shaft to a base having a diameter substantially greater than the maximum diameter of the bulbous head, wherein shaft, head, and tail comprises predetermined dimensions and a unitary structure and are formed entirely from insulin.
[0069] In another embodiment, insulin is combined in a dissolvable element containing an agent material that is used for local administration of an agent material in an internal body area. In another embodiment, the dissolvable element is made of a dissolvable polymer material and/or complex carbohydrate material which dissolve due to human body temperatures and moisture during use to release the agent material in a desired timed release and dosage.

[0070] In another embodiment, the present invention comprises a sustained release suppository comprising a fat having a melting range of from 29°C to 40°C. In another embodiment, the sustained release suppository further comprises a physiologically acceptable organic substance that is swellable in contact with water. In another embodiment, the organic substance that is swellable in contact with water is hydroxypropylmethylcellulose. In some embodiments, the sustained release suppository further comprises hydrophobic silicium dioxide.

[0071] In some embodiments, the present invention comprises a suppository for use in the vaginal or rectal cavity comprising insulin and a mixture of triglycerides of fatty acids. In some embodiments, the vaginal or rectal suppository further comprises a gel forming agent and a gel dispersing agent.

[0072] In some embodiments, the present invention comprises an effervescent vaginal suppository composition containing a stabilizer. In some embodiments, the stabilizer is selected from compounds such as anhydrous sodium sulfate, anhydrous silica gel, dried magnesium silicate, dried aluminum silicate, dried calcium carboxymethylcellulose, dried microcrystalline cellulose, dried starch and dried calcium phosphate, or mixtures thereof.

[0073] In some embodiments, the present invention comprises an insulin capsule. In another embodiment, the insulin capsule is formed of a hard capsule shell. In some embodiments, hard capsule shell is made of a mixed ester of cellulose ether, e.g. alkyl-, hydroxyalkyl- and hydroxyalkyl alkylecelluloses, esterified with aliphatic monacly groups and acidic succinyl groups. In another embodiment, the capsule is inserted into the rectum. In some embodiments, the capsule shell is disintegrated and the rectally absorbable effective insulin is released into the rectum.

[0074] In another embodiment, the suppository of the present invention comprises a biocompatible material in the form of a polymer. In another embodiment, the biocompatible polymer is polyurethane. In another embodiment, the polymer is cellulose acetate. In another embodiment, the biocompatible polymer is polyamide. In another embodiment, the polymer is
polyethylene. In another embodiment, the polymer is polyethylene terephthalate. In another embodiment, the polymer is polypropylene. In another embodiment, the polymer is polyvinyl acetate. In another embodiment, the polymer is polyvinyl chloride. In another embodiment, the polymer is siliconanother rubber. In another embodiment, the polymer is latex. In another embodiment, the polymer is polyhydroxybutyrate. In another embodiment, the polymer is Teflon. In another embodiment, the polymer is polyglycolic acid.

[0075] In another embodiment, the biocompatible polymer erodes at a substantially slower rate than the rest of the matrix. In another embodiment, the biocompatible polymer comprises a matrix of another or more substantially water soluble crystalline polymers.

[0076] In another embodiment, the pharmaceutical composition of this invention may be prepared by uniformly mixing predetermined amounts of the active ingredient, the absorption aid and optionally the base, etc. in a stirrer or a grinding mill, if required at an elevated temperature. In another embodiment, the resulting composition may be formed into a suppository in unit dosage form by, for example, casting the mixture in a mold, or by forming it into a gelatin capsule using a capsule filling machine.

[0077] In another embodiment, the coating is a gelatin coating. In another embodiment, microencapsulation is used to protect the insulin against decomposition in the rectum. In some embodiments, methods for applying a gelatin coating and for microencapsulation are well known in the art. Each method represents a separate embodiment of the present invention.

[0078] In another embodiment, the coating is a film-coating. In another embodiment, the coating is ethylcellulose. In another embodiment, the coating is a water-based dispersion of ethylcellulose, e.g. hydroxypropylmethylcelullose (HPMC) E15. In another embodiment, the coating is a monolithic matrix. In another embodiment, the coating is cellulose ether (e.g. hypromellose HPMC). Each type of coating represents a separate embodiment of the present invention.

