Pharmaceutical formulations for the oral delivery of peptide or protein drugs

The present invention relates to improved pharmaceutical formulations, uses and methods for the oral delivery of peptide or protein drugs with advantageously high bioavailability, safety and cost-effectiveness. In particular, the invention provides a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa for use as a medicament, wherein said peptide or protein drug is to be administered orally in combination with a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex, and with a pharmaceutically acceptable reducing agent. The invention also provides a pharmaceutical composition comprising: a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa; a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and a pharmaceutically acceptable reducing agent.

A growing number of proteins and polypeptides have been made available as therapeutic agents. However, the full potential of these biological drugs has not been realized because they are limited to parenteral injection. Ideally, the oral route of administration would be preferred. Oral administration is the most common and popular method of administering drugs due to its simplicity and convenience for patients. However, the gastrointestinal tract degrades these macromolecules and prevents their absorption as intact entities. Enzymatic degradation throughout the gastrointestinal tract and poor permeability through the epithelial cells are the main reasons for their low oral bioavailability.

A number of different approaches have been proposed to improve the oral bioavailability of such therapeutic proteins and polypeptides, including the use of absorption enhancing technologies or the use of protease inhibitors such as soybean trypsin inhibitor, aprotinin, bowman birk inhibitor, bacitracin, camostat mesilate and amastatin (Renukuntla J et al., *Int J Pharm.* 2013, 447(1-2):75-93; US 2007/0087957 A1). However, due to safety concerns none of these protease inhibitors has succeeded as additive in commercial polypeptide drug delivery applications. The protease inhibitors described in known oral polypeptide drug delivery technologies and their toxicity and potential side effects are summarized in the following.

Soybean trypsin inhibitor: Soy is widely accepted as one of "the big eight" allergens that causes immediate reactions such as coughing, sneezing, runny nose, hives, diarrhea, facial swelling, shortness of breath, swollen tongue, difficulty of swallowing, lowered blood pressure, excessive perspiration, fainting, anaphylactic shock and even death; the number of people suffering from soy allergies has been increasing steadily since the 1980s (Moroz LA et al., *N Engl J Med.* 1980, 302(20):1126-8; Foucard T et al., *Allergy.* 1999, 54(3):261-5; Ramesh S, *Clin Rev Allergy Immunol.* 2008, 34(2):217-30).

Bowman birk inhibitor: Another soybean derived protease inhibitor is the Bowman birk inhibitor. Bowman birk inhibitor is known to have oral bioavailability even without absorption enhancing additives and could therefore exert unwanted systemic protease inhibition after oral intake. Systemic inhibition of serine proteases such as plasmin could increase the risk of thrombosis. There are also reports about the formation of antibodies against bowman birk inhibitor (Wan XS et al., *Nutr Cancer.* 2002, 43(2):167-73).

Aprotinin: There have been several concerns about the safety of aprotinin. Anaphylaxis occurs at a rate of 1:200 in first-time use (Mahdy AM et al., *Br J Anaesth.* 2004, 93(6):842-58). A study performed in cardiac surgery patients reported in 2006 showed that there was a risk of acute renal failure, myocardial infarction and heart failure, as well as stroke and encephalopathy (Mangano DT et al., *N Engl J Med.* 2006, 354(4):353-65). Moreover, a study comparing aprotinin with aminocaproic acid found that mortality was increased by 64% (Schneeweiss S et al., *N Engl J Med.* 2008, 358(8):771-83).

The use of these protease inhibitors thus poses potential health risks and should preferably be avoided. Further disadvantages are high manufacturing costs, heterogeneity and regulatory hurdles. Furthermore, most protein based inhibitors have to be co-administrated excessively in large amounts because these compounds are susceptible to enzymatic degradation in the gut. Even large amounts of these inhibitors may not be adequate to reduce protease activity (Renukuntla J et al., *Int J Pharm.* 2013, 447(1-2):75-93).

It has also been proposed to use protease inhibitors such as bacitracin (having antibiotic activity), camostat mesilate (effective in the treatment of pancreatitis) or amastatin (having antibacterial activity) which, however, all have pharmacological effects on their own. Chronic administration of these protease inhibitors in oral polypeptide formulations would therefore not be acceptable (Renukuntla J et al., *Int J Pharm.* 2013, 447(1-2):75-93; US 2007/0087957 A1).

Another disadvantage of protease inhibitors used so far in oral drug delivery systems is their limitation to inactivate just certain intestinal proteases. However, in order to efficiently deliver therapeutic polypeptide drugs in intact form via the oral route, more than just one or two of the intestinal serine proteases, such as trypsin, chymotrypsin, aminopeptidase, carboxypeptidase, elastase and dipeptidyl-4-peptidase, and also other enzymes such as insulin degrading enzyme need to be transiently inactivated. Otherwise, oral bioavailability will remain very low.

Thus, there is still an urgent need for simple, very safe, more efficient and less expensive means and methods to deliver therapeutic polypeptide drugs via the oral route.

It has further been described that aqueous solutions of copper in the presence of ascorbate reduce the activity of plasmin and other serine proteases in the blood (Lind SE et al., *Blood.* 1993, 82(5):1522-31). However, the use of copper and ascorbate in pharmaceutical compositions, let alone for the oral delivery of peptide or protein drugs, has never been proposed.

Certain pharmaceutical formulations for absorption through oral mucosae have been described in WO 2007/062494, and specific insulin formulations have further been proposed in WO 2007/041481.

In the context of the present invention, it has been found that a combination of the trace element copper or zinc with a pharmaceutically acceptable reducing agent, optionally further in combination with a mucosal absorption enhancer that is soluble in the presence of the copper or zinc, results in a surprisingly high and advantageous oral bioavailability of different peptide or protein drugs, as also shown in the working examples (see, in particular, Example 6 and Figure 1). The required amounts of copper or zinc are well below the recommended daily intake levels of these trace elements and can therefore be regarded as safe. Moreover, copper or zinc in combination with a reducing agent exert an inhibitory effect on serine proteases in the gastrointestinal tract but do not show a systemic effect, which provides a further safety improvement as compared to the above-discussed protease inhibitors. Furthermore, copper or zinc as well as reducing agents such as ascorbate or reduced glutathione can be provided at considerably lower manufacturing costs than the above-discussed protease inhibitors that have previously been suggested for the oral delivery of peptide or protein drugs.

The present invention thus solves the problem of providing improved pharmaceutical formulations, uses and methods for the oral delivery of peptide or protein drugs, allowing the

oral administration of a wide range of different peptide or protein drugs with advantageously high bioavailability, safety and cost-effectiveness.

Accordingly, in a first aspect, the present invention provides a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa for use as a medicament, wherein said peptide or protein drug is to be administered orally in combination with: a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and a pharmaceutically acceptable reducing agent.

In accordance with this first aspect, the invention also relates to a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa for use in therapy, wherein said peptide or protein drug is to be administered orally in combination with: a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and a pharmaceutically acceptable reducing agent. The invention likewise provides a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa for use in the treatment or prevention of a disease/disorder, wherein said peptide or protein drug is to be administered orally and in combination with: a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and a pharmaceutically acceptable reducing agent. The invention further relates to a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa for use as a medicament (or for use in therapy, or for use in the treatment or prevention of a disease/disorder), wherein said peptide or protein drug is to be administered orally in combination with a pharmaceutically acceptable copper salt/complex and a pharmaceutically acceptable reducing agent. Moreover, the present invention also provides a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa for use as a medicament (or for use in therapy, or for use in the treatment or prevention of a disease/disorder), wherein said peptide or protein drug is to be administered orally in combination with a pharmaceutically acceptable zinc salt/complex and a pharmaceutically acceptable reducing agent. The invention furthermore relates to the use of a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa in the preparation of a medicament which is to be administered orally in combination with: a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and a pharmaceutically acceptable reducing agent. The invention likewise refers to the use of a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa in the preparation of a medicament for the treatment or prevention of a disease/disorder, which is to be administered orally and in combination with: a pharmaceutically acceptable copper salt/complex and/or a

pharmaceutically acceptable zinc salt/complex; and a pharmaceutically acceptable reducing agent.

In a second aspect, the present invention relates to a pharmaceutically acceptable copper salt/complex for use as a medicament (or for use in therapy, or for use in the treatment or prevention of a disease/disorder), wherein said copper salt/complex is to be administered orally in combination with: a pharmaceutically acceptable reducing agent; and a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

In accordance with this second aspect, the invention also relates to the use of a pharmaceutically acceptable copper salt/complex in the preparation of a medicament which is to be administered orally in combination with: a pharmaceutically acceptable reducing agent; and a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa. The invention further relates to the use of a pharmaceutically acceptable copper salt/complex in the preparation of a medicament for the treatment or prevention of a disease/disorder, which is to be administered orally in combination with: a pharmaceutically acceptable reducing agent; and a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

In a third aspect, the invention provides a pharmaceutically acceptable zinc salt/complex for use as a medicament (or for use in therapy, or for use in the treatment or prevention of a disease/disorder), wherein said zinc salt/complex is to be administered orally in combination with: a pharmaceutically acceptable reducing agent; and a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

In accordance with this third aspect, the invention further relates to the use of a pharmaceutically acceptable zinc salt/complex in the preparation of a medicament which is to be administered orally in combination with: a pharmaceutically acceptable reducing agent; and a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa. The invention likewise relates to the use of a pharmaceutically acceptable zinc salt/complex in the preparation of a medicament for the treatment or prevention of a disease/disorder, which is to be administered orally in combination with: a pharmaceutically acceptable reducing agent; and a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

In a fourth aspect, the present invention provides a pharmaceutically acceptable reducing agent for use as a medicament (or for use in therapy, or for use in the treatment or prevention of a disease/disorder), wherein said reducing agent is to be administered orally in combination with: a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable

zinc salt/complex; and a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

In accordance with this fourth aspect, the invention also relates to a pharmaceutically acceptable reducing agent for use as a medicament (or for use in therapy, or for use in the treatment or prevention of a disease/disorder), wherein said reducing agent is to be administered orally in combination with a pharmaceutically acceptable copper salt/complex and a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa. The invention likewise provides a pharmaceutically acceptable reducing agent for use as a medicament (or for use in therapy, or for use in the treatment or prevention of a disease/disorder), wherein said reducing agent is to be administered orally in combination with a pharmaceutically acceptable zinc salt/complex and a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa. Moreover, the invention refers to the use of a pharmaceutically acceptable reducing agent in the preparation of a medicament which is to be administered orally in combination with: a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa. The invention further relates to the use of a pharmaceutically acceptable reducing agent in the preparation of a medicament for the treatment or prevention of a disease/disorder, which is to be administered orally in combination with: a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

In a fifth aspect, the present invention provides a pharmaceutical composition comprising: a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa; a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and a pharmaceutically acceptable reducing agent.

In accordance with this fifth aspect, the invention also relates to a pharmaceutical composition comprising: a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa; a pharmaceutically acceptable copper salt/complex; and a pharmaceutically acceptable reducing agent. The invention likewise refers to a pharmaceutical composition comprising: a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa; a pharmaceutically acceptable zinc salt/complex; and a pharmaceutically acceptable reducing agent. The pharmaceutical compositions of this fifth aspect are preferably pharmaceutical compositions for oral administration.

In a sixth aspect, the invention provides a pharmaceutical dosage form comprising: a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa; a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and a pharmaceutically acceptable reducing agent; wherein the peptide or protein drug is physically separated from the pharmaceutically acceptable copper salt/complex and the pharmaceutically acceptable zinc salt/complex within the pharmaceutical dosage form. The pharmaceutical dosage form of this sixth aspect is preferably a pharmaceutical dosage form for oral administration.

In a seventh aspect, the present invention provides a method of treating or preventing a disease/disorder, the method comprising orally administering, to a subject in need thereof, a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex, and a pharmaceutically acceptable reducing agent.

In accordance with this seventh aspect, the invention further relates to a method of orally delivering a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, the method comprising orally administering said peptide or protein drug in combination with a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex and with a pharmaceutically acceptable reducing agent to a subject in need thereof. The invention also provides a method of facilitating the oral delivery of a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, the method comprising orally administering said peptide or protein drug in combination with a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex and with a pharmaceutically acceptable reducing agent to a subject in need thereof. Furthermore, the invention relates to a method of administering a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, the method comprising orally administering said peptide or protein drug in combination with a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex and with a pharmaceutically acceptable reducing agent to a subject in need thereof.

The following detailed description applies to all embodiments of the present invention, including all embodiments according to each one of the first, second, third, fourth, fifth, sixth and seventh aspect as described herein above.

The peptide or protein drug to be administered in accordance with the invention has a molecular weight of equal to or less than about 50 kDa (such as, e.g., equal to or less than

about 40 kDa, or equal to or less than about 30 kDa, or equal to or less than about 20 kDa, or equal to or less than about 10 kDa, or equal to or less than about 5 kDa, or equal to or less than about 2 kDa, or equal to or less than about 1 kDa, or equal to or less than about 500 Da). It is preferred that the peptide or protein drug has a maximum molecular weight of equal to or less than about 40 kDa, more preferably equal to or less than about 30 kDa, even more preferably equal to or less than about 20 kDa, and yet even more preferably equal to or less than about 10 kDa. It is furthermore preferred that the peptide or protein drug has a minimum molecular weight of equal to or greater than about 300 Da, more preferably equal to or greater than about 500 Da, even more preferably equal to or greater than about 800 Da, and yet even more preferably equal to or greater than about 1 kDa. Accordingly, it is particularly preferred that the peptide or protein drug has a molecular weight of about 300 Da to about 40 kDa, more preferably about 500 Da to about 30 kDa, even more preferably about 800 Da to about 20 kDa, and yet even more preferably about 1 kDa to about 10 kDa.

The molecular weight of the peptide or protein drug is indicated herein in dalton (Da), which is an alternative name for the unified atomic mass unit (u). A molecular weight of, e.g., 500 Da is thus equivalent to 500 g/mol. The term "kDa" (kilodalton) refers to 1000 Da.

The molecular weight of the peptide or protein drug can be determined using methods known in the art, such as, e.g., mass spectrometry (e.g., electrospray ionization mass spectrometry (ESI-MS) or matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS)), gel electrophoresis (e.g., polyacrylamide gel electrophoresis using sodium dodecyl sulfate (SDS-PAGE)), hydrodynamic methods (e.g., gel filtration chromatography or gradient sedimentation), or static light scattering (e.g., multi-angle light scattering (MALS)). It is preferred that the molecular weight of the peptide or protein drug is determined using mass spectrometry.

The peptide or protein drug may be any peptide or protein that is suitable to be used as a medicament. For example, the peptide or protein drug may be a linear peptide or protein drug or a cyclic peptide or protein drug. It may also be a modified or derivatized peptide or protein drug, such as a PEGylated peptide or protein drug or a fatty acid acylated peptide or protein drug or a fatty diacid acylated peptide or protein drug. Moreover, the peptide or protein drug may be free of histidine residues and/or free of cysteine residues. It is generally preferred that the peptide or protein drug is water-soluble, particularly at neutral pH (i.e., at about pH 7). It is furthermore preferred that the peptide or protein drug has at least one serine protease cleavage site, i.e., that the peptide or protein drug comprises one or more amino acid residue(s) amenable or prone to cleavage by a serine protease (particularly an intestinal serine

protease, such as trypsin, chymotrypsin, aminopeptidase, carboxypeptidase, elastase and/or dipeptidyl-4-peptidase). The term "peptide or protein drug" is used herein synonymously with "therapeutic peptide or protein" and "therapeutic peptide or protein drug".

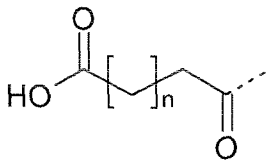
The peptide or protein drug is preferably selected from insulin (preferably human insulin), an insulin analog (e.g., a long acting basal insulin analog or a protease stabilized long acting basal insulin analog; exemplary insulin analogs include, without limitation, insulin lispro, insulin PEGlispro, the insulin derivative "A14E, B25H, B29K(N(eps)octadecanedioyl-gGlu-OEG-OEG), desB30 human insulin" (see, e.g., US 2014/0056953 A1), insulin aspart, insulin glulisine, insulin glargine, insulin detemir, NPH insulin, insulin degludec, and the insulin analogs/derivatives described in US 2014/0056953 A1, which is incorporated herein by reference, particularly each one of the insulin analogs/derivatives described in paragraphs [0225] to [0332] of US 2014/0056953 A1), GLP-1, a GLP-1 analog (e.g., an acylated GLP-1 analog or a diacylated GLP-1 analog) or GLP-1 agonist (also referred to as "glucagon-like peptide-1 receptor agonist" or "GLP-1 receptor agonist"), semaglutide, liraglutide, exenatide, exendin-4, lixisenatide, taspoglutide, albiglutide, dulaglutide, langlenatide, GLP-1(7-37), GLP-1(7-36)NH_2, a dual agonist of the GLP-1 receptor and the glucagon receptor, oxyntomodulin, GLP-2, a GLP-2 agonist or analog (e.g., teduglutide or elsiglutide), amylin, an amylin analog, pramlintide, a somatostatin analog (e.g., octreotide, lanreotide, or pasireotide), goserelin (e.g., goserelin acetate), buserelin, leptin, a leptin analog (e.g., metreleptin), peptide YY (PYY), a PYY analog, glatiramer (e.g., glatiramer acetate), leuprolide, desmopressin (e.g., desmopressin acetate, particularly desmopressin monoacetate trihydrate), osteocalcin, an osteocalcin analog or derivative, human growth hormone (hGH), a human growth hormone analog, a glycopeptide antibiotic (e.g., a glycosylated cyclic or polycyclic nonribosomal peptide such as vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin, or decaplanin), bortezomib, cosyntropin, chorionic gonadotropin, menotropin, sermorelin, luteinizing-hormone-releasing hormone (LHRH; also referred to as "gonadotropin-releasing hormone"), somatropin, calcitonin (e.g., calcitonin-salmon), pentagastrin, oxytocin, neseritide, anakinra, enfuvirtide, pegvisomant, dornase alfa, lepirudin, anidulafungin, eptifibatide, interferon alfacon-1, interferon alpha-2a, interferon alpha-2b, interferon beta-1a, interferon beta-1b, interferon gamma-1b, peginterferon alfa-2a (i.e., pegylated interferon alfa-2a), peginterferon alfa-2b (i.e., pegylated interferon alfa-2b), peginterferon beta-1a (i.e., pegylated interferon beta-1a), fibrinolysin, vasopressin, aldesleukin, epoetin alfa, darbepoetin alfa, epoetin beta, epoetin delta, epoetin omega, epoetin zeta, filgrastim, interleukin-11, cyclosporine, glucagon, urokinase, viomycin, thyrotropin-releasing hormone (TRH), leucine-enkephalin, methionine-enkephalin, substance P (CAS no. 33507-63-0), adrenocorticotropic hormone (ACTH), parathyroid hormone (PTH), a parathyroid hormone (PTH) fragment (e.g., teriparatide (also referred to as "PTH(1-34)"),

PTH(1-31), or PTH(2-34)), parathyroid hormone-related protein (PTHrP), abaloparatide, linaclotide, carfilzomib, icatibant, ecallantide, cilengitide, a prostaglandin F2α receptor modulator (e.g., PDC31), and pharmaceutically acceptable salts thereof. If the subject/patient to be treated is a human and if the peptide or protein drug is an endogenous peptide or protein in human beings (i.e., occurs naturally in humans; such as, e.g., insulin or glucagon), it is furthermore preferred to use a human isoform of the corresponding peptide or protein (which may, e.g., be recombinantly expressed or chemically synthesized).

As noted above, the peptide or protein drug may be an insulin analog. The insulin analog is preferably selected from:
B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin;
B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) desB30 human insulin;
B29K(N(ε)octadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin;
B29K(N(ε)eicosanedioyl-γ-L-Glu) A14E B25H desB30 human insulin;
B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin;
B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin;
B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin;
B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B16H B25H desB30 human insulin;
B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin; and
B29K(N(ε)octadecanedioyl) A14E B25H desB30 human insulin.
These insulin analogs are described and characterized, e.g., in US 2014/0056953 A1. It is particularly preferred that the insulin analog is B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin.

Moreover, as also described above, the peptide or protein drug may be a GLP-1 analog. The GLP-1 analog may be, in particular, a variant of the human Glucagon-Like Peptide-1, preferably a variant of GLP-1(7-37). The amino acid sequence of GLP-1(7-37) is HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG. The aforementioned "variant" of human Glucagon-Like Peptide-1 or of GLP-1(7-37) preferably refers to a compound differing by one or more amino acids from human Glucagon-Like Peptide-1 or from GLP-1(7-37), respectively, wherein such difference is caused by the addition, substitution or deletion of at least one amino acid (e.g., 1 to 10 amino acids) or any combination of such addition(s), substitution(s) and/or deletion(s). A GLP-1 analog may, e.g., exhibit at least 60% (preferably at least 65%, more preferably at least 70%, even more preferably at least 80%, and most preferably at least 90%) sequence identity to GLP-1(7-37) over the entire length of said GLP-1(7-37). As an example of a method for the determination of sequence identity between a GLP-1 analog and GLP-1(7-37), the two peptides [Aib8]GLP-1(7-37) and GLP-1(7-37) are aligned.

[Aib8]GLP-1(7-37) differs from GLP-1(7-37) in that the alanine in position 8 is replaced by α-methylalanine (Aib, i.e. 2-aminoisobutyric acid). The sequence identity of [Aib8]GLP-1(7-37) relative to GLP-1(7-37) is given by the number of aligned identical residues minus the number of different residues divided by the total number of residues in GLP-1(7-37). Accordingly, in this example the sequence identity is (31-1)/31. The C-terminus of the GLP-1 analog (including any one of the specific GLP-1 analogs described herein) may also be in the form of an amide. Moreover, the GLP-1 analog may be, e.g., GLP-1(7-37) or GLP-1(7-36)amide. The GLP-1 analog may also be, e.g., exendin-4, the amino acid sequence of which is HGEGTFITSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS. The GLP-1 analog may further be a modified form of naturally occuring GLP-1 (particularly human GLP-1), which differs from the GLP-1 peptide in that it comprises one substituent which is covalently attached to the peptide. Said substituent may comprise a fatty acid (e.g., a C16, C18 or C20 fatty acid) or a fatty diacid (e.g., a C16, C18 or C20 fatty diacid). Said substituent may also comprise a group of the following formula:



wherein n is at least 13 (e.g., 13, 14, 15, 16, 17, 18 or 19; preferably 13 to 17; more preferably 13, 15 or 17). Said substituent may also comprise one or more 8-amino-3,6-dioxaoctanoic acid (OEG) groups, such as two OEG groups. In particular, said substituent may be selected from [2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxyheptadecanoylamino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl] and [2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-({trans-4-[(19-carboxynonadecanoylamino)methyl]cyclohexanecarbonyl}amino)butyrylamino]ethoxy}ethoxy)acetylamino]ethoxy}ethoxy)acetyl]. The GLP-1 analog may also be selected from one or more of the GLP-1 agonists disclosed in WO 93/19175, WO 96/29342, WO 98/08871, WO 99/43707, WO 99/43706, WO 99/43341, WO 99/43708, WO 2005/027978, WO 2005/058954, WO 2005/058958, WO 2006/005667, WO 2006/037810, WO 2006/037811, WO 2006/097537, WO 2006/097538, WO 2008/023050, WO 2009/030738, WO 2009/030771 and WO 2009/030774.

The peptide or protein drug to be used in accordance with the invention can also be a mixture of two or more different peptide or protein drugs, including the above-mentioned specific peptide or protein drugs. For example, the peptide or protein drug may be a mixture of human insulin and a GLP-1 agonist (e.g. liraglutide, semaglutide, exenatide, lixisenatide, taspoglutide, albiglutide, or dulaglutide).