[0079] In another embodiment, a multiparticulate dosage forms is used to inhibit digestion of the composition in the stomach.

[0080] Each type of coating, dosage form, etc, that inhibits digestion of the composition in the stomach represents a separate embodiment of the present invention.
[0081] In another embodiment, methods and compositions of the present invention have the advantage of more closely mimicking physiological insulin secretion by the pancreas. When insulin is secreted into the portal vein, the liver is exposed to a greater insulin concentration than peripheral tissues. Similarly, insulin administered according to the present invention reaches the intestine and is absorbed in the body through the intestine and through the portal system to the liver. This absorption route thus resembles the physiological secretion of insulin by the pancreas, enabling, in this embodiment, delicate control of the blood glucose level and the metabolic activities of the liver and the peripheral organs controlled by insulin. By contrast, when insulin is administered to insulin-deficient diabetic patients via the peripheral venous system, the concentration of insulin in the portal vein is similar to that in the peripheral circulation, resulting in hypoinsulinemia in the portal vein and the liver and hyperinsulinemia in the peripheral venous system. This leads, in another embodiment, to an abnormal pattern of glucose disposal.

[0082] In another embodiment, different constituents of compositions of the present composition are absorbed at different rates into the blood stream.

[0083] In another embodiment, a treatment protocol of the present invention is therapeutic. In another embodiment, the protocol is prophylactic. Each possibility represents a separate embodiment of the present invention.

[0084] In another embodiment, the compositions further comprise binders (e.g. acacia, cornstarch, gelatin, caromer, ethyl cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, povidanother), disintegrating agents (e.g. cornstarch, potato starch, alginic acid, silicon dioxide, croscarmelose sodium, crospovidanother, guar gum, sodium starch glycolate), buffers (e.g., Tris-HCL, acetate, phosphate) of various pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), protease inhibitors, surfactants (e.g. sodium lauryl sulfate), permeation enhancers, solubilizing agents (e.g., glycerol, polyethylene glycerol), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite, butylated hydroxyanisole), stabilizers (e.g. hydroxypropyl cellulose, hydroxypropylmethyl cellulose), viscosity increasing agents(e.g. caromer, colloidal silicon dioxide, ethyl cellulose, guar gum), sweeteners (e.g. aspartame, citric acid), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), lubricants (e.g. stearic acid, magnesium stearate, polyethylene glycol, sodium lauryl sulfate), flow-aids (e.g. colloidal silicon dioxide), plasticizers (e.g. diethyl phthalate, triethyl citrate), emulsifiers (e.g. caromer,
hydroxypropyl cellulose, sodium lauryl sulfate), polymer coatings (e.g., poloxamers or poloxamines), coating and film forming agents (e.g. ethyl cellulose, acrylates, polymethacrylates) and/or adjuvants. Each of the above excipients represents a separate embodiment of the present invention.

[0085] In some embodiments, the dosage forms of the present invention are formulated to achieve an immediate release profile, an extended release profile, or a delayed release profile. In some embodiments, the release profile of the composition is determined by using specific excipients that serve for example as binders, disintegrants, fillers, or coating materials. In another embodiment, the composition will be formulated to achieve a particular release profile as known to another skilled in the art.

[0086] In other embodiments, controlled- or sustained-release coatings utilized in methods and compositions of the present invention include formulation in lipophilic depots (e.g. fatty acids, waxes, oils).

[0087] The compositions also include, in another embodiment, incorporation of crystalline insulin into or onto particulate preparations of polymeric compounds such as polylactic acid, polglycolic acid, hydrogels, etc, or onto liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts.) Such compositions will influence the physical state, solubility, stability, rate of in vivo release, and rate of in vivo clearance. In another embodiment, particulate compositions of the active ingredients are coated with polymers (e.g. poloxamers or poloxamines)

[0088] In another embodiment, the compositions containing crystalline insulin and an absorption enhancer are delivered in a vesicle, e.g. a liposome (see Langer, Science 249: 1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez- Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid).

[0089] Each of the above additives, excipients, formulations and methods of administration represents a separate embodiment of the present invention.