The pharmaceutically acceptable "copper salt/complex" to be used in accordance with the present invention refers to a pharmaceutically acceptable salt of copper or a pharmaceutically acceptable complex (e.g., a chelate complex) of copper. Likewise, the pharmaceutically acceptable "zinc salt/complex" to be employed in accordance with the invention refers to a pharmaceutically acceptable salt of zinc or a pharmaceutically acceptable complex (e.g., a chelate complex) of zinc. While the expression "pharmaceutically acceptable" is omitted when referring to the copper salt/complex or the zinc salt/complex in the following, it will be understood that the corresponding salts or complexes to be used in accordance with the invention are pharmaceutically acceptable.

The copper salt/complex is preferably a copper(I) salt/complex or a copper(II) salt/complex. Exemplary copper(I) salts/complexes include copper(I) chloride (CuCl) and copper(I) acetate ($CuCH_3CO_2$). Exemplary copper(II) salts/complexes include copper sulfate ($CuSO_4$), copper carbonate ($CuCO_3$), a copper(II) amino acid complex (such as, e.g., copper(II) lysine complex, or copper(II) glycinate), copper(II) EDTA complex, copper(II) chitosan complex, copper(II) citrate, copper(II) gluconate, copper(II) lactate, copper lactate gluconate (also referred to as "EZ-Copper"), and copper(II) orotate. The copper salt/complex is more preferably a copper(II) salt/complex. The use of a copper(II) salt/complex is advantageous since it provides better aqueous solubility and better oxidation state stability than a copper(I) salt/complex. Even more preferably, the copper salt/complex to be used in accordance with the invention is a copper(II) salt/complex selected from copper sulfate ($CuSO_4$), copper carbonate ($CuCO_3$), a copper(II) amino acid complex (preferably a Cu^{2+} L-amino acid complex), copper(II) lysine complex (preferably Cu^{2+} L-lysine complex), copper(II) citrate, copper(II) gluconate (preferably copper(II) D-gluconate), and copper(II) orotate.

The zinc salt/complex is preferably a zinc(II) salt/complex. Exemplary zinc(II) salts/complexes include zinc sulfate, zinc chloride, zinc acetate, zinc oxide, zinc ascorbate, zinc caprylate, zinc gluconate, zinc stearate, zinc carbonate, zinc orotate, a zinc amino acid complex (preferably a zinc L-amino acid complex), zinc glycinate, zinc arginate, zinc picolinate, zinc pidolate, zinc carnosine, zinc undecanoate, zinc undecylenate (e.g., zinc 10-undecenoate), zinc methionine, zinc lactate, zinc lactate gluconate (also referred to as "EZ-Zinc"). The zinc salt/complex is more preferably selected from zinc sulfate, zinc chloride, zinc acetate, zinc oxide, zinc ascorbate, zinc caprylate, zinc gluconate, zinc stearate, zinc carbonate, zinc orotate, and a zinc amino acid complex (particularly a zinc L-amino acid complex).

While either a copper salt/complex or a zinc salt/complex (or both a copper salt/complex and a zinc salt/complex) can be employed in accordance with the present invention, the use of a

copper salt/complex has been found to provide a greater improvement of oral bioavailability of the corresponding peptide or protein drug than the use of a zinc salt/complex, as also demonstrated in Example 6. The use of a copper salt/complex is thus preferred over the use of a zinc salt/complex. At the same time, the use of a zinc salt/complex is advantageous since zinc can safely be administered to humans at even higher doses than copper.

The pharmaceutically acceptable reducing agent to be used in accordance with the present invention is not particularly limited and may be any reducing agent that is acceptable for oral administration. It is preferred that the pharmaceutically acceptable reducing agent is selected from ascorbic acid (preferably an ascorbate, e.g., sodium ascorbate), reduced glutathione (GSH), cysteine, N-acetylcysteine, histidine, glycine, arginine, gelatin, uric acid, a reducing sugar (preferably a reducing monosaccharide, such as, e.g., glucose, glyceraldehyde, galactose, fructose, ribose, xylose, or sorbose; or a reducing disaccharide, such as, e.g., lactose (e.g., spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose®, or Fast-FloC®), maltose, or cellobiose; or a reducing polysaccharide, such as a glucose polymer, e.g., starch, a starch derivative (e.g., glucose syrup, maltodextrin, dextrin, dextrose, or dextran), or cellulose (e.g., microcrystalline cellulose (MCC), such as Avicel®)), mannitol, α-tocopherol, vitamin A, α-lipoic acid, dihydro-α-lipoic acid (DHLA), oxalic acid, phytic acid, a tannin, propyl gallate, butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA), sodium metabisulfite (also referred to as "sodium pyrosulfite", $Na_2S_2O_5$), povidone (i.e., polyvinylpyrrolidone, PVP; also referred to as "polyvidone"; see, e.g., Washio I et al. *Advanced Materials*. 2006;18(13):1745-9; examples of povidone preparations include, in particular, Kollidon® 30, Kollidon® CL, Kollidon® 90 F, or Kollidon® VA 64), crospovidone, an aldehyde (e.g., an aldehyde (C_{1-5} alkyl)-CHO, such as formaldehyde or acetaldehyde, or furfuraldehyde), a dialdehyde (e.g., glyoxal), a phenolic compound (i.e., a compound comprising at least one phenyl ring substituted with at least one hydroxy group; exemplary phenolic compounds include, in particular, phenol, a polyphenol, salicylic acid, or a salicylic acid derivative; see, e.g., Iwasaki Y et al. *Toxicol In Vitro*. 2011;25(7):1320-7), an iron(II) salt/complex (such as, e.g., iron(II) gluconate, iron(II) orotate, iron(II) tartrate, iron(II) fumarate, iron(II) sulfate, iron(II) lactate, iron(II) lactate gluconate, iron(II) acetate, iron(II) carbonate, iron(II) citrate, iron(II) oxide, iron(II) hydroxide, iron(II) ascorbate, or an iron(II) amino acid complex (e.g., an iron(II) chelate of any one of the 20 standard proteinogenic α-amino acids; preferably ferrous bis-glycinate or ferrous bis-glycinate hydrochloride)), diphosphate (E 450), disodiumdiphosphate, trisodiumdiphosphate, tetrasodiumdiphosphate, tetrapotassiumdiphosphate, dicalciumdiphosphate, calciumdihydrogendiphophate, phosphate, dipotassium hydrogen phosphate (see, e.g., Zhang X et al. *J Colloid Interface Sci*. 2013;409:1-7), calcium phosphate (e.g., calcium hydrogen phosphate, such as Emcompress®), a thiol-

bearing compound, a thiomer (also referred to as a "thiolated polymer"; may be synthesized, e.g., by immobilization of sulfhydryl bearing ligands on a polymeric backbone of well-established polymers such as, e.g., polyacrylic acid, carboxymethylcellulose or chitosan; exemplary thiomers include the thiomers that are described in Laffleur F et al., *Future Med Chem.* 2012, 4(17):2205-16 (doi: 10.4155/fmc.12.165) which is incorporated herein by reference), and pharmaceutically acceptable salts of any of the aforementioned agents. Analogs and derivatives of the above-mentioned agents can likewise be used. Mixtures of two or more reducing agents, including any of the above-described reducing agents (such as, e.g., ascorbate and reduced glutathione), can also be used. Redox reactions involving metals, reducing agents and organic compounds are described, e.g., in Sheldon R, Metal-catalyzed oxidations of organic compounds: mechanistic principles and synthetic methodology including biochemical processes, Elsevier, 2012.

As described above, iron(II) salt/complexes are preferred pharmaceutically acceptable reducing agents. Particularly preferred examples include iron(II) gluconate, iron(II) orotate, iron(II) tartrate, iron(II) fumarate, iron(II) sulfate, iron(II) lactate, iron(II) lactate gluconate (also referred to as "EZ-Ferrous"), iron(II) acetate, iron(II) carbonate, iron(II) citrate, iron(II) oxide, iron(II) hydroxide, iron(II) ascorbate, or an iron(II) amino acid complex (e.g., an iron(II) chelate of any one of the 20 standard proteinogenic α-amino acids; particularly ferrous bis-glycinate or ferrous bis-glycinate hydrochloride).

Further preferred pharmaceutically acceptable reducing agents are reducing sugars, as also described above. Reducing sugars can be selected from reducing monosaccharides (such as, e.g., glucose, galactose, fructose, ribose, xylose, sorbose and/or glyceraldehyde), reducing disaccharides (such as, e.g., lactose (e.g., spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-FloC®), maltose, or cellobiose), or reducing polysaccharides (such as, e.g., glucose polymers, for example, starch and starch derivatives, like glucose syrup, maltodextrin or dextrin, dextrose, or dextrans). Starch sugars can have different amounts of reducing sugars commonly expressed as dextrose equivalent (DE). The pharmaceutically acceptable reducing agent may also be activated *in vivo* after oral intake. A corresponding example is starch or modified starch (including, e.g., potato starch, maize starch, or rice starch), which is degraded or partially degraded by amylase to release increasing amounts of reducing components. Starch will be hydrolysed by amylase into disaccharides and trisaccharides which are converted by other enzymes to glucose. Reducing sugars can be characterized by chemical reactions with Fehling's A and B solutions. Fehling's A is a blue aqueous solution of copper(II) sulfate, while Fehling's B is a clear and colorless solution of aqueous potassium sodium tartrate and a strong

alkali (commonly sodium hydroxide). The reducing agent may also be selected from cellulose polymers with various amounts of cellulose-reducing ends (e.g., various grades of Avicel®, Elcema®, Vivacel®, Ming Tai® or Solka-Floc®). Methods for the quantification of total reducing ends on cellulose, such as, e.g., of microcrystalline cellulose (MCC), are described in Kongruang S et al. *Appl Biochem Biotechnol.* 2004;113-116:213-31). It has further been reported that reducing sugar impurities in mannitol caused a redox-reaction in an solid oral dosage form, the extent of which was influenced by the amount of mannitol used as an excipient in the formulation (Dubost DC et al. *Pharm Res.* 1996;13(12):1811-4).

Moreover, amino acids such as cysteine, histidine, glycine or arginine can be used as the pharmaceutically acceptable reducing agent, but also protein and peptide mixtures such as gelatin (see, e.g., Sae-leaw T et al. *J Food Sci Technol.* 2015:1-12; Giménez B et al. *Food Chemistry.* 2009;114(3):976-83) can be used. Gelatin is unusually high in the non-essential amino acid glycine. Gelatin will be hydrolyzed in the gastrointestinal tract after oral intake. Gelatin can be of different sources and mixtures thereof, such as from cattle, pigs, chicken and fish. In particular, the pharmaceutically acceptable reducing agent may be a pharmaceutical grade gelatin. The pharmaceutical grade gelatin may be in the form of, e.g., a gelatin capsule, such as a soft or hard capsule.

As described above, aldehydes such as, e.g., formaldehyde, acetaldehyde, furfuraldehyde, or other aldehydes can also be used as the pharmaceutically acceptable reducing agent. Reactive amounts of aldehydes are common in microcrystalline cellulose (MCC), starch, pre-gelatinized starch, crospovidone, hydroxypropyl cellulose, polyethylene glycol, polysorbate and lactose. Polyethylene glycol (PEG) 200, 400, and 600 exhibit significantly high levels of formaldehyde (65.2–107.0 ppm) and acetaldehyde (2.7–12.5 ppm). Polyethylene glycol (PEG) used in coating materials, such as Opadry II White, leads to the generation of formaldehyde (Wang G et al. *Pharm Dev Technol.* 2008;13(5):393-9). Headspace gas chromatography is the most commonly used method to determine trace amounts of reducing aldehydes in pharmaceutical excipients (Li Z et al. *J Chromatogr A.* 2006;1104(1-2):1-10). Reducing aldehydes that can be used in accordance with the present invention are further described, e.g., in: Nassar MN et al. *Pharm Dev Technol.* 2004;9(2):189-95; and Wu Y et al. *AAPS PharmSciTech.* 2011;12(4):1248-63. Moreover, pharmaceutically acceptable dialdehydes, such as glyoxal, can also be used as the pharmaceutically acceptable reducing agent, as mentioned above. Glyoxal can be found in hydroxyethylcellulose and in hydroxypropylmethylcellulose (HPMC).

In each one of the first to seventh aspects described herein, it is particularly preferred that the peptide or protein drug, the copper salt/complex and/or the zinc salt/complex, and the pharmaceutically acceptable reducing agent are orally administered in combination with an absorption enhancer (also referred to herein as a "gastrointestinal absorption enhancer"). The administration of an absorption enhancer improves or facilitates the mucosal absorption of the peptide or protein drug in the gastrointestinal tract and is advantageous particularly if the peptide or protein drug is a large molecule, e.g., a peptide or protein drug having a molecular weight of about 1 kDa or more.

The absorption enhancer is preferably selected to be compatible with the copper salt/complex and/or the zinc salt/complex that is/are used, which can readily be tested, e.g., as described in Example 1. In particular, it is preferred that the absorption enhancer is soluble in an aqueous medium at a pH of about 7 in the presence of the copper salt/complex and/or the zinc salt/complex that is/are used. The occurrence of precipitation or flocculation, as observed for certain combinations of a specific copper salt/complex and a specific absorption enhancer in an aqueous medium (see Example 1), is undesirable but does not rule out the use of a corresponding formulation in accordance with the invention.

The absorption enhancer may be, e.g., a zwitter-ionic absorption enhancer, a cationic absorption enhancer, an anionic absorption enhancer (e.g., an anionic absorption enhancer comprising one or more sulfonic acid groups (-SO_3H)), or a non-ionic absorption enhancer, particularly a zwitter-ionic absorption enhancer or a non-ionic absorption enhancer. It is preferred that the absorption enhancer is selected from C_{8-20} alkanoyl carnitine (preferably lauroyl carnitine, myristoyl carnitine or palmitoyl carnitine; e.g., lauroyl carnitine chloride, myristoyl carnitine chloride or palmitoyl carnitine chloride), salicylic acid (preferably a salicylate, e.g., sodium salicylate), a salicylic acid derivative (such as, e.g., 3-methoxysalicylic acid, 5-methoxysalicylic acid, or homovanillic acid, a C_{8-20} alkanoic acid (preferably a C_{8-20} alkanoate, more preferably a caprate, a caprylate, a myristate, a palmitate, or a stearate, such as, e.g., sodium caprate, sodium caprylate, sodium myristate, sodium palmitate, or sodium stearate), citric acid (preferably a citrate, e.g., sodium citrate), tartaric acid (preferably a tartrate), a fatty acid acylated amino acid (e.g., any of the fatty acid acylated amino acids described in US 2014/0056953 A1 which is incorporated herein by reference, including, without being limited thereto, sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-

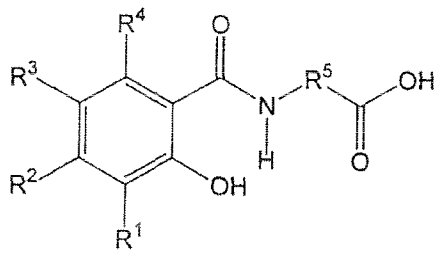
histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methioninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, sodium lauroyl sarcosinate, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, N-decanoyl-L-sarcosine, sodium oleoyl sarcosinate, sodium N-decylleucine, sodium stearoyl glutamate (e.g., Amisoft HS-11 P), sodium myristoyl glutamate (e.g., Amisoft MS-11), sodium lauroyl glutamate (e.g., Amisoft LS-11), sodium cocoyl glutamate (e.g., Amisoft CS-11), sodium cocoyl glycinate (e.g., Amilite GCS-11), sodium N-decyl leucine, sodium cocoyl glycine, sodium cocoyl glutamate, sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methinoninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, Sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine,

sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, sodium oleoyl sarcosinate, and pharmaceutically acceptable salts of any of the aforementioned compounds; or, e.g., C_{8-20} alkanoyl sarcosinate (e.g., a lauroyl sarcosinate, such as sodium lauroyl sarcosinate) or one of the 20 standard proteinogenic α-amino acids that is acylated with a C_{8-20} alkanoic acid), an alkylsaccharide (e.g., a C_{1-20} alkylsaccharide, such as, e.g., C_{8-10} alkylpolysaccharide like Multitrope™ 1620-LQ-(MV); or, e.g., n-octyl-beta-D-glucopyranoside, n-dodecyl-beta-D-maltoside, n-tetradecyl-beta-D-maltoside, tridecyl-beta-D-maltoside, sucrose laurate, sucrose myristate, sucrose palmitate, sucrose cocoate, sucrose mono-dodecanoate, sucrose mono-tridecanoate, sucrose mono-tetradecanoate, a coco-glucoside, or any of the alkylsaccharides described in US 5,661,130 or in WO 2012/112319 which are herein incorporated by reference), a cyclodextrine (e.g., α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, methyl-β-cyclodextrin, hydroxypropyl β-cyclodextrin, or sulfobutylether β-cyclodextrin), N-[8-(2-hydroxybenzoyl)amino]caprylic acid (preferably a N-[8-(2-hydroxybenzoyl)amino]caprylate, more preferably sodium N-[8-(2-hydroxybenzoyl)amino]caprylate, also referred to as "SNAC"), a N-[8-(2-hydroxybenzoyl)amino]caprylate derivative (preferably a sodium N-[8-(2-hydroxybenzoyl)amino]caprylate derivative), a thiomer (also referred to as a thiolated polymer; may be synthesized, e.g., by immobilization of sulfhydryl bearing ligands on a polymeric backbone of well-established polymers such as, e.g., polyacrylic acid, carboxymethylcellulose or chitosan; exemplary thiomers include the thiomers that are described in Laffleur F et al., *Future Med Chem.* 2012, 4(17):2205-16 (doi: 10.4155/fmc.12.165) which is incorporated herein by reference), a mucoadhesive polymer having a vitamin B partial structure (e.g., any of the mucoadhesive polymers described in US 8,980,238 B2 which is incorporated herein by reference; including, in particular, any of the polymeric compounds as defined in any one of claims 1 to 3 of US 8,980,238 B2), a calcium chelating compound (e.g., ethylenediaminetetraacetic acid (EDTA), ethylene glycol tetraacetic acid (EGTA), sodium citrate, or polyacrylic acid), cremophor EL (also referred to as "Kolliphor EL"; CAS no. 61791-12-6), chitosan, N,N,N-trimethyl chitosan, benzalkonium chloride, bestatin, cetylpyridinium chloride, cetyltrimethylammonium bromide, a C_{2-20} alkanol (e.g., ethanol, decanol, lauryl alcohol, myristyl alcohol, or palmityl alcohol), a C_{8-20} alkenol (e.g., oleyl alcohol), a C_{8-20} alkenoic acid (e.g., oleic acid), dextran sulfate, diethyleneglycol monoethyl ether (transcutol), 1-dodecylazacyclo-heptan-2-one (Azone®), caprylocaproyl polyoxylglycerides (such as, e.g.,

caprylocaproyl polyoxyl-8 glycerides; available, e.g., as Labrasol® or ACCONON® MC8-2), ethyl caprylate, glyceryl monolaurate, lysophosphatidylcholine, menthol, a C_{8-20} alkylamine, a C_{8-20} alkenylamine (e.g., oleylamine), phosphatidylcholine, a poloxamer, polyethylene glycol monolaurate, polyoxyethylene, polypropylene glycol monolaurate, a polysorbate (e.g., polysorbate 80), cholic acid (preferably a cholate, e.g., sodium chlolate), a deoxycholate (e.g., sodium deoxycholate), sodium glycocholate, sodium glycodeoxycholate, sodium lauryl sulfate (SDS), sodium decyl sulfate, sodium octyl sulfate, sodium laureth sulfate, N-lauryl sarcosinate, decyltrimethyl ammonium bromide, benzyldimethyl dodecyl ammonium chloride, myristyltrimethyl ammonium chloride, dodecyl pyridinium chloride, decyldimethyl ammonio propane sulfonate, myristyldimethyl ammonio propane sulfonate, palmityldimethyl ammonio propane sulfonate, ChemBetaine CAS, ChemBetaine Oleyl, Nonylphenoxypolyoxyethylene, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, sorbitan monooleate, Triton X-100, hexanoic acid, heptanoic acid, methyl laurate, isopropyl myristate, isopropyl palmitate, methyl palmitate, diethyl sebaccate, sodium oleate, urea, lauryl amine, caprolactam, methyl pyrrolidone, octyl pyrrolidone, methyl piperazine, phenyl piperazine, Carbopol 934P, glyccyrhetinic acid, bromelain, pinene oxide, limonene, cineole, octyl dodecanol, fenchone, menthone, trimethoxy propylene methyl benzene, a cell-penetrating peptide (e.g., KLAKLAK, polyarginine, penetratin, or HIV-1 Tat), macrogol-15-hydroxystearate (e.g., Solutol HS 15), CriticalSorb (see., e.g., Illum L et al. *J Control Release*. 2012;162(1):194-200), a taurocholate (e.g., sodium taurocholate), a taurodeoxycholate (e.g., sodium taurodeoxycholate), a sulfoxide (e.g., a (C_{1-10} alkyl)-(C_{1-10} alkyl)-sulfoxide, such as, e.g., decyl methyl sulfoxide, or dimethyl sulfoxide), cyclopentadecalactone, 8-(N-2-hydroxy-5-chloro-benzoyl)-amino-caprylic acid (also referred to as "5-CNAC"), N-(10-[2-hydroxybenzoyl]amino)decanoic acid (also referred to as "SNAD"), dodecyl-2-N,N-dimethylamino propionate (also referred to as "DDAIP"), D-α-tocopheryl polyethylene glycol-1000 succinate (also referred to as "TPGS"), and pharmaceutically acceptable salts of the aforementioned compounds. Mixtures of two or more absorption enhancers, including any of the above-described absorption enhancers, can also be used. Moreover, any of the chemical permeation enhancers described in Whitehead K et al. *Pharm Res*. 2008 Jun;25(6):1412-9 (particularly any one of those described in Table I of this reference), any one of the modified amino acids disclosed in US 5,866,536 (particularly any one of compounds I to CXXIII, as disclosed in US 5,866,536 which is incorporated herein by reference, or a pharmaceutically acceptable salt or solvate thereof, such as a disodium salt, an ethanol solvate, or a hydrate of any one of these compounds), any one of the modified amino acids disclosed in US 5,773,647 (particularly any one of compounds 1 to 193, as disclosed in US 5,773,647 which is incorporated herein by reference, or a pharmaceutically acceptable salt or solvate thereof, such as a disodium salt, an ethanol solvate, or a hydrate of any one of these compounds), any

of the nanoparticles described in WO 2011/133198, any of the polymer preparations described in US 2015/174076 and/or a hydrogel (e.g., as described in Torres-Lugo M et al. *Biotechnol Prog.* 2002;18(3):612-6) can likewise be used as absorption enhancer. A particularly preferred absorption enhancer is N-[8-(2-hydroxybenzoyl)amino]caprylate or a pharmaceutically acceptable salt thereof, in particular sodium N-[8-(2-hydroxybenzoyl)amino]caprylate. In accordance with the present invention, it is furthermore particularly preferred to use an organic copper salt/complex and/or an organic zinc salt/complex (particularly copper(II) orotate and/or zinc orotate), and to use sodium N-[8-(2-hydroxybenzoyl)amino]caprylate as an absorption enhancer.

The absorption enhancer may also be a compound of the following formula (I):



(I)

wherein:

R^1, R^2, R^3 and R^4 are each independently selected from hydrogen, -OH, $-NR^6R^7$, halogen (e.g., -F, -Cl, -Br or -I), C_{1-4} alkyl or C_{1-4} alkoxy;

R^5 is a substituted or unsubstituted C_{2-16} alkylene, substituted or unsubstituted C_{2-16} alkenylene, substituted or unsubstituted C_{1-12} alkyl(arylene) [e.g., substituted or unsubstituted C_{1-12} alkyl(phenylene)], or substituted or unsubstituted aryl(C_{1-12} alkylene) [e.g., substituted or unsubstituted phenyl(C_{1-12} alkylene)]; and

R^6 and R^7 are each independently hydrogen, oxygen, -OH or C_{1-4} alkyl;

or a pharmaceutically acceptable salt or solvate thereof, particularly a disodium salt, an alcohol solvate (e.g., a methanol solvate, an ethanol solvate, a propanol solvate, or a propylene glycol solvate, or any such solvate of the disodium salt; particularly an ethanol solvate or an ethanol solvate of the disodium salt), or a hydrate thereof (e.g., a monohydrate of the disodium salt). The above-mentioned "substituted" groups comprised in formula (I) are preferably substituted with one or more (e.g., one, two, or three) substituent groups independently selected from halogen (e.g., -F, -Cl, -Br or -I), -OH, C_{1-4} alkyl or C_{1-4} alkoxy. Such compounds and methods for their preparation are described, e.g., in WO 00/59863 which is incorporated herein by reference. Accordingly, the absorption enhancer may also be a "delivery agent" as described in WO 00/59863. Preferred examples of the compounds of formula (I) include N-(5-chlorosalicyloyl)-8-aminocaprylic acid, N-(10-[2-hydroxybenzoyl]amino)decanoic acid, N-(8-[2-hydroxybenzoyl]amino)caprylic acid, a monosodium or disodium salt of any one of the

aforementioned compounds, an ethanol solvate of the sodium salt (e.g., monosodium or disodium salt) of any one of the aforementioned compounds, a monohydrate of the sodium salt (e.g., monosodium or disodium salt) of any one of the aforementioned compounds, and any combination thereof. A particularly preferred compound of formula (I) is the disodium salt of N-(5-chlorosalicyloyl)-8-aminocaprylic acid or the monohydrate thereof.

The (i) peptide or protein drug, (ii) the copper salt/complex and/or the zinc salt/complex, (iii) the pharmaceutically acceptable reducing agent, and (iv) the optionally used absorption enhancer may be administered simultaneously/concomitantly or sequentially. In the case of sequential administration, the copper salt/complex and/or the zinc salt/complex as well as the pharmaceutically acceptable reducing agent may be administered first, followed by the administration of the peptide or protein drug and the optionally used absorption enhancer (e.g., at least about 5 min after the first administration, preferably about 5 min to about 3 hours after the first administration, more preferably about 10 min to about 1 hour after the first administration), which is particularly advantageous if the peptide or protein drug is insulin (e.g., human insulin). Also, the copper salt/complex and/or the zinc salt/complex as well as the pharmaceutically acceptable reducing agent and the optionally used absorption enhancer may be administered first, followed by the administration of the peptide or protein drug (e.g., at least about 5 min after the first administration, preferably about 5 min to about 3 hours after the first administration, more preferably about 10 min to about 1 hour after the first administration), which is likewise advantageous if the peptide or protein drug is insulin (e.g., human insulin). In the case of simultaneous administration, the (i) peptide or protein drug, (ii) the copper salt/complex and/or the zinc salt/complex, (iii) the pharmaceutically acceptable reducing agent, and (iv) the optionally used absorption enhancer may be administered in the same pharmaceutical composition, or in two or more different/separate pharmaceutical compositions, or in two or more different/separate compartments of the same pharmaceutical dosage form, as also described further below.

The peptide or protein drug, the copper salt/complex and/or the zinc salt/complex, the pharmaceutically acceptable reducing agent, and the optionally used absorption enhancer can be administered, e.g., in the form of a pharmaceutical composition as described in the fifth aspect of the invention.

Certain reducing agents, such as ascorbate and reduced glutathione, are known to chemically degrade peptide or protein drugs (Stadtman ER, *Am J Clin Nutr.* 1991, 54(6 Suppl):1125S-1128S; Schmitz T et al., *Amino Acids.* 2006, 30(1):35-42). Moreover, ascorbate is also known

to undergo autoxidation in the presence of copper (Buettner GR, *Free Radic Res Commun.* 1986, 1(6):349-53) and could therefore lose its activity during prolonged storage.

It is therefore preferred that the pharmaceutical composition according to the fifth aspect of the invention is a solid composition or a liquid substantially water-free composition. Such compositions are particularly advantageous as they provide an improved shelf-stability and thus enable prolonged storage periods. The liquid substantially water-free composition is preferably a liquid composition that contains less than about 5% (v/v) of water, more preferably less than about 3% (v/v) of water, even more preferably less than about 1% (v/v) of water, even more preferably less than about 0.5% (v/v) of water, yet even more preferably less than about 0.1% (v/v) of water, and is still more preferably free of water. Most preferably, the pharmaceutical composition of the fifth aspect is a solid composition (e.g., a tablet or a powder). It is furthermore preferred that the solid composition is substantially water-free, e.g., contains less than about 5% (w/w) of water, preferably less than about 3% (w/w) of water, more preferably less than about 1% (w/w) of water, even more preferably less than about 0.5% (w/w) of water, yet even more preferably less than about 0.1% (w/w) of water, and is still more preferably free of water.

It is also possible, although not preferred, that the pharmaceutical composition according to the fifth aspect of the invention is an aqueous liquid composition (e.g., an aqueous solution). In this case, the composition should preferably be prepared shortly before administration to the subject/patient, and prolonged storage periods should be avoided.

The pharmaceutical composition according to the fifth aspect of the present invention may also be an oral composition of a GLP-1 peptide, which composition is prepared as described in WO 2013/139694 but further comprises (i) a copper salt/complex and/or a zinc salt/complex, and (ii) a pharmaceutically acceptable reducing agent. Preferably, a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid, the copper salt/complex and/or the zinc salt/complex, and the reducing agent are present in the first type of granules and the GLP-1 peptide is present in the second type of granules. Alternatively, a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid as well as the copper salt/complex and/or the zinc salt/complex are present in the first type of granules, the GLP-1 peptide is present in the second type of granules, and the reducing agent is present in both the first and the second type of granules. As a further alternative, a salt of N-(8-(2-hydroxybenzoyl)amino)caprylic acid is present in the first type of granules and the copper salt/complex and/or the zinc salt/complex as well as the GLP-1 peptide and the reducing agent are present in the second type of granules.

Moreover, the pharmaceutical composition according to the fifth aspect may also be in the form of a mucoadhesive device, such as a mucoadhesive patch, e.g., as described in US 2015/0174076 or in US 2003/0017195.

Furthermore, it is particularly preferred that the pharmaceutical composition according to the fifth aspect is a pharmaceutical dosage form in which the peptide or protein drug is physically separated from the pharmaceutically acceptable copper salt/complex (if present) and the pharmaceutically acceptable zinc salt/complex (if present), as described in the sixth aspect of the invention.

The pharmaceutical dosage form according to the sixth aspect of the invention preferably comprises at least two separate compartments which are physically separated from one another (e.g., through a physical separation layer). Accordingly, it is preferred that the pharmaceutical dosage form comprises a physical separation layer between (i) the peptide or protein drug and (ii) the copper salt/complex (if present) and the zinc salt/complex (if present). The peptide or protein drug is present only in a first compartment, and the copper salt/complex and/or the zinc salt/complex is/are present only in a second compartment of the pharmaceutical dosage form. The pharmaceutically acceptable reducing agent may be present either in the first compartment, or in the second compartment, or in both the first and the second compartment, or in a third compartment of the pharmaceutical dosage form. In one preferred embodiment according to the sixth aspect, the invention thus provides a pharmaceutical dosage form (e.g., a double capsule) comprising: a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, which is present in a first compartment of the pharmaceutical dosage form; a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex, which is/are present in a second compartment of the pharmaceutical dosage form; and a pharmaceutically acceptable reducing agent, which is present in the first compartment and/or the second compartment of the pharmaceutical dosage form. In a further preferred embodiment of the sixth aspect, the invention provides a pharmaceutical dosage form (e.g., a multi-particulate dosage form) comprising: a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, which is present in a first compartment of the pharmaceutical dosage form; a pharmaceutically acceptable reducing agent, which is present in a second compartment of the pharmaceutical dosage form; and a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex, which is/are present in a third compartment of the pharmaceutical dosage form. It is particularly preferred that the pharmaceutical dosage form of the sixth aspect is a capsule inside a capsule (also referred to as a double capsule) or a multi-particulate dosage form. In the case of a double capsule, it is preferred that the bigger

outer capsule (the content of which will be released first) contains the copper salt/complex and/or the zinc salt/complex as well as the pharmaceutically acceptable reducing agent, and that the smaller inner capsule (the content of which will be released later) contains the peptide or protein drug. The dosage form may also be a release-modified dosage form, such as a dosage form (e.g., a capsule, multiparticulate or tablet) having an enteric coating or a dosage form (e.g., a capsule, multiparticulate or tablet) coated with Eudragit L30D55 or with Eudragit FS30D or an acid resistant capsule such as HPMCP capsules (commercially known as AR Caps®).

The pharmaceutical composition according to the fifth aspect and also the pharmaceutical dosage form according to the sixth aspect of the invention preferably comprise the copper salt/complex in an amount of about 0.1 mg to about 10 mg per dosage unit (more preferably about 0.1 mg to about 5 mg per dosage unit), and/or the zinc salt/complex in an amount of about 0.1 mg to about 50 mg (e.g., about 1 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, or about 50 mg) per dosage unit. They further comprise the pharmaceutically acceptable reducing agent in an amount of preferably about 1 mg to about 1000 mg per dosage unit, more preferably about 50 mg to about 500 mg per dosage unit. Moreover, if they comprise an absorption enhancer, the absorption enhancer is preferably included in an amount of about 10 mg to about 1000 mg per dosage unit, more preferably about 50 mg to about 500 mg per dosage unit.

It is furthermore preferred that the constitution of the pharmaceutical composition is such that, if the composition were added to ten milliliters of 5% HCl solution, it would neutralize the acid and generate a pH of higher than about 6. In addition, it is also preferred that the constitution of the pharmaceutical composition is such that, if the composition were added to ten milliliters of aqueous solution, it would generate a pH of higher than about 6 and lower than about pH 9.

The pharmaceutically acceptable salts referred to herein may be formed, e.g., by protonation of an atom carrying an electron lone pair which is susceptible to protonation, such as an amino group, with an inorganic or organic acid, or as a salt of a carboxylic acid group with a physiologically acceptable cation as they are well-known in the art. Exemplary base addition salts comprise, for example: alkali metal salts such as sodium or potassium salts; alkaline earth metal salts such as calcium or magnesium salts; zinc salts; ammonium salts; aliphatic amine salts such as trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine, procaine salts, meglumine salts, ethylenediamine salts, or choline salts; aralkyl amine salts such as N,N-dibenzylethylenediamine salts, benzathine salts, benethamine salts; heterocyclic aromatic amine salts such as pyridine salts, picoline salts,

quinoline salts or isoquinoline salts; quaternary ammonium salts such as tetramethylammonium salts, tetraethylammonium salts, benzyltrimethylammonium salts, benzyltriethylammonium salts, benzyltributylammonium salts, methyltrioctylammonium salts or tetrabutylammonium salts; and basic amino acid salts such as arginine salts, lysine salts, or histidine salts. Exemplary acid addition salts comprise, for example: mineral acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate salts, nitrate salts, phosphate salts (such as, e.g., phosphate, hydrogenphosphate, or dihydrogenphosphate salts), carbonate salts, hydrogencarbonate salts or perchlorate salts; organic acid salts such as acetate, propionate, butyrate, pentanoate, hexanoate, heptanoate, octanoate, cyclopentanepropionate, decanoate, undecanoate, oleate, stearate, lactate, maleate, oxalate, fumarate, tartrate, malate, citrate, succinate, glycolate, nicotinate, benzoate, salicylate, ascorbate, or pamoate (embonate) salts; sulfonate salts such as methanesulfonate (mesylate), ethanesulfonate (esylate), 2-hydroxyethanesulfonate (isethionate), benzenesulfonate (besylate), p-toluenesulfonate (tosylate), 2-naphthalenesulfonate (napsylate), 3-phenylsulfonate, or camphorsulfonate salts; and acidic amino acid salts such as aspartate or glutamate salts. It is to be understood that the term "pharmaceutically acceptable salt" also embraces pharmaceutically acceptable salts of the corresponding compound in any solvated form.

The peptide or protein drug, the copper salt/complex and/or the zinc salt/complex, the pharmaceutically acceptable reducing agent, and the optionally used absorption enhancer (which are collectively referred to as the "compounds to be administered" in the following) may each be administered as compounds *per se* or may be formulated as medicaments, e.g., in the form of a pharmaceutical composition according to the fifth aspect and/or a pharmaceutical dosage form according to the sixth aspect of the invention. The medicaments/pharmaceutical compositions, including also the pharmaceutical composition according to the fifth aspect and the pharmaceutical dosage form according to the sixth aspect, may optionally comprise one or more pharmaceutically acceptable excipients, such as carriers, diluents, fillers, disintegrants, lubricating agents, binders, colorants, pigments, stabilizers, preservatives, antioxidants, and/or solubility enhancers. In particular, they may comprise one or more additives selected from vitamin E, histidine, microcrystalline cellulose (MCC), mannitol, starch, sorbitol and/or lactose. The pharmaceutical compositions can be formulated by techniques known to the person skilled in the art, such as the techniques published in Remington's Pharmaceutical Sciences, 20th Edition.

As noted above, the pharmaceutical compositions may comprise one or more solubility enhancers, such as, e.g., poly(ethylene glycol), including poly(ethylene glycol) having a molecular weight in the range of about 200 to about 5,000 Da, ethylene glycol, propylene

glycol, non-ionic surfactants, tyloxapol, polysorbate 80, macrogol-15-hydroxystearate, phospholipids, lecithin, dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, cyclodextrins, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxyethyl-γ-cyclodextrin, hydroxypropyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, sulfobutylether-γ-cyclodextrin, glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin, dimaltosyl-β-cyclodextrin, methyl-β-cyclodextrin, carboxyalkyl thioethers, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, vinyl acetate copolymers, vinyl pyrrolidone, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, or any combination thereof.

The pharmaceutical compositions are preferably formulated as dosage forms for oral administration, particularly peroral administration. Accordingly, it is most preferred that the compounds to be administered or the above described pharmaceutical compositions, including also the pharmaceutical composition according to the fifth aspect and the pharmaceutical dosage form according to the sixth aspect, are administered to a subject/patient orally, particularly perorally. It is thus preferred that the peptide or protein drug, the copper salt/complex and/or the zinc salt/complex, the pharmaceutically acceptable reducing agent, and the optionally used absorption enhancer are all to be administered orally.

Dosage forms for oral administration include, e.g., tablets (e.g., coated or uncoated tablets), capsules (e.g., soft gelatin capsules, hard gelatin capsules, HPMC capsules, or HPMCP capsules), a capsule inside a capsule, lozenges, troches, ovules, solutions, emulsions, suspensions, syrups, elixirs, powders and granules for reconstitution, dispersible powders and granules, medicated gums, chewing tablets, effervescent tablets, and multiparticulate dosage forms.

The tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included. Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, or high molecular weight polyethylene glycols. For aqueous suspensions and/or

elixirs, the agent may be combined with various sweetening or flavoring agents, coloring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject. The specific dose level and frequency of dosage for any particular individual subject may be varied and will depend upon a variety of factors including the activity of the specific peptide or protein drug employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the individual subject undergoing therapy. The precise dose will ultimately be at the discretion of the attendant physician or veterinarian.

The subject or patient to be treated, such as the subject in need of treatment or prevention, may be an animal (e.g., a non-human animal), a vertebrate animal, a mammal, a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), a murine (e.g., a mouse), a canine (e.g., a dog), a feline (e.g., a cat), a porcine (e.g., a pig), an equine (e.g., a horse), a primate, a simian (e.g., a monkey or ape), a monkey (e.g., a marmoset, a baboon), an ape (e.g., a gorilla, chimpanzee, orang-utan, gibbon), or a human. In the context of this invention, it is also envisaged that animals are to be treated which are economically or agronomically important. Non-limiting examples of agronomically important animals are sheep, cattle and pigs, while, for example, cats and dogs may be considered as economically important animals. Preferably, the subject/patient is a mammal; more preferably, the subject/patient is a human or a non-human mammal (such as, e.g., a guinea pig, a hamster, a rat, a mouse, a rabbit, a dog, a cat, a horse, a monkey, an ape, a marmoset, a baboon, a gorilla, a chimpanzee, an orang-utan, a gibbon, a sheep, cattle, or a pig); most preferably, the subject/patient is a human.

The term “treatment” of a disorder or disease as used herein is well known in the art. “Treatment” of a disorder or disease implies that a disorder or disease is suspected or has been diagnosed in a patient/subject. A patient/subject suspected of suffering from a disorder or disease typically shows specific clinical and/or pathological symptoms which a skilled person can easily attribute to a specific pathological condition (i.e., diagnose a disorder or disease).

The “treatment” of a disorder or disease may, for example, lead to a halt in the progression of the disorder or disease (e.g., no deterioration of symptoms) or a delay in the progression of the disorder or disease (in case the halt in progression is of a transient nature only). The “treatment” of a disorder or disease may also lead to a partial response (e.g., amelioration of

symptoms) or complete response (e.g., disappearance of symptoms) of the subject/patient suffering from the disorder or disease. Accordingly, the "treatment" of a disorder or disease may also refer to an amelioration of the disorder or disease, which may, e.g., lead to a halt in the progression of the disorder or disease or a delay in the progression of the disorder or disease. Such a partial or complete response may be followed by a relapse. It is to be understood that a subject/patient may experience a broad range of responses to a treatment (such as the exemplary responses as described herein above). The treatment of a disorder or disease may, *inter alia*, comprise curative treatment (preferably leading to a complete response and eventually to healing of the disorder or disease) and palliative treatment (including symptomatic relief).

The term "prevention" of a disorder or disease as used herein is also well known in the art. For example, a patient/subject suspected of being prone to suffer from a disorder or disease may particularly benefit from a prevention of the disorder or disease. The subject/patient may have a susceptibility or predisposition for a disorder or disease, including but not limited to hereditary predisposition. Such a predisposition can be determined by standard methods or assays, using, e.g., genetic markers or phenotypic indicators. It is to be understood that a disorder or disease to be prevented in accordance with the present invention has not been diagnosed or cannot be diagnosed in the patient/subject (for example, the patient/subject does not show any clinical or pathological symptoms). Thus, the term "prevention" comprises the use of a peptide or protein drug according to the invention before any clinical and/or pathological symptoms are diagnosed or determined or can be diagnosed or determined by the attending physician.

The terms "peptide" and "protein", as in the expression "peptide or protein drug", are used herein interchangeably and refer to a polymer of two or more amino acids linked via amide bonds that are formed between an amino group of one amino acid and a carboxyl group of another amino acid. The amino acids comprised in the peptide or protein, which are also referred to as amino acid residues, may be selected from the 20 standard proteinogenic α-amino acids (i.e., Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val) but also from non-proteinogenic and/or non-standard α-amino acids (such as, e.g., ornithine, citrulline, homolysine, pyrrolysine, or 4-hydroxyproline) as well as β-amino acids (e.g., β-alanine), γ-amino acids and δ-amino acids. Preferably, the amino acid residues comprised in the peptide or protein are selected from α-amino acids, more preferably from the 20 standard proteinogenic α-amino acids (which can be present as the L-isomer or the D-isomer, and are preferably all present as the L-isomer). The peptide or protein may be unmodified or may be modified, e.g., at its N-terminus, at its C-terminus and/or

at a functional group in the side chain of any of its amino acid residues (particularly at the side chain functional group of one or more Lys, His, Ser, Thr, Tyr, Cys, Asp, Glu, and/or Arg residues). Such modifications may include, e.g., the attachment of any of the protecting groups described for the corresponding functional groups in: Wuts PG & Greene TW, Greene's protective groups in organic synthesis, John Wiley & Sons, 2006. Such modifications may also include the covalent attachment of one or more polyethylene glycol (PEG) chains (forming a PEGylated peptide or protein), the glycosylation and/or the acylation with one or more fatty acids (e.g., one or more C_{8-30} alkanoic or alkenoic acids; forming a fatty acid acylated peptide or protein). The amino acid residues comprised in the peptide or protein may, e.g., be present as a linear molecular chain (forming a linear peptide or protein) or may form one or more rings (corresponding to a cyclic peptide or protein). The peptide or protein may also form oligomers consisting of two or more identical or different molecules.

The term "amino acid" refers, in particular, to any one of the 20 standard proteinogenic α-amino acids (i.e., Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val) but also to non-proteinogenic and/or non-standard α-amino acids (such as, e.g., ornithine, citrulline, homolysine, pyrrolysine, or 4-hydroxyproline) as well as β-amino acids (e.g., β-alanine), γ-amino acids and/or δ-amino acids. Unless defined otherwise, an "amino acid" preferably refers to an α-amino acid, more preferably to any one of the 20 standard proteinogenic α-amino acids (which can be present as the L-isomer or the D-isomer, and are preferably present as the L-isomer).

As used herein, the term "complex" refers to a chelate complex (in which coordinate bonds are formed between a single central atom/ion and a polydentate ligand) or a coordination complex composed of monodentate ligands coordinating a single central atom/ion.

As used herein, the term "reducing sugar" refers to a sugar that has an open-chain form with an aldehyde group or a free hemiacetal group and can thus act as a reducing agent. A reducing sugar may be, e.g., a reducing monosaccharide (e.g., glucose, glyceraldehyde, galactose, fructose, ribose, xylose, or sorbose), a reducing disaccharide (e.g., lactose (such as spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose®, or Fast-FloC®), maltose, or cellobiose), or a reducing polysaccharide (e.g., a glucose polymer, such as starch, a starch derivative (like, e.g., glucose syrup, maltodextrin, dextrin, dextrose, or dextran), or cellulose (e.g., microcrystalline cellulose (MCC), such as Avicel®)).

As used herein, the terms “optional”, “optionally” and “may” denote that the indicated feature may be present but can also be absent. Whenever the term “optional”, “optionally” or “may” is used, the present invention specifically relates to both possibilities, i.e., that the corresponding feature is present or, alternatively, that the corresponding feature is absent. For example, if a component of a composition is indicated to be “optional”, the invention specifically relates to both possibilities, i.e., that the corresponding component is present (contained in the composition) or that the corresponding component is absent from the composition.

As used herein, the term "about" refers to ±10% of the indicated numerical value, preferably to ±5% of the indicated numerical value, and in particular to the exact numerical value indicated. For example, the expression “about 100” refers to the range of 90 to 110, in particular the range of 95 to 105, and preferably refers to the specific value of 100. If the term “about” is used in connection with the endpoints of a range, it refers to the range from the lower endpoint -10% of its indicated numerical value to the upper endpoint +10% of its indicated numerical value, in particular to the range from of the lower endpoint -5% to the upper endpoint +5%, and preferably to the range defined by the exact numerical values of the lower endpoint and the upper endpoint. Thus, the expression “about 10 to about 20” refers to the range of 9 to 22, in particular 9.5 to 21, and preferably 10 to 20. If the term “about” is used in connection with the endpoint of an open-ended range, it refers to the corresponding range starting from the lower endpoint -10% or from the upper endpoint +10%, in particular to the range starting from the lower endpoint -5% or from the upper endpoint +5%, and preferably to the open-ended range defined by the exact numerical value of the corresponding endpoint. For example, the expression “at least about 10%” refers to at least 9%, particularly at least 9.5%, and preferably at least 10%.

Furthermore, it is to be understood that the present invention specifically relates to each and every combination of features and embodiments described herein, including any combination of general and/or preferred features/embodiments. In particular, the invention specifically relates to all combinations of preferred features described herein.

In this specification, a number of documents including patent applications and scientific literature are cited. The disclosure of these documents, while not considered relevant for the patentability of this invention, is herewith incorporated by reference in its entirety. More specifically, all referenced documents are incorporated by reference to the same extent as if each individual document was specifically and individually indicated to be incorporated by reference.

The invention is also described by the following illustrative figures. The appended figures show:

Figure 1: Plasma liraglutide levels after intestinal (mid-jejunum) administration of different liraglutide formulations to rats (see Example 6).

Figure 2: Blood glucose levels after intestinal (mid-jejunum) administration of different formulations to rats (see Example 8).