[0090] In another embodiment, the term "treating" refers to curing a disease. In another embodiment, "treating" refers to preventing a disease. In another embodiment, "treating" refers to
reducing the incidence of a disease. In another embodiment, "treating" refers to ameliorating symptoms of a disease. In another embodiment, "treating" refers to inducing remission. In another embodiment, "treating" refers to slowing the progression of a disease.

EXPERIMENTAL DETAILS SECTION

EXAMPLE 1

RECTAL INSULIN PREPARATION

MATERIALS AND EXPERIMENTAL METHODS

Formulation

<table>
<thead>
<tr>
<th>Companothernt of the capsule fill</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Soybean oil</td>
<td>876 mg</td>
</tr>
<tr>
<td>SNAC</td>
<td>100   mg</td>
</tr>
<tr>
<td>RD-T recombinant human insulin</td>
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</table>

EXPERIMENTAL DESIGN

[0091] To test whether insulin can be absorbed via the rectum, a gelatin capsule composition containing insulin, SNAC, and soybean oil was administered directly to rectum of an 11.0 kg beagle dog. Blood glucose was measured every 10 minutes following administration. Thus, the compositions of the present enable direct absorption of rectally administered insulin.

Table 1. Blood glucose concentrations following rectal administration of insulin.
RESULTS

[0092] According to the results obtained in Example 1 intra-rectal insulin preparations of the present invention are effective in lowering blood glucose levels (Figure 1). Additionally, the intra-rectal insulin preparations of the present invention have comparable efficacy in lowering blood glucose levels to the oral insulin formulations presented in Example 2.

EXAMPLE 2

ORAL INSULIN PREPARATIONS

[0093] To test whether insulin can be protected from proteases and absorbed via the duodenum, a composition containing insulin, SBTI, EDTA, and fish oil was administered directly to the duodenum of an 8.8 kg beagle dog. Blood glucose was measured every 10 minutes following
administration. As depicted below in Table 1, blood glucose levels were significantly reduced in response to the insulin.

Thus, compositions comprising an omega-3 fatty acid can protect insulin from proteases in the small intestine and enable direct absorption of orally administered insulin.

Table 1. Blood glucose concentrations following administration of insulin to the duodenum in experiment #1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Glucose in milligrams/deciliter (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>67</td>
</tr>
<tr>
<td>0</td>
<td>71</td>
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<td>10</td>
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<tr>
<td>105</td>
<td>64</td>
</tr>
<tr>
<td>120</td>
<td>75</td>
</tr>
</tbody>
</table>
EXAMPLE 3

PREPARATION OF RECTAL CAPSULE FILL

[0095] The raw materials of example 1 were weighed on electronic balances within the pilot plant area. The soybean oil was weighed into a 300 mL beaker and heated to 60°C on a heatable magnetic stirrer. The fat comanothernts were weighed onto PE foil and added to the heated oil. After melting and dissolving in the soybean oil the mixture was let cooling to room temperature. Then SNAC or EDTA was added under intense manual stirring. Finally, insulin was added to the bulk fill and mixed thoroughly. The appearance of the bulk fill was a stable suspension. The bulk fill was then homogenized on a rolling mill at 20°C and sealed with aluminum foil and stored at 2-8°C until used for encapsulation.

[0096] After encapsulation the capsules were mechanically cleaned from lubricating oil in a tumble dryer for about 20 minutes. Last, the capsules were coated and stored in polyethylene boxes at 2-8°C.

EXAMPLE 4

OPTIMIZATION OF ENHANCER

[0097] Various enhancers (e.g. those listed above in the specification) are compared for their ability to facilitate absorption of insulin following rectal administration in methods and compositions of the present invention. Insulin rectal capsules and suppositories are formulated as described, except that the alternate enhancers are substituted for EDTA or SNAC. Amounts of the enhancers are also varied, to determine the optimal amounts. The most effective enhancer/amount is used in subsequent experiments.