The present invention particularly relates to the following items:

1. A peptide or protein drug having a molecular weight of equal to or less than about 50 kDa for use as a medicament, wherein said peptide or protein drug is to be administered orally in combination with:
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a pharmaceutically acceptable reducing agent.

2. A pharmaceutically acceptable copper salt/complex for use in therapy, wherein said copper salt/complex is to be administered orally in combination with:
a pharmaceutically acceptable reducing agent; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

3. A pharmaceutically acceptable zinc salt/complex for use in therapy, wherein said zinc salt/complex is to be administered orally in combination with:
a pharmaceutically acceptable reducing agent; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

4. A pharmaceutically acceptable reducing agent for use in therapy, wherein said reducing agent is to be administered orally in combination with:
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

5. A pharmaceutical composition comprising:
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa;
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a pharmaceutically acceptable reducing agent.

6. The pharmaceutical composition of item 5, wherein said pharmaceutical composition is for oral administration.

7. A pharmaceutical dosage form comprising:
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa;
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a pharmaceutically acceptable reducing agent;
wherein the peptide or protein drug is physically separated from the pharmaceutically acceptable copper salt/complex and the pharmaceutically acceptable zinc salt/complex within the pharmaceutical dosage form.

8. The pharmaceutical dosage form of item 7, which is a pharmaceutical dosage form comprising:
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, which is present in a first compartment of the pharmaceutical dosage form;
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex, which is/are present in a second compartment of the pharmaceutical dosage form; and
a pharmaceutically acceptable reducing agent, which is present in the first compartment and/or the second compartment of the pharmaceutical dosage form.

9. The pharmaceutical dosage form of item 7 or 8, which is in the form of a double capsule.

10. The pharmaceutical dosage form of item 7, which is a pharmaceutical dosage form comprising:
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, which is present in a first compartment of the pharmaceutical dosage form;

a pharmaceutically acceptable reducing agent, which is present in a second compartment of the pharmaceutical dosage form; and

a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex, which is/are present in a third compartment of the pharmaceutical dosage form.

11. The pharmaceutical dosage form of item 7 or 10, which is in the form of a multi-particulate dosage form.

12. The pharmaceutical dosage form of any one of items 7 to 11, wherein said pharmaceutical dosage form is for oral administration.

13. The peptide or protein drug for use according to item 1 or the copper salt/complex for use according to item 2 or the zinc salt/complex for use according to item 3 or the reducing agent for use according to item 4 or the pharmaceutical composition of item 5 or 6 or the pharmaceutical dosage form of any one of items 7 to 12, wherein the peptide or protein drug has a molecular weight of about 500 Da to about 30 kDa.

14. The peptide or protein drug for use according to item 1 or 13 or the copper salt/complex for use according to item 2 or 13 or the zinc salt/complex for use according to item 3 or 13 or the reducing agent for use according to item 4 or 13 or the pharmaceutical composition of item 5, 6 or 13 or the pharmaceutical dosage form of any one of items 7 to 13, wherein the peptide or protein drug has a molecular weight of about 1 kDa to about 10 kDa.

15. The peptide or protein drug for use according to item 1 or the copper salt/complex for use according to item 2 or the zinc salt/complex for use according to item 3 or the reducing agent for use according to item 4 or the pharmaceutical composition of item 5 or 6 or the pharmaceutical dosage form of any one of items 7 to 12, wherein the peptide or protein drug is selected from insulin, an insulin analog, insulin lispro, insulin PEGlispro, insulin aspart, insulin glulisine, insulin glargine, insulin detemir, NPH insulin, insulin degludec, B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin,

B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin, B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B16H B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin, B29K(N(ε)octadecanedioyl) A14E B25H desB30 human insulin, GLP-1, a GLP-1 analog, an acylated GLP-1 analog, a diacylated GLP-1 analog, a GLP-1 agonist, semaglutide, liraglutide, exenatide, exendin-4, lixisenatide, taspoglutide, albiglutide, dulaglutide, langlenatide, GLP-1(7-37), GLP-1(7-36)NH_2, a dual agonist of the GLP-1 receptor and the glucagon receptor, oxyntomodulin, GLP-2, a GLP-2 analog, a GLP-2 agonist, teduglutide, elsiglutide, amylin, an amylin analog, pramlintide, a somatostatin analog, octreotide, lanreotide, pasireotide, goserelin, buserelin, leptin, a leptin analog, metreleptin, peptide YY, a peptide YY analog, glatiramer, leuprolide, desmopressin, osteocalcin, an osteocalcin analog or derivative, human growth hormone, a human growth hormone analog, a glycopeptide antibiotic, a glycosylated cyclic or polycyclic nonribosomal peptide antibiotic, vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin, decaplanin, bortezomib, cosyntropin, chorionic gonadotropin, menotropin, sermorelin, luteinizing-hormone-releasing hormone, somatropin, calcitonin, calcitonin-salmon, pentagastrin, oxytocin, neseritide, anakinra, enfuvirtide, pegvisomant, dornase alfa, lepirudin, anidulafungin, eptifibatide, interferon alfacon-1, interferon alpha-2a, interferon alpha-2b, interferon beta-1a, interferon beta-1b, interferon gamma-1b, peginterferon alfa-2a, peginterferon alfa-2b, peginterferon beta-1a, fibrinolysin, vasopressin, aldesleukin, epoetin alfa, darbepoetin alfa, epoetin beta, epoetin delta, epoetin omega, epoetin zeta, filgrastim, interleukin-11, cyclosporine, glucagon, urokinase, viomycin, thyrotropin-releasing hormone, leucine-enkephalin, methionine-enkephalin, substance P, adrenocorticotropic hormone, parathyroid hormone, a parathyroid hormone fragment, teriparatide, PTH(1-31), PTH(2-34), parathyroid hormone-related protein, abaloparatide, linaclotide, carfilzomib, icatibant, ecallantide, cilengitide, a prostaglandin F2α receptor modulator, PDC31, and pharmaceutically acceptable salts thereof.

16. The peptide or protein drug for use according to any one of items 1 or 13 to 15, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable copper salt/complex.

17. The peptide or protein drug for use according to any one of items 1 or 13 to 16 or the copper salt/complex for use according to any one of items 2 or 13 to 15 or the reducing agent for use according to any one of items 4 or 13 to 15 or the pharmaceutical composition of any one of items 5, 6 or 13 to 15 or the pharmaceutical dosage form of

any one of items 7 to 15, wherein said copper salt/complex is a copper(I) salt/complex or a copper(II) salt/complex.

18. The peptide or protein drug for use according to item 17 or the copper salt/complex for use according to item 17 or the reducing agent for use according to item 17 or the pharmaceutical composition of item 17 or the pharmaceutical dosage form of item 17, wherein said copper salt/complex is a copper(II) salt/complex which is selected from copper sulfate, copper carbonate, a copper(II) amino acid complex, copper(II) lysine complex, copper(II) glycinate, copper(II) EDTA complex, copper(II) chitosan complex, copper(II) citrate, copper(II) gluconate, copper(II) lactate, copper lactate gluconate, and copper(II) orotate.

19. The peptide or protein drug for use according to item 17 or the copper salt/complex for use according to item 17 or the reducing agent for use according to item 17 or the pharmaceutical composition of item 17 or the pharmaceutical dosage form of item 17, wherein said copper salt/complex is a copper(I) salt/complex which is selected from copper(I) chloride and copper(I) acetate.

20. The peptide or protein drug for use according to any one of items 1 or 13 to 15, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable zinc salt/complex.

21. The peptide or protein drug for use according to any one of items 1, 13 to 15 or 20 or the zinc salt/complex for use according to any one of items 3 or 13 to 15 or the reducing agent for use according to any one of items 4 or 13 to 15 or the pharmaceutical composition of any one of items 5, 6 or 13 to 15 or the pharmaceutical dosage form of any one of items 7 to 15, wherein said zinc salt/complex is a zinc(II) salt/complex.

22. The peptide or protein drug for use according to item 21 or the zinc salt/complex for use according to item 21 or the reducing agent for use according to item 21 or the pharmaceutical composition of item 21 or the pharmaceutical dosage form of item 21, wherein said zinc salt/complex is a zinc(II) salt/complex which is selected from zinc sulfate, zinc chloride, zinc acetate, zinc oxide, zinc ascorbate, zinc caprylate, zinc gluconate, zinc stearate, zinc carbonate, zinc orotate, a zinc amino acid complex, zinc glycinate, zinc arginate, zinc picolinate, zinc pidolate, zinc carnosine, zinc undecanoate, zinc undecylenate, zinc methionine, zinc lactate, and zinc lactate gluconate.

23. The peptide or protein drug for use according to any one of items 1 or 13 to 22 or the copper salt/complex for use according to any one of items 2, 13 to 15 or 17 to 19 or the zinc salt/complex for use according to any one of items 3, 13 to 15, 21 or 22 or the reducing agent for use according to any one of items 4, 13 to 15, 17 to 19, 21 or 22 or the pharmaceutical composition of any one of items 5, 6, 13 to 15, 17 to 19, 21 or 22 or the pharmaceutical dosage form of any one of items 7 to 15, 17 to 19, 21 or 22, wherein said reducing agent is selected from ascorbic acid, reduced glutathione, cysteine, N-acetylcysteine, histidine, glycine, arginine, gelatin, uric acid, a reducing sugar, glucose, glyceraldehyde, galactose, fructose, ribose, xylose, sorbose, lactose, maltose, cellobiose, a glucose polymer, starch, a starch derivative, glucose syrup, maltodextrin, dextrin, dextrose, dextran, cellulose, microcrystalline cellulose, mannitol, α-tocopherol, vitamin A, α-lipoic acid, dihydro-α-lipoic acid, oxalic acid, phytic acid, a tannin, propyl gallate, butylated hydroxy toluene, butylated hydroxy anisole, sodium metabisulfite, povidone, crospovidone, an aldehyde, formaldehyde, acetaldehyde, furfuraldehyde, a dialdehyde, glyoxal, a phenolic compound, phenol, a polyphenol, salicylic acid, a salicylic acid derivative, an iron(II) salt/complex, diphosphate, disodiumdiphosphate, trisodiumdiphosphate, tetrasodiumdiphosphate, tetrapotassiumdiphosphate, dicalciumdiphosphate, calciumdihydrogendiphophate, phosphate, dipotassium hydrogen phosphate, calcium phosphate, calcium hydrogen phosphate, a thiol-bearing compound, a thiomer, and pharmaceutically acceptable salts thereof.

24. The peptide or protein drug for use according to item 23 or the copper salt/complex for use according to item 23 or the zinc salt/complex for use according to item 23 or the reducing agent for use according to item 23 or the pharmaceutical composition of item 23 or the pharmaceutical dosage form of item 23, wherein said reducing agent is an iron(II) salt/complex selected from iron(II) gluconate, iron(II) orotate, iron(II) tartrate, iron(II) fumarate, iron(II) sulfate, iron(II) lactate, iron(II) lactate gluconate, iron(II) acetate, iron(II) carbonate, iron(II) citrate, iron(II) oxide, iron(II) hydroxide, iron(II) ascorbate, an iron(II) amino acid complex, and ferrous bis-glycinate.

25. The peptide or protein drug for use according to any one of items 1 or 13 to 24 or the copper salt/complex for use according to any one of items 2, 13 to 15, 17 to 19, 23 or 24 or the zinc salt/complex for use according to any one of items 3, 13 to 15 or 21 to 24 or the reducing agent for use according to any one of items 4, 13 to 15, 17 to 19 or 21 to 24, wherein said peptide or protein drug or said copper salt/complex or said zinc

salt/complex or said reducing agent is to be administered orally in combination with an absorption enhancer.

26. The pharmaceutical composition of any one of items 5, 6, 13 to 15, 17 to 19 or 21 to 24 or the pharmaceutical dosage form of any one of items 7 to 15, 17 to 19 or 21 to 24, wherein said pharmaceutical composition or said pharmaceutical dosage form further comprises an absorption enhancer.

27. The peptide or protein drug for use according to item 25 or the copper salt/complex for use according to item 25 or the zinc salt/complex for use according to item 25 or the reducing agent for use according to item 25 or the pharmaceutical composition of item 26 or the pharmaceutical dosage form of item 26, wherein said absorption enhancer is selected from C_{8-20} alkanoyl carnitine, salicylic acid, a salicylic acid derivative, 3-methoxysalicylic acid, 5-methoxysalicylic acid, homovanillic acid, a C_{8-20} alkanoic acid, citric acid, tartaric acid, a fatty acid acylated amino acid, a C_{8-20} alkanoyl sarcosinate, an alkylsaccharide, a C_{8-10} alkylpolysaccharide, n-octyl-beta-D-glucopyranoside, n-dodecyl-beta-D-maltoside, n-tetradecyl-beta-D-maltoside, tridecyl-beta-D-maltoside, sucrose laurate, sucrose myristate, sucrose palmitate, sucrose cocoate, sucrose mono-dodecanoate, sucrose mono-tridecanoate, sucrose mono-tetradecanoate, a coco-glucoside, a cyclodextrine, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, methyl-β-cyclodextrin, hydroxypropyl β-cyclodextrin, sulfobutylether β-cyclodextrin, N-[8-(2-hydroxybenzoyl)amino]caprylic acid, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate, a sodium N-[8-(2-hydroxybenzoyl)amino]caprylate derivative, a thiomer, a mucoadhesive polymer having a vitamin B partial structure, a calcium chelating compound, ethylenediaminetetraacetic acid, ethylene glycol tetraacetic acid, polyacrylic acid, cremophor EL, chitosan, N,N,N-trimethyl chitosan, benzalkonium chloride, bestatin, cetylpyridinium chloride, cetyltrimethylammonium bromide, a C_{2-20} alkanol, a C_{8-20} alkenol, a C_{8-20} alkenoic acid, dextran sulfate, diethyleneglycol monoethyl ether, 1-dodecylazacyclo-heptan-2-one, caprylocaproyl polyoxylglycerides, ethyl caprylate, glyceryl monolaurate, lysophosphatidylcholine, menthol, a C_{8-20} alkylamine, a C_{8-20} alkenylamine, phosphatidylcholine, a poloxamer, polyethylene glycol monolaurate, polyoxyethylene, polypropylene glycol monolaurate, a polysorbate, cholic acid, a deoxycholate, sodium glycocholate, sodium glycodeoxycholate, sodium lauryl sulfate, sodium decyl sulfate, sodium octyl sulfate, sodium laureth sulfate, N-lauryl sarcosinate, decyltrimethyl ammonium bromide, benzyldimethyl dodecyl ammonium chloride, myristyltrimethyl ammonium chloride, dodecyl pyridinium chloride, decyldimethyl ammonio propane sulfonate, myristyldimethyl ammonio propane sulfonate,

palmityldimethyl ammonio propane sulfonate, ChemBetaine CAS, ChemBetaine Oleyl, Nonylphenoxypolyoxyethylene, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, sorbitan monooleate, Triton X-100, hexanoic acid, heptanoic acid, methyl laurate, isopropyl myristate, isopropyl palmitate, methyl palmitate, diethyl sebaccate, sodium oleate, urea, lauryl amine, caprolactam, methyl pyrrolidone, octyl pyrrolidone, methyl piperazine, phenyl piperazine, Carbopol 934P, glyccyrhetinic acid, bromelain, pinene oxide, limonene, cineole, octyl dodecanol, fenchone, menthone, trimethoxy propylene methyl benzene, a cell-penetrating peptide, KLAKLAK, polyarginine, penetratin, HIV-1 Tat, macrogol-15-hydroxystearate, Solutol HS 15, CriticalSorb, a taurocholate, a taurodeoxycholate, a sulfoxide, decyl methyl sulfoxide, dimethyl sulfoxide, cyclopentadecalactone, 8-(N-2-hydroxy-5-chloro-benzoyl)-amino-caprylic acid, N-(10-[2-hydroxybenzoyl]amino)decanoic acid, dodecyl-2-N,N-dimethylamino propionate, D-α-tocopheryl polyethylene glycol-1000 succinate, and pharmaceutically acceptable salts thereof.

28. The peptide or protein drug for use according to item 27 or the copper salt/complex for use according to item 27 or the zinc salt/complex for use according to item 27 or the reducing agent for use according to item 27 or the pharmaceutical composition of item 27 or the pharmaceutical dosage form of item 27, wherein said absorption enhancer is a fatty acid acylated amino acid selected from sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methioninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, sodium lauroyl sarcosinate, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-

histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, N-decanoyl-L-sarcosine, sodium oleoyl sarcosinate, sodium N-decylleucine, sodium stearoyl glutamate, sodium myristoyl glutamate, sodium lauroyl glutamate, sodium cocoyl glutamate, sodium cocoyl glycinate, sodium N-decyl leucine, sodium cocoyl glycine, sodium cocoyl glutamate, sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methinoninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, Sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, sodium oleoyl sarcosinate, and pharmaceutically acceptable salts thereof.

29. The peptide or protein drug for use according to item 25 or the copper salt/complex for use according to item 25 or the zinc salt/complex for use according to item 25 or the reducing agent for use according to item 25 or the pharmaceutical composition of item 26 or the pharmaceutical dosage form of item 26, wherein said absorption enhancer is sodium N-[8-(2-hydroxybenzoyl)amino]caprylate.

30. The pharmaceutical composition of any one of items 5, 6, 13 to 15, 17 to 19, 21 to 24 or 26 to 29, wherein said pharmaceutical composition is a solid composition or a liquid composition that contains less than about 5% (v/v) of water.

31. The pharmaceutical composition of any one of items 5, 6, 13 to 15, 17 to 19, 21 to 24 or 26 to 30 or the pharmaceutical dosage form of any one of items 7 to 15, 17 to 19, 21 to 24 or 26 to 29, wherein said pharmaceutical composition or said pharmaceutical dosage form comprises:

the copper salt/complex in an amount of about 0.1 mg to about 5 mg per dosage unit, and/or the zinc salt/complex in an amount of about 0.1 mg to about 50 mg per dosage unit;

the reducing agent in an amount of about 1 mg to about 1000 mg per dosage unit; and

the absorption enhancer in an amount of about 10 mg to about 1000 mg per dosage unit.

32. Use of a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa in the preparation of a medicament which is to be administered orally in combination with:

a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and

a pharmaceutically acceptable reducing agent.

33. Use of a pharmaceutically acceptable copper salt/complex in the preparation of a medicament which is to be administered orally in combination with:

a pharmaceutically acceptable reducing agent; and

a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

34. Use of a pharmaceutically acceptable zinc salt/complex in the preparation of a medicament which is to be administered orally in combination with:

a pharmaceutically acceptable reducing agent; and

a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

35. Use of a pharmaceutically acceptable reducing agent in the preparation of a medicament which is to be administered orally in combination with:
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

36. A method of treating or preventing a disease/disorder, the method comprising orally administering, to a subject in need thereof, a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex, and a pharmaceutically acceptable reducing agent.

37. A method of orally delivering a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, the method comprising orally administering said peptide or protein drug in combination with a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex and with a pharmaceutically acceptable reducing agent to a subject in need thereof.

38. The use of any one of items 32 to 35 or the method of item 36 or 37, wherein the peptide or protein drug has a molecular weight of about 500 Da to about 30 kDa.

39. The use of any one of items 32 to 35 or 38 or the method of any one of items 36 to 38, wherein the peptide or protein drug has a molecular weight of about 1 kDa to about 10 kDa.

40. The use of any one of items 32 to 35 or the method of item 36 or 37, wherein the peptide or protein drug is selected from insulin, an insulin analog, insulin lispro, insulin PEGlispro, insulin aspart, insulin glulisine, insulin glargine, insulin detemir, NPH insulin, insulin degludec, B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin,

B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin, B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B16H B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin, B29K(N(ε)octadecanedioyl) A14E B25H desB30 human insulin, GLP-1, a GLP-1 analog, an acylated GLP-1 analog, a diacylated GLP-1 analog, a GLP-1 agonist, semaglutide, liraglutide, exenatide, exendin-4, lixisenatide, taspoglutide, albiglutide, dulaglutide, langlenatide, GLP-1(7-37), GLP-1(7-36)NH_2, a dual agonist of the GLP-1 receptor and the glucagon receptor, oxyntomodulin, GLP-2, a GLP-2 analog, a GLP-2 agonist, teduglutide, elsiglutide, amylin, an amylin analog, pramlintide, a somatostatin analog, octreotide, lanreotide, pasireotide, goserelin, buserelin, leptin, a leptin analog, metreleptin, peptide YY, a peptide YY analog, glatiramer, leuprolide, desmopressin, osteocalcin, an osteocalcin analog or derivative, human growth hormone, a human growth hormone analog, a glycopeptide antibiotic, a glycosylated cyclic or polycyclic nonribosomal peptide antibiotic, vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin, decaplanin, bortezomib, cosyntropin, chorionic gonadotropin, menotropin, sermorelin, luteinizing-hormone-releasing hormone, somatropin, calcitonin, calcitonin-salmon, pentagastrin, oxytocin, neseritide, anakinra, enfuvirtide, pegvisomant, dornase alfa, lepirudin, anidulafungin, eptifibatide, interferon alfacon-1, interferon alpha-2a, interferon alpha-2b, interferon beta-1a, interferon beta-1b, interferon gamma-1b, peginterferon alfa-2a, peginterferon alfa-2b, peginterferon beta-1a, fibrinolysin, vasopressin, aldesleukin, epoetin alfa, darbepoetin alfa, epoetin beta, epoetin delta, epoetin omega, epoetin zeta, filgrastim, interleukin-11, cyclosporine, glucagon, urokinase, viomycin, thyrotropin-releasing hormone, leucine-enkephalin, methionine-enkephalin, substance P, adrenocorticotropic hormone, parathyroid hormone, a parathyroid hormone fragment, teriparatide, PTH(1-31), PTH(2-34), parathyroid hormone-related protein, abaloparatide, linaclotide, carfilzomib, icatibant, ecallantide, cilengitide, a prostaglandin F2α receptor modulator, PDC31, and pharmaceutically acceptable salts thereof.

41. The use of any one of items 32 or 38 to 40 or the method of any of items 36 to 40, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable copper salt/complex.

42. The use of any one of items 32 to 35 or 38 to 41 or the method of any one of items 36 to 41, wherein said copper salt/complex is a copper(I) salt/complex or a copper(II) salt/complex.

43. The use of item 42 or the method of item 42, wherein said copper salt/complex is a copper(II) salt/complex which is selected from copper sulfate, copper carbonate, a copper(II) amino acid complex, copper(II) lysine complex, copper(II) glycinate, copper(II) EDTA complex, copper(II) chitosan complex, copper(II) citrate, copper(II) gluconate, copper(II) lactate, copper lactate gluconate, and copper(II) orotate.

44. The use of item 42 or the method of item 42, wherein said copper salt/complex is a copper(I) salt/complex which is selected from copper(I) chloride and copper(I) acetate.

45. The use of any one of items 32 or 38 to 40 or the method of any of items 36 to 40, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable zinc salt/complex.

46. The use of any one of items 32, 38 to 40 or 45 or the method of any of items 36 to 40 or 45, wherein said zinc salt/complex is a zinc(II) salt/complex.

47. The use of item 46 or the method of item 46, wherein said zinc salt/complex is a zinc(II) salt/complex which is selected from zinc sulfate, zinc chloride, zinc acetate, zinc oxide, zinc ascorbate, zinc caprylate, zinc gluconate, zinc stearate, zinc carbonate, zinc orotate, a zinc amino acid complex, zinc glycinate, zinc arginate, zinc picolinate, zinc pidolate, zinc carnosine, zinc undecanoate, zinc undecylenate, zinc methionine, zinc lactate, and zinc lactate gluconate.

48. The use of any one of items 32 to 35 or 38 to 47 or the method of any of items 36 to 47, wherein said reducing agent is selected from ascorbic acid, reduced glutathione, cysteine, N-acetylcysteine, histidine, glycine, arginine, gelatin, uric acid, a reducing sugar, glucose, glyceraldehyde, galactose, fructose, ribose, xylose, sorbose, lactose, maltose, cellobiose, a glucose polymer, starch, a starch derivative, glucose syrup, maltodextrin, dextrin, dextrose, dextran, cellulose, microcrystalline cellulose, mannitol, α-tocopherol, vitamin A, α-lipoic acid, dihydro-α-lipoic acid, oxalic acid, phytic acid, a tannin, propyl gallate, butylated hydroxy toluene, butylated hydroxy anisole, sodium metabisulfite, povidone, crospovidone, an aldehyde, formaldehyde, acetaldehyde, furfuraldehyde, a dialdehyde, glyoxal, a phenolic compound, phenol, a polyphenol, salicylic acid, a salicylic acid derivative, an iron(II) salt/complex, diphosphate, disodiumdiphosphate, trisodiumdiphosphate, tetrasodiumdiphosphate, tetrapotassiumdiphosphate, dicalciumdiphosphate, calciumdihydrogendiphophate,

phosphate, dipotassium hydrogen phosphate, calcium phosphate, calcium hydrogen phosphate, a thiol-bearing compound, a thiomer, and pharmaceutically acceptable salts thereof.

49. The use of item 48 or the method of item 48, wherein said reducing agent is an iron(II) salt/complex selected from iron(II) gluconate, iron(II) orotate, iron(II) tartrate, iron(II) fumarate, iron(II) sulfate, iron(II) lactate, iron(II) lactate gluconate, iron(II) acetate, iron(II) carbonate, iron(II) citrate, iron(II) oxide, iron(II) hydroxide, iron(II) ascorbate, an iron(II) amino acid complex, and ferrous bis-glycinate.

50. The use of any one of items 32 to 35 or 38 to 49 or the method of any of items 36 to 49, wherein an absorption enhancer is further to be administered orally.

51. The use of item 50 or the method of item 50, wherein said absorption enhancer is selected from C_{8-20} alkanoyl carnitine, salicylic acid, a salicylic acid derivative, 3-methoxysalicylic acid, 5-methoxysalicylic acid, homovanillic acid, a C_{8-20} alkanoic acid, citric acid, tartaric acid, a fatty acid acylated amino acid, a C_{8-20} alkanoyl sarcosinate, an alkylsaccharide, a C_{8-10} alkylpolysaccharide, n-octyl-beta-D-glucopyranoside, n-dodecyl-beta-D-maltoside, n-tetradecyl-beta-D-maltoside, tridecyl-beta-D-maltoside, sucrose laurate, sucrose myristate, sucrose palmitate, sucrose cocoate, sucrose mono-dodecanoate, sucrose mono-tridecanoate, sucrose mono-tetradecanoate, a coco-glucoside, a cyclodextrine, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, methyl-β-cyclodextrin, hydroxypropyl β-cyclodextrin, sulfobutylether β-cyclodextrin, N-[8-(2-hydroxybenzoyl)amino]caprylic acid, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate, a sodium N-[8-(2-hydroxybenzoyl)amino]caprylate derivative, a thiomer, a mucoadhesive polymer having a vitamin B partial structure, a calcium chelating compound, ethylenediaminetetraacetic acid, ethylene glycol tetraacetic acid, polyacrylic acid, cremophor EL, chitosan, N,N,N-trimethyl chitosan, benzalkonium chloride, bestatin, cetylpyridinium chloride, cetyltrimethylammonium bromide, a C_{2-20} alkanol, a C_{8-20} alkenol, a C_{8-20} alkenoic acid, dextran sulfate, diethyleneglycol monoethyl ether, 1-dodecylazacyclo-heptan-2-one, caprylocaproyl polyoxylglycerides, ethyl caprylate, glyceryl monolaurate, lysophosphatidylcholine, menthol, a C_{8-20} alkylamine, a C_{8-20} alkenylamine, phosphatidylcholine, a poloxamer, polyethylene glycol monolaurate, polyoxyethylene, polypropylene glycol monolaurate, a polysorbate, cholic acid, a deoxycholate, sodium glycocholate, sodium glycodeoxycholate, sodium lauryl sulfate, sodium decyl sulfate, sodium octyl sulfate, sodium laureth sulfate, N-lauryl sarcosinate, decyltrimethyl ammonium bromide,

benzyldimethyl dodecyl ammonium chloride, myristyltrimethyl ammonium chloride, dodecyl pyridinium chloride, decyldimethyl ammonio propane sulfonate, myristyldimethyl ammonio propane sulfonate, palmityldimethyl ammonio propane sulfonate, ChemBetaine CAS, ChemBetaine Oleyl, Nonylphenoxypolyoxyethylene, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, sorbitan monooleate, Triton X-100, hexanoic acid, heptanoic acid, methyl laurate, isopropyl myristate, isopropyl palmitate, methyl palmitate, diethyl sebaccate, sodium oleate, urea, lauryl amine, caprolactam, methyl pyrrolidone, octyl pyrrolidone, methyl piperazine, phenyl piperazine, Carbopol 934P, glyccyrhetinic acid, bromelain, pinene oxide, limonene, cineole, octyl dodecanol, fenchone, menthone, trimethoxy propylene methyl benzene, a cell-penetrating peptide, KLAKLAK, polyarginine, penetratin, HIV-1 Tat, macrogol-15-hydroxystearate, Solutol HS 15, CriticalSorb, a taurocholate, a taurodeoxycholate, a sulfoxide, decyl methyl sulfoxide, dimethyl sulfoxide, cyclopentadecalactone, 8-(N-2-hydroxy-5-chloro-benzoyl)-amino-caprylic acid, N-(10-[2-hydroxybenzoyl]amino)decanoic acid, dodecyl-2-N,N-dimethylamino propionate, D-α-tocopheryl polyethylene glycol-1000 succinate, and pharmaceutically acceptable salts thereof.

52. The use of item 51 or the method of item 51, wherein said absorption enhancer is a fatty acid acylated amino acid selected from sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methioninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, sodium lauroyl sarcosinate, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-

histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, N-decanoyl-L-sarcosine, sodium oleoyl sarcosinate, sodium N-decylleucine, sodium stearoyl glutamate, sodium myristoyl glutamate, sodium lauroyl glutamate, sodium cocoyl glutamate, sodium cocoyl glycinate, sodium N-decyl leucine, sodium cocoyl glycine, sodium cocoyl glutamate, sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methinoninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, Sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, sodium oleoyl sarcosinate, and pharmaceutically acceptable salts thereof.

53. The use of item 50 or the method of item 50, wherein said absorption enhancer is sodium N-[8-(2-hydroxybenzoyl)amino]caprylate.

The invention furthermore relates to the following embodiments:

1. A peptide or protein drug having a molecular weight of equal to or less than about 50 kDa for use as a medicament, wherein said peptide or protein drug is to be administered orally in combination with:
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a pharmaceutically acceptable reducing agent.

2. A pharmaceutically acceptable copper salt/complex for use in therapy, wherein said copper salt/complex is to be administered orally in combination with:
a pharmaceutically acceptable reducing agent; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

3. A pharmaceutically acceptable zinc salt/complex for use in therapy, wherein said zinc salt/complex is to be administered orally in combination with:
a pharmaceutically acceptable reducing agent; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

4. A pharmaceutically acceptable reducing agent for use in therapy, wherein said reducing agent is to be administered orally in combination with:
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

5. A pharmaceutical composition comprising:
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa;
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a pharmaceutically acceptable reducing agent.

6. The pharmaceutical composition of embodiment 5, wherein said pharmaceutical composition is for oral administration.

7. A pharmaceutical dosage form comprising:
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa;
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a pharmaceutically acceptable reducing agent;
wherein the peptide or protein drug is physically separated from the pharmaceutically acceptable copper salt/complex and the pharmaceutically acceptable zinc salt/complex within the pharmaceutical dosage form.

8. The pharmaceutical dosage form of embodiment 7, which is a pharmaceutical dosage form comprising:
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, which is present in a first compartment of the pharmaceutical dosage form;
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex, which is/are present in a second compartment of the pharmaceutical dosage form; and
a pharmaceutically acceptable reducing agent, which is present in the first compartment and/or the second compartment of the pharmaceutical dosage form.

9. The pharmaceutical dosage form of embodiment 7 or 8, which is in the form of a double capsule.

10. The pharmaceutical dosage form of embodiment 7, which is a pharmaceutical dosage form comprising:
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, which is present in a first compartment of the pharmaceutical dosage form;
a pharmaceutically acceptable reducing agent, which is present in a second compartment of the pharmaceutical dosage form; and
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex, which is/are present in a third compartment of the pharmaceutical dosage form.

11. The pharmaceutical dosage form of embodiment 7 or 10, which is in the form of a multi-particulate dosage form.

12. The pharmaceutical dosage form of any one of embodiments 7 to 11, wherein said pharmaceutical dosage form is for oral administration.

13. The peptide or protein drug for use according to embodiment 1 or the copper salt/complex for use according to embodiment 2 or the zinc salt/complex for use according to embodiment 3 or the reducing agent for use according to embodiment 4 or the pharmaceutical composition of embodiment 5 or 6 or the pharmaceutical dosage form of any one of embodiments 7 to 12, wherein the peptide or protein drug has a molecular weight of about 500 Da to about 30 kDa.

14. The peptide or protein drug for use according to embodiment 1 or 13 or the copper salt/complex for use according to embodiment 2 or 13 or the zinc salt/complex for use according to embodiment 3 or 13 or the reducing agent for use according to embodiment 4 or 13 or the pharmaceutical composition of embodiment 5, 6 or 13 or the pharmaceutical dosage form of any one of embodiments 7 to 13, wherein the peptide or protein drug has a molecular weight of about 1 kDa to about 10 kDa.

15. The peptide or protein drug for use according to embodiment 1 or the copper salt/complex for use according to embodiment 2 or the zinc salt/complex for use according to embodiment 3 or the reducing agent for use according to embodiment 4 or the pharmaceutical composition of embodiment 5 or 6 or the pharmaceutical dosage form of any one of embodiments 7 to 12, wherein the peptide or protein drug is selected from insulin, an insulin analog, insulin lispro, insulin PEGlispro, insulin aspart, insulin glulisine, insulin glargine, insulin detemir, NPH insulin, insulin degludec, B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin, B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B16H B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin, B29K(N(ε)octadecanedioyl) A14E B25H desB30 human insulin, GLP-1, a GLP-1

analog, an acylated GLP-1 analog, a diacylated GLP-1 analog, semaglutide, liraglutide, exenatide, lixizenatide, a dual agonist of the GLP-1 receptor and the glucagon receptor, amylin, an amylin analog, pramlintide, a somatostatin analog, octreotide, lanreotide, pasireotide, goserelin, buserelin, leptin, a leptin analog, metreleptin, peptide YY, a peptide YY analog, glatiramer, leuprolide, teriparatide, desmopressin, human growth hormone, a human growth hormone analog, a glycopeptide antibiotic, a glycosylated cyclic or polycyclic nonribosomal peptide antibiotic, vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin, decaplanin, bortezomib, cosyntropin, chorionic gonadotropin, menotropin, sermorelin, luteinizing-hormone-releasing hormone, somatropin, calcitonin, calcitonin-salmon, pentagastrin, oxytocin, neseritide, anakinra, enfuvirtide, pegvisomant, dornase alfa, lepirudin, anidulafungin, eptifibatide, interferon alfacon-1, interferon alpha-2a, interferon alpha-2b, interferon beta-1a, interferon beta-1b, interferon gamma-1b, peginterferon alfa-2a, peginterferon alfa-2b, peginterferon beta-1a, fibrinolysin, vasopressin, aldesleukin, epoetin alfa, darbepoetin alfa, epoetin beta, epoetin delta, epoetin omega, epoetin zeta, filgrastim, interleukin-11, cyclosporine, glucagon, urokinase, viomycin, thyrotropin-releasing hormone, leucine-enkephalin, methionine-enkephalin, substance P, adrenocorticotropic hormone, parathyroid hormone, and pharmaceutically acceptable salts thereof.

16. The peptide or protein drug for use according to any one of embodiments 1 or 13 to 15, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable copper salt/complex.

17. The peptide or protein drug for use according to any one of embodiments 1 or 13 to 16 or the copper salt/complex for use according to any one of embodiments 2 or 13 to 15 or the reducing agent for use according to any one of embodiments 4 or 13 to 15 or the pharmaceutical composition of any one of embodiments 5, 6 or 13 to 15 or the pharmaceutical dosage form of any one of embodiments 7 to 15, wherein said copper salt/complex is a copper(I) salt/complex or a copper(II) salt/complex.

18. The peptide or protein drug for use according to embodiment 17 or the copper salt/complex for use according to embodiment 17 or the reducing agent for use according to embodiment 17 or the pharmaceutical composition of embodiment 17 or the pharmaceutical dosage form of embodiment 17, wherein said copper salt/complex is a copper(II) salt/complex which is selected from copper sulfate, copper carbonate, copper(II) lysine complex, copper(II) citrate, and copper(II) gluconate.

19. The peptide or protein drug for use according to embodiment 17 or the copper salt/complex for use according to embodiment 17 or the reducing agent for use according to embodiment 17 or the pharmaceutical composition of embodiment 17 or the pharmaceutical dosage form of embodiment 17, wherein said copper salt/complex is a copper(I) salt/complex which is selected from copper(I) chloride and copper(I) acetate.

20. The peptide or protein drug for use according to any one of embodiments 1 or 13 to 15, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable zinc salt/complex.

21. The peptide or protein drug for use according to any one of embodiments 1, 13 to 15 or 20 or the zinc salt/complex for use according to any one of embodiments 3 or 13 to 15 or the reducing agent for use according to any one of embodiments 4 or 13 to 15 or the pharmaceutical composition of any one of embodiments 5, 6 or 13 to 15 or the pharmaceutical dosage form of any one of embodiments 7 to 15, wherein said zinc salt/complex is a zinc(II) salt/complex.

22. The peptide or protein drug for use according to embodiment 21 or the zinc salt/complex for use according to embodiment 21 or the reducing agent for use according to embodiment 21 or the pharmaceutical composition of embodiment 21 or the pharmaceutical dosage form of embodiment 21, wherein said zinc salt/complex is a zinc(II) salt/complex which is selected from zinc sulfate, zinc chloride, zinc acetate, zinc oxide, zinc ascorbate, zinc caprylate, zinc gluconate, zinc stearate, and zinc carbonate.

23. The peptide or protein drug for use according to any one of embodiments 1 or 13 to 22 or the copper salt/complex for use according to any one of embodiments 2, 13 to 15 or 17 to 19 or the zinc salt/complex for use according to any one of embodiments 3, 13 to 15, 21 or 22 or the reducing agent for use according to any one of embodiments 4, 13 to 15, 17 to 19, 21 or 22 or the pharmaceutical composition of any one of embodiments 5, 6, 13 to 15, 17 to 19, 21 or 22 or the pharmaceutical dosage form of any one of embodiments 7 to 15, 17 to 19, 21 or 22, wherein said reducing agent is selected from ascorbic acid, reduced glutathione, cysteine, uric acid, a reducing sugar, glucose, glyceraldehyde, galactose, lactose, maltose, mannitol, α-tocopherol, vitamin A, α-lipoic acid, dihydro-α-lipoic acid, a thiol-bearing compound, a thiomer, and pharmaceutically acceptable salts thereof.

24. The peptide or protein drug for use according to any one of embodiments 1 or 13 to 23 or the copper salt/complex for use according to any one of embodiments 2, 13 to 15, 17 to 19 or 23 or the zinc salt/complex for use according to any one of embodiments 3, 13 to 15 or 21 to 23 or the reducing agent for use according to any one of embodiments 4, 13 to 15, 17 to 19 or 21 to 23, wherein said peptide or protein drug or said copper salt/complex or said zinc salt/complex or said reducing agent is to be administered orally in combination with an absorption enhancer.

25. The pharmaceutical composition of any one of embodiments 5, 6, 13 to 15, 17 to 19 or 21 to 23 or the pharmaceutical dosage form of any one of embodiments 7 to 15, 17 to 19 or 21 to 23, wherein said pharmaceutical composition or said pharmaceutical dosage form further comprises an absorption enhancer.

26. The peptide or protein drug for use according to embodiment 24 or the copper salt/complex for use according to embodiment 24 or the zinc salt/complex for use according to embodiment 24 or the reducing agent for use according to embodiment 24 or the pharmaceutical composition of embodiment 25 or the pharmaceutical dosage form of embodiment 25, wherein said absorption enhancer is selected from C_{8-20} alkanoyl carnitine, salicylic acid, a salicylic acid derivative, 3-methoxysalicylic acid, 5-methoxysalicylic acid, homovanillic acid, a C_{8-20} alkanoic acid, citric acid, a fatty acid acylated amino acid, a C_{8-20} alkanoyl sarcosinate, an alkylsaccharide, a C_{8-10} alkylpolysaccharide, n-octyl-beta-D-glucopyranoside, n-dodecyl-beta-D-maltoside, a cyclodextrine, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, methyl-β-cyclodextrin, hydroxypropyl β-cyclodextrin, sulfobutylether β-cyclodextrin, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate, a thiomer, a calcium chelating compound, ethylenediaminetetraacetic acid, ethylene glycol tetraacetic acid, polyacrylic acid, cremophor EL, chitosan, N,N,N-trimethyl chitosan, benzalkonium chloride, bestatin, cetylpyridinium chloride, cetyltrimethylammonium bromide, a C_{2-20} alkanol, a C_{8-20} alkenol, a C_{8-20} alkenoic acid, dextran sulfate, diethyleneglycol monoethyl ether, 1-dodecylazacyclo-heptan-2-one, ethyl caprylate, glyceryl monolaurate, lysophosphatidylcholine, menthol, a C_{8-20} alkylamine, a C_{8-20} alkenylamine, phosphatidylcholine, a poloxamer, polyethylene glycol monolaurate, polyoxyethylene, polypropylene glycol monolaurate, a polysorbate, a deoxycholate, sodium glycocholate, sodium glycodeoxycholate, sodium lauryl sulfate, a taurocholate, a taurodeoxycholate, sucrose laurate, a sulfoxide, decyl methyl sulfoxide, dimethyl sulfoxide, cyclopentadecalactone, 8-(N-2-hydroxy-5-chloro-benzoyl)-amino-caprylic acid, dodecyl-

2-N,N-dimethylamino propionate, D-α-tocopheryl polyethylene glycol-1000 succinate, and pharmaceutically acceptable salts thereof.

27. The peptide or protein drug for use according to embodiment 26 or the copper salt/complex for use according to embodiment 26 or the zinc salt/complex for use according to embodiment 26 or the reducing agent for use according to embodiment 26 or the pharmaceutical composition of embodiment 26 or the pharmaceutical dosage form of embodiment 26, wherein said absorption enhancer is a fatty acid acylated amino acid selected from sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methioninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, sodium lauroyl sarcosinate, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, N-decanoyl-L-sarcosine, sodium oleoyl sarcosinate, sodium N-decylleucine, sodium stearoyl glutamate, sodium myristoyl glutamate, sodium lauroyl glutamate, sodium cocoyl glutamate, sodium cocoyl glycinate, sodium N-decyl leucine, sodium cocoyl glycine, sodium cocoyl glutamate, sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-

dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methinoninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, Sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, sodium oleoyl sarcosinate, and pharmaceutically acceptable salts thereof.

28. The pharmaceutical composition of any one of embodiments 5, 6, 13 to 15, 17 to 19, 21 to 23 or 25 to 27, wherein said pharmaceutical composition is a solid composition or a liquid composition that contains less than about 5% (v/v) of water.

29. The pharmaceutical composition of any one of embodiments 5, 6, 13 to 15, 17 to 19, 21 to 23 or 25 to 28 or the pharmaceutical dosage form of any one of embodiments 7 to 15, 17 to 19, 21 to 23 or 25 to 27, wherein said pharmaceutical composition or said pharmaceutical dosage form comprises:

the copper salt/complex in an amount of about 0.1 mg to about 5 mg per dosage unit, and/or the zinc salt/complex in an amount of about 0.1 mg to about 50 mg per dosage unit;

the reducing agent in an amount of about 1 mg to about 1000 mg per dosage unit; and

the absorption enhancer in an amount of about 10 mg to about 1000 mg per dosage unit.

30. Use of a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa in the preparation of a medicament which is to be administered orally in combination with:
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a pharmaceutically acceptable reducing agent.

31. Use of a pharmaceutically acceptable copper salt/complex in the preparation of a medicament which is to be administered orally in combination with:
a pharmaceutically acceptable reducing agent; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

32. Use of a pharmaceutically acceptable zinc salt/complex in the preparation of a medicament which is to be administered orally in combination with:
a pharmaceutically acceptable reducing agent; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

33. Use of a pharmaceutically acceptable reducing agent in the preparation of a medicament which is to be administered orally in combination with:
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

34. A method of treating or preventing a disease/disorder, the method comprising orally administering, to a subject in need thereof, a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex, and a pharmaceutically acceptable reducing agent.

35. A method of orally delivering a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, the method comprising orally administering said

peptide or protein drug in combination with a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex and with a pharmaceutically acceptable reducing agent to a subject in need thereof.

36. The use of any one of embodiments 30 to 33 or the method of embodiment 34 or 35, wherein the peptide or protein drug has a molecular weight of about 500 Da to about 30 kDa.

37. The use of any one of embodiments 30 to 33 or 36 or the method of any one of embodiments 34 to 36, wherein the peptide or protein drug has a molecular weight of about 1 kDa to about 10 kDa.

38. The use of any one of embodiments 30 to 33 or the method of embodiment 34 or 35, wherein the peptide or protein drug is selected from insulin, an insulin analog, insulin lispro, insulin PEGlispro, insulin aspart, insulin glulisine, insulin glargine, insulin detemir, NPH insulin, insulin degludec, B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin, B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B16H B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin, B29K(N(ε)octadecanedioyl) A14E B25H desB30 human insulin, GLP-1, a GLP-1 analog, an acylated GLP-1 analog, a diacylated GLP-1 analog, semaglutide, liraglutide, exenatide, lixizenatide, a dual agonist of the GLP-1 receptor and the glucagon receptor, amylin, an amylin analog, pramlintide, a somatostatin analog, octreotide, lanreotide, pasireotide, goserelin, buserelin, leptin, a leptin analog, metreleptin, peptide YY, a peptide YY analog, glatiramer, leuprolide, teriparatide, desmopressin, human growth hormone, a human growth hormone analog, a glycopeptide antibiotic, a glycosylated cyclic or polycyclic nonribosomal peptide antibiotic, vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin, decaplanin, bortezomib, cosyntropin, chorionic gonadotropin, menotropin, sermorelin, luteinizing-hormone-releasing hormone, somatropin, calcitonin, calcitonin-salmon, pentagastrin, oxytocin, neseritide, anakinra, enfuvirtide, pegvisomant, dornase alfa, lepirudin, anidulafungin, eptifibatide, interferon alfacon-1, interferon alpha-2a, interferon alpha-2b, interferon beta-1a, interferon beta-1b,

interferon gamma-1b, peginterferon alfa-2a, peginterferon alfa-2b, peginterferon beta-1a, fibrinolysin, vasopressin, aldesleukin, epoetin alfa, darbepoetin alfa, epoetin beta, epoetin delta, epoetin omega, epoetin zeta, filgrastim, interleukin-11, cyclosporine, glucagon, urokinase, viomycin, thyrotropin-releasing hormone, leucine-enkephalin, methionine-enkephalin, substance P, adrenocorticotropic hormone, parathyroid hormone, and pharmaceutically acceptable salts thereof.

39. The use of any one of embodiments 30 or 36 to 38 or the method of any of embodiments 34 to 38, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable copper salt/complex.

40. The use of any one of embodiments 30 to 33 or 36 to 39 or the method of any one of embodiments 34 to 39, wherein said copper salt/complex is a copper(I) salt/complex or a copper(II) salt/complex.