EXAMPLE 5

OPTIMIZATION OF TYPE AND AMOUNT OF INSULIN

[0098] Various types and amounts of insulin e.g. those listed above in the specification are compared for their ability to regulate blood sugar in methods and compositions of the present invention. Insulin rectal capsules and suppositories are formulated as described hereinabove, except that the type and amount of insulin is varied. The most effective type/amount of insulin is used in clinical trials.
EXAMPLE 6

EFFICACY OF RECTALLY ADMINISTERED INSULIN IN HUMANS

Formulation

[0099] Formulations comprising EDTA or SNAC and crystalline insulin were formulated as follows: (1) formulation containing 200 mg EDTA, 100 U (4mg) crystalline insulin, 876 mg soybean oil in a rectal gelatin capsule composed of 186 mg gelatin, 102.3 mg glycerol (98%), 5 mg titanium oxide, and 36.7 mg water; (2) formulation containing 100 mg SNAC, 100 U (4 mg) crystalline insulin, 876 mg soybean oil in a rectal gelatin capsule composed of 186 mg gelatin, 102.3 mg glycerol (98%), 5 mg titanium oxide, and 36.7 mg water.

[00100] Formulations (1) and (2) are administered rectally to 8 healthy volunteers divided to two groups (4 healthy volunteers in each group) entering the clinic on the morning of dosing after an 8 hour overnight fast. No food is allowed until the last blood sample is collected (approximately 3.0 hours post study drug administration).

[00101] Blood samples are collected 15 minutes prior to study drug administration, at 0 min, and then every 10 min for the first 60 min and every 15 minutes after drug administration up to 180 minutes. Treatment Phase will consist of two periods and will be approximately 10 days in duration.

[00102] Glucose tests (another-drop) to monitor real-time glucose values are performed using 2 gluco-meters.

[00103] The Treatment Phase consists of two periods and is 10 days in duration. At each study period prior to study drug administration an indwelling catheter is inserted for blood sample collection; glucose test (another drop) is performed 15 minutes prior to study drug administration; vital signs (blood pressure, heart rate) are recorded 20 minutes prior to study drug administration. Vital signs are measured in the sitting position after at least 5 minutes of rest; blood samples for insulin, plasma glucose and C-peptide analysis are collected 15 minutes prior to study drug administration; vital signs (blood pressure, heart rate) are recorded at approximately 1 and 3 hours post study drug administration. Vital signs are measured in the sitting position.
WHAT IS CLAIMED IS:

1. A composition comprising a recombinant insulin protein and a chelating agent.

2. The composition of claim 1, wherein said recombinant insulin protein is a crystalline insulin protein.

3. The composition of claim 1, wherein said chelating agent is an EDTA or a SNAC.

4. The composition of claim 1, wherein said insulin is porcine insulin, bovine insulin, human insulin, or human recombinant insulin.

5. The composition of claim 1, further comprising: tolmetin or a salt thereof, sodium caprate, salicylic acid, oleic acid, lecithin, linoleic acid, linolenic acid, EPA, DHA, benzoic acid, or a mixture thereof.

6. The composition of claim 1, wherein said composition further comprises a pharmaceutical excipient suitable for rectal administration.

7. The composition of claim 1, wherein said composition is in the form of a suppository.

8. The composition of claim 1, wherein said composition is in the form of a capsule.

9. The composition of claim 8, wherein said capsule is a gelatin capsule.

10. A composition comprising a recombinant insulin protein and a rectal absorption enhancer.

11. The composition of claim 10, wherein said recombinant insulin protein is a crystalline insulin protein.

12. The composition of claim 10, wherein said a rectal absorption enhancer is a chelating agent.

13. The composition of claim 12, wherein said chelating agent is an EDTA or a SNAC.

14. The composition of claim 10, wherein said insulin is porcine insulin, bovine insulin, human insulin, or human recombinant insulin.
15. The composition of claim 10, wherein said rectal absorption enhancer is: tolmetin or a salt thereof, sodium caprate, salicylic acid, oleic acid, lecithin, linoleic acid, linolenic acid, EPA, DHA, benzilic acid, or a mixture thereof.

16. The composition of claim 10, wherein said composition further comprises a pharmaceutical excipient suitable for rectal administration.