41. The use of embodiment 40 or the method of embodiment 40, wherein said copper salt/complex is a copper(II) salt/complex which is selected from copper sulfate, copper carbonate, copper(II) lysine complex, copper(II) citrate, and copper(II) gluconate.

42. The use of embodiment 40 or the method of embodiment 40, wherein said copper salt/complex is a copper(I) salt/complex which is selected from copper(I) chloride and copper(I) acetate.

43. The use of any one of embodiments 30 or 36 to 38 or the method of any of embodiments 34 to 38, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable zinc salt/complex.

44. The use of any one of embodiments 30, 36 to 38 or 43 or the method of any of embodiments 34 to 38 or 43, wherein said zinc salt/complex is a zinc(II) salt/complex.

45. The use of embodiment 44 or the method of embodiment 44, wherein said zinc salt/complex is a zinc(II) salt/complex which is selected from zinc sulfate, zinc chloride, zinc acetate, zinc oxide, zinc ascorbate, zinc caprylate, zinc gluconate, zinc stearate, and zinc carbonate.

46. The use of any one of embodiments 30 to 33 or 36 to 45 or the method of any of embodiments 34 to 45, wherein said reducing agent is selected from ascorbic acid,

reduced glutathione, cysteine, uric acid, a reducing sugar, glucose, glyceraldehyde, galactose, lactose, maltose, mannitol, α-tocopherol, vitamin A, α-lipoic acid, dihydro-α-lipoic acid, a thiol-bearing compound, a thiomer, and pharmaceutically acceptable salts thereof.

47. The use of any one of embodiments 30 to 33 or 36 to 46 or the method of any of embodiments 34 to 46, wherein an absorption enhancer is further to be administered orally.

48. The use of embodiment 47 or the method of embodiment 47, wherein said absorption enhancer is selected from C_{8-20} alkanoyl carnitine, salicylic acid, a salicylic acid derivative, 3-methoxysalicylic acid, 5-methoxysalicylic acid, homovanillic acid, a C_{8-20} alkanoic acid, citric acid, a fatty acid acylated amino acid, a C_{8-20} alkanoyl sarcosinate, an alkylsaccharide, a C_{8-10} alkylpolysaccharide, n-octyl-beta-D-glucopyranoside, n-dodecyl-beta-D-maltoside, a cyclodextrine, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, methyl-β-cyclodextrin, hydroxypropyl β-cyclodextrin, sulfobutylether β-cyclodextrin, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate, a thiomer, a calcium chelating compound, ethylenediaminetetraacetic acid, ethylene glycol tetraacetic acid, polyacrylic acid, cremophor EL, chitosan, N,N,N-trimethyl chitosan, benzalkonium chloride, bestatin, cetylpyridinium chloride, cetyltrimethylammonium bromide, a C_{2-20} alkanol, a C_{8-20} alkenol, a C_{8-20} alkenoic acid, dextran sulfate, diethyleneglycol monoethyl ether, 1-dodecylazacyclo-heptan-2-one, ethyl caprylate, glyceryl monolaurate, lysophosphatidylcholine, menthol, a C_{8-20} alkylamine, a C_{8-20} alkenylamine, phosphatidylcholine, a poloxamer, polyethylene glycol monolaurate, polyoxyethylene, polypropylene glycol monolaurate, a polysorbate, a deoxycholate, sodium glycocholate, sodium glycodeoxycholate, sodium lauryl sulfate, a taurocholate, a taurodeoxycholate, sucrose laurate, a sulfoxide, decyl methyl sulfoxide, dimethyl sulfoxide, cyclopentadecalactone, 8-(N-2-hydroxy-5-chloro-benzoyl)-amino-caprylic acid, dodecyl-2-N,N-dimethylamino propionate, D-α-tocopheryl polyethylene glycol-1000 succinate, and pharmaceutically acceptable salts thereof.

49. The use of embodiment 48 or the method of embodiment 48, wherein said absorption enhancer is a fatty acid acylated amino acid selected from sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-

dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methioninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, sodium lauroyl sarcosinate, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, N-decanoyl-L-sarcosine, sodium oleoyl sarcosinate, sodium N-decylleucine, sodium stearoyl glutamate, sodium myristoyl glutamate, sodium lauroyl glutamate, sodium cocoyl glutamate, sodium cocoyl glycinate, sodium N-decyl leucine, sodium cocoyl glycine, sodium cocoyl glutamate, sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methinoninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-

aspartic acid, Sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, sodium oleoyl sarcosinate, and pharmaceutically acceptable salts thereof.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES

General description of methods

Administration into mid-jejunum in rats:

After checking of the depth of anesthesia the animal was placed on its back and a 3 – 5 cm long midline incision was made in the skin of abdomen. The wound margins were released from the base. The muscle layer of the abdominal wall was carefully cut in the middle line (linea alba).

The caecum was exposed and the small intestine was gradually pulled out of the abdominal cavity and the position of the spot convenient for introduction of catheter was measured using a PE tubing with marks at a distance of 40, 50, and 60 cm. Pulling the intestine was performed very carefully to avoid injury of blood vessels and mesentery. The intestine was penetrated by the catheter tip and the catheter was inserted downstream into the jejunal lumen at a distance of 50 (35-65) cm from caecum in a spot without feces, outside the area with accumulated lymphatic tissue and outside the blood vessels and fixed with ligature. The distance of the spot from caecum was measured and recorded.

The pulled loops of small intestine were replaced into the abdominal cavity, 2 ml of sterile saline were flushed over the intestine and the abdominal cavity was closed with metal wound clips in two layers. The prepared syringes filled with the formulations were gradually attached to the inserted catheters. Dosing was performed slowly. The syringes with peptide or protein drug were attached to the inserted cannula until the end of the experiment.

Correctness of the application was checked. The abdominal cavity was opened by cutting next to the surgical wound to see if the catheter was still in place. About 1 ml of air was flushed into the lumen of the intestine with a syringe to reveal possible penetration of intestinal wall. The site of application was inspected and possible changes were identified.

Example 1: Compatibility of absorption enhancers with the trace element copper

Various absorption enhancers were screened regarding their compatibility with the trace element copper in the two main oxidation states as Cu^{2+} and Cu^{+}. The results of this test are shown in the following Table 1:

Absorption enhancer (10 mg/ml)	**Copper salt (1 mg/ml)**	**Reducing agent (10 mg/ml)**	**Dissolution in aqueous medium (2 ml)**
Sodium caprate	$CuSO_4$	Sodium ascorbate	Precipitation
Sodium caprylate	$CuSO_4$	Sodium ascorbate	Precipitation
Sodium lauroyl sarcosinate	$CuSO_4$	Sodium ascorbate	Precipitation
Lauroyl carnitine	$CuSO_4$	Sodium ascorbate	Clear solution
Lauroyl carnitine	$CuSO_4$	Glutathione	Clear solution
Sodium dodecyl sulfate	$CuSO_4$	Sodium ascorbate	Clear solution
Multitrope 1620 LQ (alkylsaccharide)	$CuSO_4$	Sodium ascorbate	Clear solution
n-Octyl-beta-D-glucopyranoside	$CuSO_4$	Sodium ascorbate	Clear solution
n-Dodecyl-beta-D-maltoside	$CuSO_4$	Sodium ascorbate	Clear solution
Cremophor EL	$CuSO_4$	Sodium ascorbate	Clear solution
Sodium salicylate	$CuSO_4$	Sodium ascorbate	Clear solution
EDTA	$CuSO_4$	Sodium ascorbate	Clear solution
Sodium citrate	$CuSO_4$	Sodium ascorbate	Clear solution
Methyl-beta-cyclodextrin	$CuSO_4$	Sodium ascorbate	Clear solution
Sodium caprylate	Copper (I) acetate	Sodium ascorbate	Clear solution
Sodium caprate	Copper (I) acetate	Sodium ascorbate	Clear solution

Sodium caprate	Cu(I)Cl	Sodium ascorbate	Clear solution
Sodium caprylate	Cu(I)Cl	Sodium ascorbate	Clear solution

Table 1: Compatibility of various absorption enhancers with Cu^{2+} and Cu^{+} salts.

The term clear solution as used in this table refers to that no clear visible precipitation or flocculation has been observed. The term clear solution also includes slightly colored clear solutions such as yellowish or orange solutions.

Conclusion: Certain absorption enhancers such as medium chain fatty acid salts and derivatives are not well compatible with divalent copper salts. However, zwitter-ionic as well as non-ionic surfactants showed good compatibility with copper salts. Moreover, monovalent copper also showed compatibility with sodium caprate and caprylate. A disadvantage of monovalent copper salts is their low aqueous solubility and the instability of the Cu^{+} oxidation state in aqueous solutions. The monovalent copper salt Cu(I)Cl, on the other hand, has aqueous solubility and oxidation state stability.

Example 2: The pharmacodynamic and pharmacokinetic profiles of human insulin formulations after administration into mid-jejunum of Sprague Dawley rats

Method – Administration into rat jejunum: The direct application of peptide or protein drugs and their formulations into mid-jejunum (the middle part of the small intestine – jejunum) enables to study their ability to pass through the intestinal barrier and to resist the degradation caused by the digestive enzymes. Sprague-Dawley rats, males, weighing 250 – 300 g were used. The studies were preformed under anesthesia. The results obtained are indicated in the following Table 2:

Human insulin	**Absorption enhancer (10 mg/ml)**	**Trace element (1 mg/ml)**	**Reducing agent**	**$AUC_{(0-t)}$ (pmol/l x min)**	**C_{max} (pmol/l)**
22 IU/kg	Sodium caprate	-	-	2093±1759	28±24
22 IU/kg	Sodium caprate	$CuSO_4$	Ascorbate	2505±2921	37±54

Table 2: Pharmacokinetic profiles of human insulin formulations.

Conclusion: A simple physical blend of human insulin and the classical absorption enhancer sodium caprate in the presence of the trace element copper with ascorbate as a reducing agent moderately improved the oral bioavailability of human insulin. A more pronounced improvement of the oral bioavailability was not observed in this experiment because of the poor aqueous solubility of both sodium caprate and insulin in the presence of 1 mg/ml Cu^{2+}.

Example 3: The pharmacodynamic and pharmacokinetic profiles of human insulin formulations after administration into mid-jejunum of Sprague Dawley rats

In order to improve insulin solubility, Cu^{2+} and insulin were dosed separately. Experimental design – 10 minutes predosing of the trace element copper with sodium ascorbate followed by dosing of an insulin solution comprising one of various absorption enhancers. In such a setup, insulin was found to retain good aqueous solubility.

Predosing solution: 1 mg/ml $CuSO_4$ and 10 mg/ml sodium ascorbate

The respective insulin solutions: 22 IU/kg human insulin, and absorption enhancer

a) 22 IU/kg human insulin and 50 mg/ml sodium caprate
b) 22 IU/kg human insulin and 100 mg/ml Cremophor EL and 10 mg/ml Na_2HPO_4
c) 22 IU/kg human insulin and 50 mg/ml lauroyl-DL-carnitine-chloride and 40 mg/ml Na_2HPO_4

Predosing solution	**Human insulin**	**Absorption enhancer**	**Buffer agent**	**$AUC_{(0-t)}$ (pmol/l x min)**	**C_{max} (pmol/l)**
$CuSO_4$ and ascorbate	22 IU/kg	Sodium caprate	-	5351 ± 2289	72 ± 26
$CuSO_4$ and ascorbate	22 IU/kg	Cremophor EL	Na_2HPO_4	2340 ± 899	48 ± 23
$CuSO_4$ and ascorbate	22 IU/kg	Lauroyl carnitine chloride	Na_2HPO_4	145896 ± 89530	1850 ± 1117

Table 3: Pharmacokinetic profiles of human insulin formulations comprising different absorption enhancers after pre-dosing of copper sulfate and sodium ascorbate.

Conclusion: The results show that compositions comprising the zwitter-ionic absorption enhancer lauroyl-carnitine resulted in 27 to 62-fold improved insulin absorption ($AUC_{(0-t)}$) as compared with compositions comprising absorption enhancers such as sodium caprate or Cremophor EL, respectively. Moreover, the predosing of $CuSO_4$ and sodium ascorbate prior to the administration of insulin and sodium caprate was found to provide a more favorable insulin absorption than the simultaneous administration of these agents, as tested in Example 2.

Example 4: Pharmacodynamics in non human primates after oral administration of solid oral compositions of human insulin

Composition A:

Double capsule formulations providing a physical barrier between insulin and Cu^{2+} and the reducing agent sodium ascorbate are described. A small size 4 capsule is placed into a larger size 1 capsule. In such a solid oral dosage form the therapeutic polypeptide drug is not in intimate contact with the trace element copper and the reducing agent. Further, copper and ascorbate will be released *in vivo* prior to insulin. Such a composition will also improve insulin solubility.

The composition comprises 4 mg human insulin and 50 mg sodium salicylate in size 4 hard capsule and 100 mg sodium ascorbate, 1 mg $CuSO_4$ and 100 mg sodium salicylate in size 1 capsule. The size 4 capsule is placed into the size 1 capsule. The capsule was dosed per oral to a female cynomolgus monkey with additional 5 ml of tap water.

As control, a capsule comprising 4 mg of human insulin and 200 mg of the known absorption enhancer sodium caprylate was used.

4 mg Insulin	0 min	20 min	40 min	60 min	120 min	150 min
Control: 200 mg sodium caprylate	0	+16	+20	+47	1	0
150 mg sodium salicylate, 100 mg sodium ascorbate, 1 mg $CuSO_4$	0	+59	-14	-19	-14	-1

Table 4: % Glucose reduction in non human primate after oral administration of composition A

Conclusion: A solid oral insulin composition according to the invention comprising the absorption enhancer sodium salicylate in the presence of the trace element copper and the reducing agent sodium ascorbate resulted in a clear pharmacodynamic effect (reduction of the

blood glucose levels). The control formulation did not show any reduction of the blood glucose levels.

Composition B:

Double capsule:

Double capsule formulations providing a physical barrier between insulin and Cu^{2+} and the reducing agent sodium ascorbate are described. A small size 4 capsule is placed into a larger size 1 capsule. In such a solid oral dosage form the therapeutic polypeptide drug is not in intimate contact with the trace element copper and the reducing agent. Further, copper and ascorbate will be released *in vivo* prior to insulin.

The composition comprises 4 mg human insulin and 200 mg Multitrope 1620 LQ-(MV) which is a C8 and C10 fatty acid acylated polysaccharide and 5 mg sodium citrate in size 4 hard capsule and 180 mg sodium ascorbate, 0.5 mg $CuSO_4$ in size 1 hard capsule. The size 4 capsule is placed into the size 1 capsule. In addition, 5 ml of TRIS (4 mg/ml) were dosed per oral to a female cynomolgus monkey.

4 mg Insulin	0 min	20 min	40 min	60 min	90 min	120 min	150 min
Control: 200 mg sodium caprylate	0	+16	+20	+47	+16	1	0
200 mg Multitrope 1620 LQ-(MV), 180 mg sodium ascorbate, 0.5 mg $CuSO_4$, 5 mg sodium citrate	0	-33	-21	-12	-15	-15	-19

Table 5: % Glucose reduction in non human primate after oral administration of composition B

Conclusion: An oral insulin composition according to the invention comprising the non-ionic absorption enhancer Multitrope 1620 LQ which is an alkylsaccharide in the presence of the trace element copper and the reducing agent sodium ascorbate resulted in a substantial pharmacodynamic effect (reduction of the blood glucose levels).

Example 5: Pharmacokinetic profile of the glycopeptide vancomycin after administration into ileum of Sprague Dawley rats

Vancomycin hydrochloride is a glycopeptide antibiotic with an negligible oral bioavailability in the 0.1% range but usually under detection limit.

a) Vancomycin was administered i.v. in dosing volume of 1 ml/kg (final concentration of 5 mg/ml) to anesthetized rats.

b) Vancomycin was dosed into ileum in volume of 0.4 ml/kg (final concentration of 50 mg/ml) to anesthetized rats.

The vancomycin plasma concentrations were determined on biochemical autoanalyser Hitachi 912 using commercial vancomycin kit VANC2 (Roche Diagnostics GmbH, Germany). The absolute bioavailability (F) was calculated using equation F (%) = ($AUC_{ileum}/AUC_{i.v.}$) x ($Dose_{i.v.}/Dose_{ileum}$) x 100.

Vancomycin	**Lauroyl carnitine**	**Trace element $CuSO_4$**	**Reducing agent sodium ascorbate**	**$AUC_{(0-t)}$ (µg/ml x min)**	**C_{max} (µg/ml)**	**F (%)**
5 mg/kg i.v.	-	-	-	662 ± 60	8,8 ± 0,3	100 ± 7
20 mg/kg ileum	50 mg/ml	1 mg/ml	250 mg/ml	180 ± 45	2,4 ± 0,2	8 ± 0,4

Table 6: Pharmacokinetic profile of vancomycin formulation.

Conclusion: An oral vancomycin formulation according to the invention increased markedly its bioavailability in comparison with published F values after oral administration (Prasad YV et al., *Int J Pharm.* 2003, 250(1):181-90; Van Bambeke F, *Curr Opin Investig Drugs.* 2006, 7(8):740-9).

Example 6: Pharmacokinetic profiles of liraglutide after administration into mid-jejunum of Sprague Dawley rats

2.4 mg/kg of the polypeptide liraglutide were dosed into the mid-jejunum of anesthetized Sprague Dawley rats in the presence of the zwitter-ionic absorption enhancer lauroyl carnitine chloride ("LCC") (20 mg/ml) with and without the addition of (i) the trace element $CuSO_4$ (1 mg/ml) and the reducing agent sodium ascorbate (40 mg/ml) or (ii) the trace element $ZnSO_4$ (1 mg/ml) and the reducing agent glutathione (40 mg/ml). All formulations further comprised Na_2HPO_4 to result in a neutral pH between 7 to 8. The results of these experiments are shown in Figure 1.

Conclusion: The combination of the zwitter-ionic absorption enhancer lauroyl carnitine (LCC) in the presence of the trace element copper and the reducing agent sodium ascorbate substantially increased the intestinal absorption of the polypeptide drug liraglutide. The reducing agent glutathione (GSH) in the presence of Zn^{2+} also showed improved liraglutide absorption albeit less pronounced than the composition comprising Cu^{2+}.

Example 7: Pharmacokinetic profiles of liraglutide after administration into mid-jejunum of Sprague Dawley rats

2.4 mg/kg of the polypeptide liraglutide were dosed into the mid-jejunum of anesthetized Sprague Dawley rats in the presence of the anionic absorption enhancer sodium dodecyl sulfate (SDS) (20 mg/ml) and the trace element $CuSO_4$ (1 mg/ml) with and without the reducing agent reduced glutathione (40 mg/ml).

Liraglutide	**Enhancer: Sodium dodecyl sulfate**	**Trace element: $CuSO_4$**	**Reducing agent: Reduced glutathione (GSH)**	**$AUC_{(0-t)}$ (µg/ml x min)**	**C_{max} (ng/ml)**
2.4 mg/kg into jejunum	20 mg/ml	1 mg/ml	-	5504 ± 5729	32
2.4 mg/kg into jejunum	20 mg/ml	1 mg/ml	40 mg/ml	49090 ± 23073	416

Table 7: Pharmacokinetic profiles of liraglutide formulations.

Conclusion: The combination of an absorption enhancer in the presence of the trace element copper and the reducing agent glutathione substantially increased the intestinal absorption of the polypeptide drug liraglutide.

Example 8: Pharmacodynamic profiles after insulin and liraglutide administration into mid-jejunum of Sprague Dawley rats

A combination of human insulin (22 IU/kg) and liraglutide (2.4 mg/kg) was dosed together into the mid-jejunum of Sprague Dawley rats in the presence of the absorption enhancer lauroyl carnitine chloride ("LCC") (50 mg/ml) and Na_2HPO_4 (40 mg/ml). A solution of the trace element

copper as $CuSO_4$ (1 mg/ml) and sodium ascorbate (10 mg/ml) was dosed 10 minutes prior to insulin and liraglutide into the mid-jejunum of rats. The results of this experiment are shown in Figure 2.

Conclusion: A combination of insulin and the GLP-1 receptor agonist liraglutide in the presence of lauroyl carnitine after predosing of Cu^{2+} and sodium ascorbate resulted in a substantial reduction of the blood glucose levels.

Example 9: Pharmacokinetic profile of the somatostatin analog octreotide after administration into ileum of Sprague Dawley rats

Octreotide is an octapeptide with very low oral bioavailability of less than 1%.

a) Octreotide was administered s.c. at a concentration of 1 mg/kg body weight to anesthetized rats (n=3).
b) Octreotide was dosed into distal small intestine (ileum) at a concentration of 0.92 mg/kg body weight to anesthetized rats (n=8). TRIS buffer was used to generate a neutral pH.

The octreotide plasma concentrations were determined using a commercial octreotide kit (AB Biolabs, USA, cat. number CEK 0110-01).

Octreotide	**Enhancer:** Lauroyl carnitine chloride	**Trace element:** $CuSO_4$	**Reducing agent:** Sodium ascorbate	**Buffering agent:** TRIS	**$AUC_{(0-90)}$** (ng/ml x min)	**C_{max}** (ng/ml)	**F (%)**
1 mg/kg s.c. (n=3)	-	-	-	-	10045 ± 1837	153.7 ± 29.8	100 ± 18.3
0.92 mg/kg ileum (n=8)	30 mg/ml	1 mg/ml	30 mg/ml	22.5 mg/ml	1504 ± 725	25.8 ± 14.2	16.3 ± 7.8

Table 8: Pharmacokinetic profiles of octreotide formulations.

Conclusion: An oral octreotide formulation according to the invention, comprising a copper(II) salt, sodium ascorbate as reducing agent and lauroyl carnitine chloride as an exemplary absorption enhancer, showed a markedly increased bioavailability.

Example 10: Pharmacokinetic profiles of leuprolide formulations after intestinal administration to Sprague Dawley rats

Leuprolide was dosed subcutaneously in volume of 1 ml/kg (final concentration 0.1 mg/ml leuprolide) to anaesthetized rats (n=3). Two formulations of leuprolide (final concentration 0.4 mg/kg) according to the invention were dosed into ileum of Sprague Dawley rats (n=5-6). Blood was taken from tail vessels at the time points 0, 10, 20, 40, 60, 90, 120 and 180 min after dosing. The leuprolide plasma concentrations were determined using commercial leuprolide kit (AB Biolabs, USA, cat. number CEK 0100-01).

Composition:
LEU001
1 mg/ml Leuprolide
30 mg/ml Lauroylcarnitine HCl
21 mg/ml TRIS
1 mg/ml $CuSO_4$
40 mg/ml Sodium ascorbate

Composition:
LEU002
1 mg/ml Leuprolide
30 mg/ml Sodium dodecyl sulfate
22 mg/ml TRIS
1 mg/ml $CuSO_4$
40 mg/ml reduced glutathione

Results: The maximal plasma concentrations of leuprolide in dose of 0.1 mg/kg s.c. reached 50-100 ng/ml with peak within 20-40 min. The application of leuprolide formulations in dose of 0.4 mg/kg into ileum resulted in relatively high leuprolide plasma concentrations in range of 40-500 ng/ml and peak within 10-60 min. The high plasma concentrations persisted up to 120 min after dosing. The mean relative bioavailability was 70% for LEU001 and 47% for LEU002 in comparison with s.c. administration.

	$AUC_{(0-t)}$ (ng/ml x min)	Cmax (ng/ml)	Tmax (min)	F (%)
Leuprolide s.c.	7771 ± 1514	78.9 ± 14.7	20-40	100 ± 19.5
LEU001 ileum	21840 ± 6735	202 ± 61.0	10-40	70 ± 21.7

LEU002 ileum	14695 ± 4251	133.2 ± 46.1	10-60	47 ± 13.7

Conclusion: Formulations according to the present invention comprising the peptide drug leuprolide, the trace element copper, a reducing agent and an absorption enhancer result in very high relative bioavailability.

Example 11: Pharmacokinetic profile of liraglutide formulations after intestinal administration to Sprague Dawley rats

Liraglutide formulations comprising different reducing agents in presence of the essential trace element copper (1 mg/ml) or increased amounts of zinc (5 mg/ml) and an absorption enhancer were dissolved in distilled water and dosed into ileum in volume of 0.4 ml/kg (final concentration 6 mg/ml) to anaesthetized rats. Blood was taken from tail vessels at the time points 0, 30, 60, 90, 120, 180 and 240 min after dosing. The liraglutide plasma concentrations were determined using commercial liraglutide kit (AB Biolabs, USA, cat. number CEK 0130-03). A formulation comprising liraglutide and sodium dodecyl sulfate without trace element and reducing agent served as control (LIRA-SDS).

Composition:
LIRA-SDS (control formulation)
6 mg/ml Liraglutide
20 mg/ml SDS

Composition:
LIRA001
6 mg/ml Liraglutide
40 mg/ml Sodium ascorbate
1 mg/ml $CuSO_4$
20 mg/ml SDS

Composition:
LIRA002
6 mg/ml Liraglutide
40 mg/ml reduced glutathione
40 mg/ml TRIS
1 mg/ml $CuSO_4$

20 mg/ml SDS

Composition:
LIRA003
6 mg/ml Liraglutide
40 mg/ml Cysteine
40 mg/ml TRIS
1 mg/ml $CuSO_4$
20 mg/ml SDS

Composition:
LIRA004
6 mg/ml Liraglutide
40 mg/ml N-Acetylcysteine
40 mg/ml TRIS
1 mg/ml $CuSO_4$
20 mg/ml SDS

Composition:
LIRA005
6 mg/ml Liraglutide
40 mg/ml alpha-Lipoic acid
80 mg/ml Chremophor EL
40 mg/ml TRIS
1 mg/ml $CuSO_4$
20 mg/ml SDS

Composition:
LIRA006
6 mg/ml Liraglutide
10 mg/ml Fe(2)gluconate
10 mg/ml TRIS
1 mg/ml $CuSO_4$
20 mg/ml SDS

Composition:
LIRA007

6 mg/ml Liraglutide
10 mg/ml TRIS
5 mg/ml Fe(2)gluconate
5 mg/ml $ZnSO_4$
20 mg/ml SDS

Composition:
LIRA008
6 mg/ml Liraglutide
40 mg/ml Lactose (reducing sugar)
5 mg/ml TRIS
5 mg/ml $ZnSO_4$
20 mg/ml SDS

Results:

	$AUC_{(0-t)}$ (ng/ml x min)	Cmax (ng/ml)	Tmax (min)
LIRA-SDS	1304 ± 298	12 ± 1	40-90
LIRA001	11198 ± 2389	62.1 ± 15.3	60-120
LIRA002	19256 ± 8762	137.9 ± 67.2	60-120
LIRA003	10153 ± 4026	120.2 ± 87.3	60-240
LIRA004	29891 ± 22388	170.3 ± 132	90-120
LIRA005	2134 ± 489	19.8 ± 10.3	30-120
LIRA006	16368 ± 3365	87.5 ± 18.4	60-120
LIRA007	55671 ± 9189	441.7 ± 112.1	60-180
LIRA008	14481 ± 4324	80.3 ± 25.7	90-120

Conclusion: Compositions with a GLP-1 peptide drug, the trace element copper, an absorption enhancer and various reducing agents showed up to 23-fold increased oral bioavailability (shown as AUC) compared with a control formulation only comprising an absorption enhancer and the GLP-1 peptide. Reducing agents with a functional thiol group such as reduced glutathione or N-acetyl cysteine showed especially high efficacy in presence of copper. A composition comprising 5 mg/ml zinc, the reducing agent Fe(2)gluconate and an absorption enhancer increased AUC 42-fold compared to control.

Example 12: Pharmacokinetic profiles of PTH(1-34) formulations after intestinal administration to Sprague Dawley rats.

Teriparatide (PTH1-34) was dosed subcutaneously in volume of 1 ml/kg (final concentration 0.024 mg/ml teriparatide) to anaesthetized rats. TER001, TER002, TER003, TER004, TER007, TER008, TER009 and TER010 were dosed into ileum in volume of 0.4 ml/kg (final concentration 0.24 mg/ml teriparatide) to anaesthetized rats. Blood was taken from tail vessels at the time points 0, 10, 20, 40, 60, 90, 120 and 180 min after dosing. The teriparatide plasma concentrations were determined using commercial pTH (1-34) human ELISA kit (Biovendor, EU, cat. number RS-1163.0001).

Composition:
TER001
0.24 mg/ml PTH(1-34)
30 mg/ml Lauroylcarnitine HCl
21 mg/ml TRIS
1 mg/ml $CuSO_4$
40 mg/ml Sodium ascorbate

Composition:
TER002
0.24 mg/ml PTH(1-34)
30 mg/ml Sodium dodecyl sulfate
22 mg/ml TRIS
5 mg/ml $ZnSO_4$
40 mg/ml reduced glutathione

Composition:
TER003
0.38 mg/ml PTH(1-34)
30 mg/ml Lauroylcarnitine HCl
7.5 mg/ml TRIS
5 mg/ml Mannitol
1 mg/ml $CuSO_4$
40 mg/ml Sodium ascorbate
(Final pH = 5.8)

Composition:
TER004
0.38 mg/ml PTH(1-34)
30 mg/ml Lauroylcarnitine HCl
30 mg/ml TRIS
5 mg/ml Mannitol
1 mg/ml $CuSO_4$
40 mg/ml Sodium ascorbate
(Final pH = 8.0)

Composition:
TER007
0.38 mg/ml PTH(1-34)
30 mg/ml Lauroylcarnitine HCl
7.5 mg/ml TRIS
5 mg/ml Mannitol
5 mg/ml $ZnSO_4$
6 mg/ml Fe(2)gluconate
(Final pH = 5.1)

Composition:
TER008
0.38 mg/ml PTH(1-34)
30 mg/ml Lauroylcarnitine HCl
30 mg/ml TRIS
5 mg/ml Mannitol
5 mg/ml $ZnSO_4$
6 mg/ml Fe(2)gluconate
(Final pH = 8.3)

Composition:
TER009
0.375 mg/ml PTH(1-34)
30 mg/ml Lauroylcarnitine HCl
40 mg/ml reduced glutathione
1 mg/ml $CuSO_4$
(Final pH = 2.5)

Composition:
TER010
0.375 mg/ml PTH(1-34)
35 mg/ml Sucrose laurate
5 mg/ml $ZnSO_4$
5 mg/ml Fe(2)gluconate
(Final pH = 4.9)

Results: The maximal plasma concentrations of teriparatide in dose of 0.024 mg/kg s.c. reached 0.67-4.04 ng/ml with peak at 10 min. The application of TER001 formulation in dose of 0.096 mg/kg into ileum resulted in variable teriparatide plasma concentrations in range of 0.07-10.01 ng/ml and peak at 10 min in most of animals. The teriparatide plasma concentrations after TER002 administration were lower, but less variable, with peak 10 min in most of rats. The mean relative bioavailability was 34% for TER001 and 12% for TER002 in comparison with s.c. administration. The results for these formulations as well as the further tested formulations TER003, TER004 and TER007 to TER010 are summarized in the following table:

	$AUC_{(0-t)}$ (ng/ml x min)	Cmax (ng/ml)	Tmax (min)	F (%)	Half-life (min)
PTH(1-34) s.c.	136 ± 32	2.8 ± 0.8	10	100 ± 23	44 ± 8
TER001	184 ± 136	2.8 ± 1.9	10-90	34 ± 25	-
TER002	64 ± 16	0.9 ± 0.1	10-90	12 ± 3	-
TER003	302 ± 120	3.5 ± 1.1	10-90	35 ± 14	90 ± 8
TER004	145 ± 20	2.4 ± 0.5	10-20	17 ± 2	67 ± 6
TER007	79 ± 16	1.0 ± 0.2	10-40	9 ± 2	63 ± 14
TER008	46 ± 16	0.6 ± 0.2	10-40	5 ± 2	153 ± 84
TER009	178 ± 67	3.8 ± 1.0	10	21 ± 8	45 ± 6
TER010	87 ± 23	1.2 ± 0.4	34	10 ± 3	77 ± 5

Conclusion: Significant oral bioavailability could be achieved with formulations according to the invention at different pH values ranging from 2.5 to 8.0. Further, the presence of trace elements resulted in increased plasma half-life of PTH(1-34) compared to s.c. administration, most likely due to a prolonged gastro-intestinal absorption phase.

Example 13: Pharmacokinetic profile of human Growth Hormone formulation after intestinal administration to Sprague Dawley rats

Human growth hormone was dosed subcutaneously in volume of 1 ml/kg (final concentration 0.2 mg/ml human growth hormone) to anaesthetized rats. HGH001 was dosed into ileum in volume of 0.4 ml/kg (final concentration 2 mg/ml human growth hormone) to anaesthetized rats. Blood was taken from tail vessels at the time points 0, 15, 30, 60, 90, 120, 180 and 240 min after dosing. The human growth hormone plasma concentrations were determined using commercial growth hormone sensitive human ELISA kit (Biovendor, EU, cat. number RMEE022).

Composition:
HGH001
2 mg/ml hGH
30 mg/ml Sodium dodecyl sulfate
1 mg/ml $CuSO_4$
40 mg/ml Sodium ascorbate

Results: The mean maximal human growth hormone plasma concentration after s.c. treatment reached 44 ng/ml with peak 30 min after dosing. The mean plasma human growth hormone level after administration of HGH001 formulation into ileum was 4 ng/ml with the peak 15 min after application. The relative bioavailability of the formulation was 1%.

	$AUC_{(0-t)}$ (ng/ml x min)	Cmax (ng/ml)	Tmax (min)	F (%)
hGH s.c.	7630 ± 471	44.0 ± 2.5	30	100 ± 6
HGH001	256 ± 177	4.0 ± 2.0	15	1 ± 0.6

Example 14: Pharmacokinetic profiles of desmopressin acetate formulations after administration to duodenum of Sprague Dawley rats

Desmopressin formulations were dissolved in distilled water and dosed into duodenum in volume of 0.4 ml/kg (final concentration 0.2 mg/ml desmopressin) to anaesthetized rats. Blood was taken from tail vessels at the time points 0, 30, 60, 90, 120, 180 and 240 min after dosing. The desmopressin plasma concentrations were determined using commercial desmopressin EIA kit (AB Biolabs, USA, cat. number CEK 0120-01).

Composition:
DES001
0.2 mg/ml Desmopressin acetate

Composition:
DES002
0.2 mg/ml Desmopressin acetate
50 mg/ml Sodium ascorbate
1 mg/ml $CuSO_4$

Composition:
DES003
0.2 mg/ml Desmopressin acetate
50 mg/ml Sodium ascorbate
1 mg/ml $CuSO_4$
40 mg/ml TRIS
50 mg/ml Lauroyl carnitine HCl

Composition:
DES004
0.2 mg/ml Desmopressin acetate
50 mg/ml Sodium ascorbate
1 mg/ml $CuSO_4$
2 mg/ml TRIS
25 mg/ml n-Dodecyl-b-D-maltoside
25 mg/ml n-Octyl-b-D-glucopyranoside

Composition:
DES005
0.2 mg/ml Desmopressin acetate
50 mg/ml Sodium ascorbate
1 mg/ml $CuSO_4$
50 mg/ml SNAC

Composition:
DES006

0.2 mg/ml Desmopressin acetate

10 mg/ml TRIS

5 mg/ml $ZnSO_4$

5 mg/ml Fe(2)gluconate

Composition:

DES007

0.2 mg/ml Desmopressin acetate

50 mg/ml Sodium ascorbate

1 mg/ml $CuSO_4$

50 mg/ml Methyl-b-cyclodextrin

Results:

	Delta $AUC_{(0-t)}$ (ng/ml x min)	Cmax (ng/ml)	Tmax (min)
DES001	98 ± 43	2.0 ± 0.4	60-90
DES002	215 ± 52	2.7 ± 0.4	30-120
DES003	1536 ± 422	12.3 ± 3.3	30-60
DES004	1676 ± 576	12.2 ± 4.0	30-60
DES005	221 ± 66	3.0 ± 0.6	60-90
DES006	109 ± 26	2.0 ± 0.5	30-240
DES007	124 ± 20	2.9 ± 0.6	60-240

Conclusion: The addition of essential trace elements and a reducing agent to oral desmopressin formulations increased its oral bioavailability and also reduced variability. Further addition of absorption enhancers increased AUC levels up to 17 fold compared to unformulated desmopressin.

Example 15: Pharmacokinetic profile of exenatide formulations after oral administration to Beagle dogs

Exenatide was dosed subcutaneously in volume of 2x40 µl/dog (2x10 µg/dog) to two injection sites in the area of shoulder blade. EXE001 capsules were dosed orally (n=3) directly on the root of the tongue. Administered capsule was washed down by 5 ml of water via a syringe to ensure that the drug was correctly swallowed and to ensure complete oesophageal clearance. The swallowing of the whole administered dose was checked. Blood was taken by

venepuncture from v. cephalica antebrachii at the time points 0, 30, 60, 90, 120, 150, 180, 240, 300 and 360 min after oral dosing. The exenatide plasma concentrations were determined using commercial exenatide kit (AB Biolabs, USA, cat. number SEK 0130-01).

Composition (per capsule):
EXE001
HPMCP ARCaps (CapsCanada) size 0
0.57 mg Exenatide
50 mg Mannitol
160 mg Lauroyl carnitine HCl
210 mg TRIS
100 mg Sodium ascorbate
2 mg $CuSO_4$

Results:

	$AUC_{(0-t)}$ (ng/ml x min)	Cmax (ng/ml)	Tmax (min)	F (%)
EXE s.c.	1001 ± 59	6.2 ± 1.0	30-240	100 ± 5.9
EXE001	1140 ± 625	3.4 ± 1.9	120-180	4.0 ± 2.2

Conclusion: A solid gastric resistant oral dosage form comprising a GLP-1 peptide agonist, the trace element copper, a reducing agent and an absorption enhancer resulted in significant oral bioavailability.

Example 16: *In vitro* compatibility of different absorption enhancers and trace elements

Solid dry powder mixtures of desmopressin acetate, zinc sulfate and different absorption enhancers were prepared and dissolved in 2 ml aqua purificata. Visual examination was performed to observe either a clear solution or visible precipitation. The results of these experiments are summarized in the following table:

Polypeptide	**Trace element (5 mg/ml)**	**Absorption enhancer (10 mg/ml)**	**Dissolution in aqueous medium (2 ml)**
Desmopressin	$ZnSO_4$	Sodium caprate	Precipitation

Desmopressin	$ZnSO_4$	Sodium caprylate	Precipitation
Desmopressin	$ZnSO_4$	Lauroyl sarcosinate	Precipitation
Desmopressin	$ZnSO_4$	Cholic acid	Precipitation
Desmopressin	$ZnSO_4$	Sodium cholate	Precipitation
Desmopressin	$ZnSO_4$	Chitosan	Precipitation
Desmopressin	$ZnSO_4$	Sodium dodecyl sulfate	Clear solution
Desmopressin	$ZnSO_4$	Lauroyl carnitine HCl	Clear solution
Desmopressin	$ZnSO_4$	Sucrose laurate	Clear solution
Desmopressin	$ZnSO_4$	n-Dodecyl-b-D-maltoside	Clear solution
Desmopressin	$ZnSO_4$	n-Octyl-b-D-glucopyranoside	Clear solution
Desmopressin	$ZnSO_4$	Labrasol	Clear solution
Desmopressin	$ZnSO_4$	EDTA	Clear solution

Example 17: Solid compositions comprising a polypeptide, the trace element zinc or copper, a reducing agent and optionally an absorption enhancer

Solid dry powder mixtures of PTH(1-34), a zinc or copper salt, different reducing agents and different absorption enhancers were prepared and dissolved in 5 ml aqua purificata. The pH of the solutions was measured immediately at RT. The results of these experiments are summarized in the following table:

Polypeptide	**Trace element (10 mg)**	**Absorption enhancer (10 mg)**	**Reducing agent (50 mg)**	**Buffer**	**Dissolution pH in 5 ml Aqua purificata**
PTH(1-34)	$ZnSO_4$	Lauroyl carnitine	Lactose	-	3.1
PTH(1-34)	$ZnSO_4$	Lauroyl carnitine	Lactose	10 mg TRIS	7.5
PTH(1-34)	$ZnSO_4$	Sucrose laurate	Lactose	-	6.5
PTH(1-34)	$ZnCl_2$	Lauroyl carnitine	Lactose		2.9
PTH(1-34)	$ZnCl_2$	Lauroyl carnitine	Lactose	10 mg TRIS	7.1
PTH(1-34)	$ZnCl_2$	Lauroyl carnitine	Gelatin capsule	-	4.3
PTH(1-34)	$ZnCl_2$	Lauroyl carnitine	Gelatin capsule	10 mg	6.8

				TRIS	
PTH(1-34)	$ZnCl_2$	Lauroyl carnitine	MCC	-	3.5
PTH(1-34)	$ZnCl_2$	Lauroyl carnitine	MCC	5 mg TRIS	6.3
PTH(1-34)	$CuSO_4$	Lauroyl carnitine	MCC	-	3.6
PTH(1-34)	$CuSO_4$	Lauroyl carnitine	Gelatin capsule	-	4.4
PTH(1-34)	$CuSO_4$	Lauroyl carnitine	Lactose		3.2
PTH(1-34)	$CuSO_4$	Lauroyl carnitine	Lactose	10 mg TRIS	6.5
PTH(1-34)	$CuSO_4$	Sucrose laurate	Lactose	-	5.0
Desmopressin	$ZnSO_4$	Citric acid	Lactose	-	2.7
Desmopressin	$ZnSO_4$	-	Lactose	-	5.5
Desmopressin	$CuSO_4$	Citric acid	Lactose	-	2.6
Desmopressin	$CuSO_4$	-	Lactose	-	4.7

CLAIMS

1. A peptide or protein drug having a molecular weight of equal to or less than about 50 kDa for use as a medicament, wherein said peptide or protein drug is to be administered orally in combination with:
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a pharmaceutically acceptable reducing agent.

2. A pharmaceutically acceptable copper salt/complex for use in therapy, wherein said copper salt/complex is to be administered orally in combination with:
a pharmaceutically acceptable reducing agent; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

3. A pharmaceutically acceptable zinc salt/complex for use in therapy, wherein said zinc salt/complex is to be administered orally in combination with:
a pharmaceutically acceptable reducing agent; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

4. A pharmaceutically acceptable reducing agent for use in therapy, wherein said reducing agent is to be administered orally in combination with:
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

5. A pharmaceutical composition comprising:
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa;
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and

a pharmaceutically acceptable reducing agent.

6. A pharmaceutical dosage form comprising:
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa;
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a pharmaceutically acceptable reducing agent;
wherein the peptide or protein drug is physically separated from the pharmaceutically acceptable copper salt/complex and the pharmaceutically acceptable zinc salt/complex within the pharmaceutical dosage form.

7. The peptide or protein drug for use according to claim 1 or the copper salt/complex for use according to claim 2 or the zinc salt/complex for use according to claim 3 or the reducing agent for use according to claim 4 or the pharmaceutical composition of claim 5 or the pharmaceutical dosage form of claim 6, wherein the peptide or protein drug has a molecular weight of about 500 Da to about 30 kDa.

8. The peptide or protein drug for use according to claim 1 or the copper salt/complex for use according to claim 2 or the zinc salt/complex for use according to claim 3 or the reducing agent for use according to claim 4 or the pharmaceutical composition of claim 5 or the pharmaceutical dosage form of claim 6, wherein the peptide or protein drug has a molecular weight of about 1 kDa to about 10 kDa.

9. The peptide or protein drug for use according to claim 1 or the copper salt/complex for use according to claim 2 or the zinc salt/complex for use according to claim 3 or the reducing agent for use according to claim 4 or the pharmaceutical composition of claim 5 or the pharmaceutical dosage form of claim 6, wherein the peptide or protein drug is selected from insulin, an insulin analog, insulin lispro, insulin PEGlispro, insulin aspart, insulin glulisine, insulin glargine, insulin detemir, NPH insulin, insulin degludec, B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin,

B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B16H B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin, B29K(N(ε)octadecanedioyl) A14E B25H desB30 human insulin, GLP-1, a GLP-1 analog, an acylated GLP-1 analog, a diacylated GLP-1 analog, a GLP-1 agonist, semaglutide, liraglutide, exenatide, exendin-4, lixisenatide, taspoglutide, albiglutide, dulaglutide, langlenatide, GLP-1(7-37), GLP-1(7-36)NH_2, a dual agonist of the GLP-1 receptor and the glucagon receptor, oxyntomodulin, GLP-2, a GLP-2 analog, a GLP-2 agonist, teduglutide, elsiglutide, amylin, an amylin analog, pramlintide, a somatostatin analog, octreotide, lanreotide, pasireotide, goserelin, buserelin, leptin, a leptin analog, metreleptin, peptide YY, a peptide YY analog, glatiramer, leuprolide, desmopressin, osteocalcin, an osteocalcin analog or derivative, human growth hormone, a human growth hormone analog, a glycopeptide antibiotic, a glycosylated cyclic or polycyclic nonribosomal peptide antibiotic, vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin, decaplanin, bortezomib, cosyntropin, chorionic gonadotropin, menotropin, sermorelin, luteinizing-hormone-releasing hormone, somatropin, calcitonin, calcitonin-salmon, pentagastrin, oxytocin, neseritide, anakinra, enfuvirtide, pegvisomant, dornase alfa, lepirudin, anidulafungin, eptifibatide, interferon alfacon-1, interferon alpha-2a, interferon alpha-2b, interferon beta-1a, interferon beta-1b, interferon gamma-1b, peginterferon alfa-2a, peginterferon alfa-2b, peginterferon beta-1a, fibrinolysin, vasopressin, aldesleukin, epoetin alfa, darbepoetin alfa, epoetin beta, epoetin delta, epoetin omega, epoetin zeta, filgrastim, interleukin-11, cyclosporine, glucagon, urokinase, viomycin, thyrotropin-releasing hormone, leucine-enkephalin, methionine-enkephalin, substance P, adrenocorticotropic hormone, parathyroid hormone, a parathyroid hormone fragment, teriparatide, PTH(1-31), PTH(2-34), parathyroid hormone-related protein, abaloparatide, linaclotide, carfilzomib, icatibant, ecallantide, cilengitide, a prostaglandin F2α receptor modulator, PDC31, and pharmaceutically acceptable salts thereof.

10. The peptide or protein drug for use according to any one of claims 1 or 7 to 9, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable copper salt/complex.

11. The peptide or protein drug for use according to any one of claims 1 or 7 to 10 or the copper salt/complex for use according to any one of claims 2 or 7 to 9 or the reducing agent for use according to any one of claims 4 or 7 to 9 or the pharmaceutical composition of any one of claims 5 or 7 to 9 or the pharmaceutical dosage form of any

one of claims 6 to 9, wherein said copper salt/complex is a copper(I) salt/complex or a copper(II) salt/complex.

12. The peptide or protein drug for use according to claim 11 or the copper salt/complex for use according to claim 11 or the reducing agent for use according to claim 11 or the pharmaceutical composition of claim 11 or the pharmaceutical dosage form of claim 11, wherein said copper salt/complex is a copper(II) salt/complex selected from copper sulfate, copper carbonate, a copper(II) amino acid complex, copper(II) lysine complex, copper(II) glycinate, copper(II) EDTA complex, copper(II) chitosan complex, copper(II) citrate, copper(II) gluconate, copper(II) lactate, copper lactate gluconate, and copper(II) orotate.

13. The peptide or protein drug for use according to claim 11 or the copper salt/complex for use according to claim 11 or the reducing agent for use according to claim 11 or the pharmaceutical composition of claim 11 or the pharmaceutical dosage form of claim 11, wherein said copper salt/complex is a copper(I) salt/complex selected from copper(I) chloride and copper(I) acetate.