17. The composition of claim 10, wherein said composition is in the form of a suppository.

18. The composition of claim 10, wherein said composition is in the form of a capsule.

19. The composition of claim 18, wherein said capsule is a gelatin capsule.

20. A method for rectal administration of a recombinant insulin protein to a subject, whereby a substantial fraction of said insulin retains its activity after absorption through a rectal mucosal barrier of said subject, comprising administering rectally to said subject a pharmaceutical composition comprising said insulin and a chelating agent.

21. The method of claim 20, wherein said chelating agent is EDTA or SNAC.

22. The method of claim 20, wherein said insulin is crystalline insulin.

23. The method of claim 20, wherein said insulin comprises porcine insulin, bovine insulin, human insulin, or human recombinant insulin.

24. The method of claim 20, further comprising: tolmetin or a salt thereof, sodium caprate, salicylic acid, oleic acid, lecithin, linoleic acid, linolenic acid, EPA, DHA, benzilic acid, or a mixture thereof.

25. The method of claim 20, wherein said pharmaceutical composition form is a suppository.

26. The method of claim 20, wherein said pharmaceutical composition form is a capsule.

27. The method of claim 26, wherein said capsule is a gelatin capsule.

28. A method for rectal administration of a recombinant insulin protein to a subject, whereby a
substantial fraction of said insulin retains its activity after absorption through a rectal mucosal barrier of said subject, comprising administering rectally to said subject a pharmaceutical composition comprising said insulin and a rectal absorption enhancer.

29. The method of claim 20, wherein said rectal absorption enhancer is a chelating agent.

30. The method of claim 29, wherein said chelating agent is EDTA or SNAC.

31. The method of claim 28, wherein said insulin is crystalline insulin.

32. The method of claim 28, wherein said insulin comprises porcine insulin, bovine insulin, human insulin, or human recombinant insulin.

33. The method of claim 28, wherein said rectal absorption enhancer is: tolmetin or a salt thereof, sodium caprate, salicylic acid, oleic acid, lecithin, linoleic acid, linolenic acid, EPA, DHA, benzilic acid, or a mixture thereof.

34. The method of claim 28, wherein said pharmaceutical composition form is a suppository.

35. The method of claim 28, wherein said pharmaceutical composition form is a capsule.

36. The method of claim 35, wherein said capsule is a gelatin capsule.

37. A method for treating diabetes mellitus in a subject, comprising administering rectally to said subject a pharmaceutical composition comprising recombinant insulin protein and a chelating agent, thereby treating diabetes mellitus.

38. The method of claim 37, wherein said chelating agent is EDTA or SNAC.

39. The method of claim 37, wherein said insulin is crystalline insulin.

40. The method of claim 37, wherein said insulin comprises porcine insulin, bovine insulin, human insulin, or a human recombinant insulin.

41. The method of claim 37, further comprising: tolmetin or a salt thereof, sodium caprate, salicylic acid, oleic acid, lecithin, linoleic acid, linolenic acid, EPA, DHA, benzilic acid, or a mixture
thereof.

42. The method of claim 37, wherein said pharmaceutical composition form is a suppository.

43. The method of claim 37, wherein said pharmaceutical composition form is a capsule.

44. The method of claim 43, wherein said capsule is a gelatin capsule.

45. A method for treating diabetes mellitus in a subject, comprising administering rectally to said subject a pharmaceutical composition comprising recombinant insulin protein and a rectal absorption enhancer, thereby treating diabetes mellitus.

46. The method of claim 45, wherein said rectal absorption enhancer is a chelating agent.

47. The method of claim 46, wherein said chelating agent is EDTA or SNAC.

48. The method of claim 45, wherein said insulin is crystalline insulin.

49. The method of claim 45, wherein said insulin comprises porcine insulin, bovine insulin, human insulin, or a human recombinant insulin.

50. The method of claim 45, wherein said rectal absorption enhancer is: tolmetin or a salt thereof, sodium caprate, salicylic acid, oleic acid, lecithin, linoleic acid, linolenic acid, EPA, DHA, benzilic acid, or a mixture thereof.

51. The method of claim 45, wherein said pharmaceutical composition form is a suppository.

52. The method of claim 45, wherein said pharmaceutical composition form is a capsule.

53. The method of claim 52, wherein said capsule is a gelatin capsule.