14. The peptide or protein drug for use according to any one of claims 1 or 7 to 9, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable zinc salt/complex.

15. The peptide or protein drug for use according to any one of claims 1, 7 to 9 or 14 or the zinc salt/complex for use according to any one of claims 3 or 7 to 9 or the reducing agent for use according to any one of claims 4 or 7 to 9 or the pharmaceutical composition of any one of claims 5 or 7 to 9 or the pharmaceutical dosage form of any one of claims 6 to 9, wherein said zinc salt/complex is a zinc(II) salt/complex.

16. The peptide or protein drug for use according to claim 15 or the zinc salt/complex for use according to claim 15 or the reducing agent for use according to claim 15 or the pharmaceutical composition of claim 15 or the pharmaceutical dosage form of claim 15, wherein said zinc salt/complex is a zinc(II) salt/complex selected from zinc sulfate, zinc chloride, zinc acetate, zinc oxide, zinc ascorbate, zinc caprylate, zinc gluconate, zinc stearate, zinc carbonate, zinc orotate, a zinc amino acid complex, zinc glycinate, zinc arginate, zinc picolinate, zinc pidolate, zinc carnosine, zinc undecanoate, zinc undecylenate, zinc methionine, zinc lactate, and zinc lactate gluconate.

17. The peptide or protein drug for use according to any one of claims 1 or 7 to 16 or the copper salt/complex for use according to any one of claims 2, 7 to 9 or 11 to 13 or the zinc salt/complex for use according to any one of claims 3, 7 to 9, 15 or 16 or the reducing agent for use according to any one of claims 4, 7 to 9, 11 to 13, 15 or 16 or the pharmaceutical composition of any one of claims 5, 7 to 9, 11 to 13, 15 or 16 or the pharmaceutical dosage form of any one of claims 6 to 9, 11 to 13, 15 or 16, wherein said reducing agent is selected from ascorbic acid, reduced glutathione, cysteine, N-acetylcysteine, histidine, glycine, arginine, gelatin, uric acid, a reducing sugar, glucose, glyceraldehyde, galactose, fructose, ribose, xylose, sorbose, lactose, maltose, cellobiose, a glucose polymer, starch, a starch derivative, glucose syrup, maltodextrin, dextrin, dextrose, dextran, cellulose, microcrystalline cellulose, mannitol, α-tocopherol, vitamin A, α-lipoic acid, dihydro-α-lipoic acid, oxalic acid, phytic acid, a tannin, propyl gallate, butylated hydroxy toluene, butylated hydroxy anisole, sodium metabisulfite, povidone, crospovidone, an aldehyde, formaldehyde, acetaldehyde, furfuraldehyde, a dialdehyde, glyoxal, a phenolic compound, phenol, a polyphenol, salicylic acid, a salicylic acid derivative, an iron(II) salt/complex, diphosphate, disodiumdiphosphate, trisodiumdiphosphate, tetrasodiumdiphosphate, tetrapotassiumdiphosphate, dicalciumdiphosphate, calciumdihydrogendiphophate, phosphate, dipotassium hydrogen phosphate, calcium phosphate, calcium hydrogen phosphate, a thiol-bearing compound, a thiomer, and pharmaceutically acceptable salts thereof.

18. The peptide or protein drug for use according to claim 17 or the copper salt/complex for use according to claim 17 or the zinc salt/complex for use according to claim 17 or the reducing agent for use according to claim 17 or the pharmaceutical composition of claim 17 or the pharmaceutical dosage form of claim 17, wherein said reducing agent is an iron(II) salt/complex selected from iron(II) gluconate, iron(II) orotate, iron(II) tartrate, iron(II) fumarate, iron(II) sulfate, iron(II) lactate, iron(II) lactate gluconate, iron(II) acetate, iron(II) carbonate, iron(II) citrate, iron(II) oxide, iron(II) hydroxide, iron(II) ascorbate, an iron(II) amino acid complex, and ferrous bis-glycinate.

19. The peptide or protein drug for use according to any one of claims 1 or 7 to 18 or the copper salt/complex for use according to any one of claims 2, 7 to 9, 11 to 13 or 18 or the zinc salt/complex for use according to any one of claims 3, 7 to 9 or 15 to 18 or the reducing agent for use according to any one of claims 4, 7 to 9, 11 to 13 or 15 to 18 or the pharmaceutical composition of any one of claims 5, 7 to 9, 11 to 13 or 15 to 18 or the pharmaceutical dosage form of any one of claims 6 to 9, 11 to 13 or 15 to 18, wherein said peptide or protein drug or said copper salt/complex or said zinc

salt/complex or said reducing agent is to be administered orally in combination with an absorption enhancer, or wherein said pharmaceutical composition or said pharmaceutical dosage form further comprises an absorption enhancer.

20. The peptide or protein drug for use according to claim 19 or the copper salt/complex for use according to claim 19 or the zinc salt/complex for use according to claim 19 or the reducing agent for use according to claim 19 or the pharmaceutical composition of claim 19 or the pharmaceutical dosage form of claim 19, wherein said absorption enhancer is selected from C_{8-20} alkanoyl carnitine, salicylic acid, a salicylic acid derivative, 3-methoxysalicylic acid, 5-methoxysalicylic acid, homovanillic acid, a C_{8-20} alkanoic acid, citric acid, tartaric acid, a fatty acid acylated amino acid, a C_{8-20} alkanoyl sarcosinate, an alkylsaccharide, a C_{8-10} alkylpolysaccharide, n-octyl-beta-D-glucopyranoside, n-dodecyl-beta-D-maltoside, n-tetradecyl-beta-D-maltoside, tridecyl-beta-D-maltoside, sucrose laurate, sucrose myristate, sucrose palmitate, sucrose cocoate, sucrose mono-dodecanoate, sucrose mono-tridecanoate, sucrose mono-tetradecanoate, a coco-glucoside, a cyclodextrine, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, methyl-β-cyclodextrin, hydroxypropyl β-cyclodextrin, sulfobutylether β-cyclodextrin, N-[8-(2-hydroxybenzoyl)amino]caprylic acid, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate, a sodium N-[8-(2-hydroxybenzoyl)amino]caprylate derivative, a thiomer, a mucoadhesive polymer having a vitamin B partial structure, a calcium chelating compound, ethylenediaminetetraacetic acid, ethylene glycol tetraacetic acid, polyacrylic acid, cremophor EL, chitosan, N,N,N-trimethyl chitosan, benzalkonium chloride, bestatin, cetylpyridinium chloride, cetyltrimethylammonium bromide, a C_{2-20} alkanol, a C_{8-20} alkenol, a C_{8-20} alkenoic acid, dextran sulfate, diethyleneglycol monoethyl ether, 1-dodecylazacyclo-heptan-2-one, caprylocaproyl polyoxylglycerides, ethyl caprylate, glyceryl monolaurate, lysophosphatidylcholine, menthol, a C_{8-20} alkylamine, a C_{8-20} alkenylamine, phosphatidylcholine, a poloxamer, polyethylene glycol monolaurate, polyoxyethylene, polypropylene glycol monolaurate, a polysorbate, cholic acid, a deoxycholate, sodium glycocholate, sodium glycodeoxycholate, sodium lauryl sulfate, sodium decyl sulfate, sodium octyl sulfate, sodium laureth sulfate, N-lauryl sarcosinate, decyltrimethyl ammonium bromide, benzyldimethyl dodecyl ammonium chloride, myristyltrimethyl ammonium chloride, dodecyl pyridinium chloride, decyldimethyl ammonio propane sulfonate, myristyldimethyl ammonio propane sulfonate, palmityldimethyl ammonio propane sulfonate, ChemBetaine CAS, ChemBetaine Oleyl, Nonylphenoxypolyoxyethylene, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, sorbitan monooleate, Triton X-100, hexanoic acid, heptanoic acid, methyl laurate,

isopropyl myristate, isopropyl palmitate, methyl palmitate, diethyl sebaccate, sodium oleate, urea, lauryl amine, caprolactam, methyl pyrrolidone, octyl pyrrolidone, methyl piperazine, phenyl piperazine, Carbopol 934P, glyccyrhetinic acid, bromelain, pinene oxide, limonene, cineole, octyl dodecanol, fenchone, menthone, trimethoxy propylene methyl benzene, a cell-penetrating peptide, KLAKLAK, polyarginine, penetratin, HIV-1 Tat, macrogol-15-hydroxystearate, Solutol HS 15, CriticalSorb, a taurocholate, a taurodeoxycholate, a sulfoxide, decyl methyl sulfoxide, dimethyl sulfoxide, cyclopentadecalactone, 8-(N-2-hydroxy-5-chloro-benzoyl)-amino-caprylic acid, N-(10-[2-hydroxybenzoyl]amino)decanoic acid, dodecyl-2-N,N-dimethylamino propionate, D-α-tocopheryl polyethylene glycol-1000 succinate, and pharmaceutically acceptable salts thereof.

21. The peptide or protein drug for use according to claim 20 or the copper salt/complex for use according to claim 20 or the zinc salt/complex for use according to claim 20 or the reducing agent for use according to claim 20 or the pharmaceutical composition of claim 20 or the pharmaceutical dosage form of claim 20, wherein said absorption enhancer is a fatty acid acylated amino acid selected from sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methioninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, sodium lauroyl sarcosinate, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-

L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, N-decanoyl-L-sarcosine, sodium oleoyl sarcosinate, sodium N-decylleucine, sodium stearoyl glutamate, sodium myristoyl glutamate, sodium lauroyl glutamate, sodium cocoyl glutamate, sodium cocoyl glycinate, sodium N-decyl leucine, sodium cocoyl glycine, sodium cocoyl glutamate, sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methinoninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, Sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, sodium oleoyl sarcosinate, and pharmaceutically acceptable salts thereof.

22. The peptide or protein drug for use according to claim 19 or the copper salt/complex for use according to claim 19 or the zinc salt/complex for use according to claim 19 or the reducing agent for use according to claim 19 or the pharmaceutical composition of

claim 19 or the pharmaceutical dosage form of claim 19, wherein said absorption enhancer is sodium N-[8-(2-hydroxybenzoyl)amino]caprylate.

23. The pharmaceutical composition of any one of claims 5, 7 to 9, 11 to 13 or 15 to 22, wherein said pharmaceutical composition is a solid composition or a liquid composition that contains less than about 5% (v/v) of water.

24. The pharmaceutical composition of any one of claims 19 to 23 or the pharmaceutical dosage form of any one of claims 19 to 23, wherein said pharmaceutical composition or said pharmaceutical dosage form comprises:
the copper salt/complex in an amount of about 0.1 mg to about 5 mg per dosage unit, and/or the zinc salt/complex in an amount of about 0.1 mg to about 50 mg per dosage unit;
the reducing agent in an amount of about 1 mg to about 1000 mg per dosage unit; and
the absorption enhancer in an amount of about 10 mg to about 1000 mg per dosage unit.

25. Use of a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa in the preparation of a medicament which is to be administered orally in combination with:
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a pharmaceutically acceptable reducing agent.

26. Use of a pharmaceutically acceptable copper salt/complex in the preparation of a medicament which is to be administered orally in combination with:
a pharmaceutically acceptable reducing agent; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

27. Use of a pharmaceutically acceptable zinc salt/complex in the preparation of a medicament which is to be administered orally in combination with:
a pharmaceutically acceptable reducing agent; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

28. Use of a pharmaceutically acceptable reducing agent in the preparation of a medicament which is to be administered orally in combination with:
a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex; and
a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa.

29. A method of treating or preventing a disease/disorder, the method comprising orally administering, to a subject in need thereof, a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex, and a pharmaceutically acceptable reducing agent.

30. A method of orally delivering a peptide or protein drug having a molecular weight of equal to or less than about 50 kDa, the method comprising orally administering said peptide or protein drug in combination with a pharmaceutically acceptable copper salt/complex and/or a pharmaceutically acceptable zinc salt/complex and with a pharmaceutically acceptable reducing agent to a subject in need thereof.

31. The use of any one of claims 25 to 28 or the method of claim 29 or 30, wherein the peptide or protein drug has a molecular weight of about 500 Da to about 30 kDa.

32. The use of any one of claims 25 to 28 or 31 or the method of any one of claims 29 to 31, wherein the peptide or protein drug has a molecular weight of about 1 kDa to about 10 kDa.

33. The use of any one of claims 25 to 28 or the method of claim 29 or 30, wherein the peptide or protein drug is selected from insulin, an insulin analog, insulin lispro, insulin PEGlispro, insulin aspart, insulin glulisine, insulin glargine, insulin detemir, NPH insulin, insulin degludec, B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu) A14E B25H desB30 human insulin, B29K(N(ε)octadecanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B25H desB30 human insulin, B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin, B29K(N(ε)hexadecanedioyl-γ-L-Glu) A14E B16H B25H desB30 human insulin,

B29K(N(ε)eicosanedioyl-γ-L-Glu-OEG-OEG) A14E B16H B25H desB30 human insulin, B29K(N(ε)octadecanedioyl) A14E B25H desB30 human insulin, GLP-1, a GLP-1 analog, an acylated GLP-1 analog, a diacylated GLP-1 analog, a GLP-1 agonist, semaglutide, liraglutide, exenatide, exendin-4, lixisenatide, taspoglutide, albiglutide, dulaglutide, langlenatide, GLP-1(7-37), GLP-1(7-36)NH_2, a dual agonist of the GLP-1 receptor and the glucagon receptor, oxyntomodulin, GLP-2, a GLP-2 analog, a GLP-2 agonist, teduglutide, elsiglutide, amylin, an amylin analog, pramlintide, a somatostatin analog, octreotide, lanreotide, pasireotide, goserelin, buserelin, leptin, a leptin analog, metreleptin, peptide YY, a peptide YY analog, glatiramer, leuprolide, desmopressin, osteocalcin, an osteocalcin analog or derivative, human growth hormone, a human growth hormone analog, a glycopeptide antibiotic, a glycosylated cyclic or polycyclic nonribosomal peptide antibiotic, vancomycin, teicoplanin, telavancin, bleomycin, ramoplanin, decaplanin, bortezomib, cosyntropin, chorionic gonadotropin, menotropin, sermorelin, luteinizing-hormone-releasing hormone, somatropin, calcitonin, calcitonin-salmon, pentagastrin, oxytocin, neseritide, anakinra, enfuvirtide, pegvisomant, dornase alfa, lepirudin, anidulafungin, eptifibatide, interferon alfacon-1, interferon alpha-2a, interferon alpha-2b, interferon beta-1a, interferon beta-1b, interferon gamma-1b, peginterferon alfa-2a, peginterferon alfa-2b, peginterferon beta-1a, fibrinolysin, vasopressin, aldesleukin, epoetin alfa, darbepoetin alfa, epoetin beta, epoetin delta, epoetin omega, epoetin zeta, filgrastim, interleukin-11, cyclosporine, glucagon, urokinase, viomycin, thyrotropin-releasing hormone, leucine-enkephalin, methionine-enkephalin, substance P, adrenocorticotropic hormone, parathyroid hormone, a parathyroid hormone fragment, teriparatide, PTH(1-31), PTH(2-34), parathyroid hormone-related protein, abaloparatide, linaclotide, carfilzomib, icatibant, ecallantide, cilengitide, a prostaglandin F2α receptor modulator, PDC31, and pharmaceutically acceptable salts thereof.

34. The use of any one of claims 25 or 31 to 33 or the method of any of claims 29 to 33, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable copper salt/complex.

35. The use of any one of claims 25 to 28 or 31 to 34 or the method of any one of claims 29 to 34, wherein said copper salt/complex is a copper(I) salt/complex or a copper(II) salt/complex.

36. The use of claim 35 or the method of claim 35, wherein said copper salt/complex is a copper(II) salt/complex which is selected from copper sulfate, copper carbonate, a

copper(II) amino acid complex, copper(II) lysine complex, copper(II) glycinate, copper(II) EDTA complex, copper(II) chitosan complex, copper(II) citrate, copper(II) gluconate, copper(II) lactate, copper lactate gluconate, and copper(II) orotate.

37. The use of claim 35 or the method of claim 35, wherein said copper salt/complex is a copper(I) salt/complex which is selected from copper(I) chloride and copper(I) acetate.

38. The use of any one of claims 25 or 31 to 33 or the method of any of claims 29 to 33, wherein said peptide or protein drug is to be administered in combination with a pharmaceutically acceptable zinc salt/complex.

39. The use of any one of claims 25, 31 to 33 or 38 or the method of any of claims 29 to 33 or 38, wherein said zinc salt/complex is a zinc(II) salt/complex.

40. The use of claim 39 or the method of claim 39, wherein said zinc salt/complex is a zinc(II) salt/complex which is selected from zinc sulfate, zinc chloride, zinc acetate, zinc oxide, zinc ascorbate, zinc caprylate, zinc gluconate, zinc stearate, zinc carbonate, zinc orotate, a zinc amino acid complex, zinc glycinate, zinc arginate, zinc picolinate, zinc pidolate, zinc carnosine, zinc undecanoate, zinc undecylenate, zinc methionine, zinc lactate, and zinc lactate gluconate.

41. The use of any one of claims 25 to 28 or 31 to 40 or the method of any of claims 29 to 40, wherein said reducing agent is selected from ascorbic acid, reduced glutathione, cysteine, N-acetylcysteine, histidine, glycine, arginine, gelatin, uric acid, a reducing sugar, glucose, glyceraldehyde, galactose, fructose, ribose, xylose, sorbose, lactose, maltose, cellobiose, a glucose polymer, starch, a starch derivative, glucose syrup, maltodextrin, dextrin, dextrose, dextran, cellulose, microcrystalline cellulose, mannitol, α-tocopherol, vitamin A, α-lipoic acid, dihydro-α-lipoic acid, oxalic acid, phytic acid, a tannin, propyl gallate, butylated hydroxy toluene, butylated hydroxy anisole, sodium metabisulfite, povidone, crospovidone, an aldehyde, formaldehyde, acetaldehyde, furfuraldehyde, a dialdehyde, glyoxal, a phenolic compound, phenol, a polyphenol, salicylic acid, a salicylic acid derivative, an iron(II) salt/complex, diphosphate, disodiumdiphosphate, trisodiumdiphosphate, tetrasodiumdiphosphate, tetrapotassiumdiphosphate, dicalciumdiphosphate, calciumdihydrogendiphophate, phosphate, dipotassium hydrogen phosphate, calcium phosphate, calcium hydrogen phosphate, a thiol-bearing compound, a thiomer, and pharmaceutically acceptable salts thereof.

42. The use of claim 41 or the method of claim 41, wherein said reducing agent is an iron(II) salt/complex selected from iron(II) gluconate, iron(II) orotate, iron(II) tartrate, iron(II) fumarate, iron(II) sulfate, iron(II) lactate, iron(II) lactate gluconate, iron(II) acetate, iron(II) carbonate, iron(II) citrate, iron(II) oxide, iron(II) hydroxide, iron(II) ascorbate, an iron(II) amino acid complex, and ferrous bis-glycinate.

43. The use of any one of claims 25 to 28 or 31 to 42 or the method of any of claims 29 to 42, wherein an absorption enhancer is further to be administered orally.

44. The use of claim 43 or the method of claim 43, wherein said absorption enhancer is selected from C_{8-20} alkanoyl carnitine, salicylic acid, a salicylic acid derivative, 3-methoxysalicylic acid, 5-methoxysalicylic acid, homovanillic acid, a C_{8-20} alkanoic acid, citric acid, tartaric acid, a fatty acid acylated amino acid, a C_{8-20} alkanoyl sarcosinate, an alkylsaccharide, a C_{8-10} alkylpolysaccharide, n-octyl-beta-D-glucopyranoside, n-dodecyl-beta-D-maltoside, n-tetradecyl-beta-D-maltoside, tridecyl-beta-D-maltoside, sucrose laurate, sucrose myristate, sucrose palmitate, sucrose cocoate, sucrose mono-dodecanoate, sucrose mono-tridecanoate, sucrose mono-tetradecanoate, a coco-glucoside, a cyclodextrine, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, methyl-β-cyclodextrin, hydroxypropyl β-cyclodextrin, sulfobutylether β-cyclodextrin, N-[8-(2-hydroxybenzoyl)amino]caprylic acid, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate, a sodium N-[8-(2-hydroxybenzoyl)amino]caprylate derivative, a thiomer, a mucoadhesive polymer having a vitamin B partial structure, a calcium chelating compound, ethylenediaminetetraacetic acid, ethylene glycol tetraacetic acid, polyacrylic acid, cremophor EL, chitosan, N,N,N-trimethyl chitosan, benzalkonium chloride, bestatin, cetylpyridinium chloride, cetyltrimethylammonium bromide, a C_{2-20} alkanol, a C_{8-20} alkenol, a C_{8-20} alkenoic acid, dextran sulfate, diethyleneglycol monoethyl ether, 1-dodecylazacyclo-heptan-2-one, caprylocaproyl polyoxylglycerides, ethyl caprylate, glyceryl monolaurate, lysophosphatidylcholine, menthol, a C_{8-20} alkylamine, a C_{8-20} alkenylamine, phosphatidylcholine, a poloxamer, polyethylene glycol monolaurate, polyoxyethylene, polypropylene glycol monolaurate, a polysorbate, cholic acid, a deoxycholate, sodium glycocholate, sodium glycodeoxycholate, sodium lauryl sulfate, sodium decyl sulfate, sodium octyl sulfate, sodium laureth sulfate, N-lauryl sarcosinate, decyltrimethyl ammonium bromide, benzyldimethyl dodecyl ammonium chloride, myristyltrimethyl ammonium chloride, dodecyl pyridinium chloride, decyldimethyl ammonio propane sulfonate, myristyldimethyl ammonio propane sulfonate, palmityldimethyl ammonio propane

sulfonate, ChemBetaine CAS, ChemBetaine Oleyl, Nonylphenoxypolyoxyethylene, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, sorbitan monooleate, Triton X-100, hexanoic acid, heptanoic acid, methyl laurate, isopropyl myristate, isopropyl palmitate, methyl palmitate, diethyl sebaccate, sodium oleate, urea, lauryl amine, caprolactam, methyl pyrrolidone, octyl pyrrolidone, methyl piperazine, phenyl piperazine, Carbopol 934P, glyccyrhetinic acid, bromelain, pinene oxide, limonene, cineole, octyl dodecanol, fenchone, menthone, trimethoxy propylene methyl benzene, a cell-penetrating peptide, KLAKLAK, polyarginine, penetratin, HIV-1 Tat, macrogol-15-hydroxystearate, Solutol HS 15, CriticalSorb, a taurocholate, a taurodeoxycholate, a sulfoxide, decyl methyl sulfoxide, dimethyl sulfoxide, cyclopentadecalactone, 8-(N-2-hydroxy-5-chloro-benzoyl)-amino-caprylic acid, N-(10-[2-hydroxybenzoyl]amino)decanoic acid, dodecyl-2-N,N-dimethylamino propionate, D-α-tocopheryl polyethylene glycol-1000 succinate, and pharmaceutically acceptable salts thereof.

45. The use of claim 44 or the method of claim 44, wherein said absorption enhancer is a fatty acid acylated amino acid selected from sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methioninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, sodium lauroyl sarcosinate, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-

decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, N-decanoyl-L-sarcosine, sodium oleoyl sarcosinate, sodium N-decylleucine, sodium stearoyl glutamate, sodium myristoyl glutamate, sodium lauroyl glutamate, sodium cocoyl glutamate, sodium cocoyl glycinate, sodium N-decyl leucine, sodium cocoyl glycine, sodium cocoyl glutamate, sodium lauroyl alaninate, N-dodecanoyl-L-alanine, sodium lauroyl asparaginate, N-dodecanoyl-L-asparagine, sodium lauroyl aspartic acid, N-dodecanoyl-L-aspartic acid, sodium lauroyl cysteinate, N-dodecanoyl-L-cysteine, sodium lauroyl glutamic acid, N-dodecanoyl-L-glutamic acid, sodium lauroyl glutaminate, N-dodecanoyl-L-glutamine, sodium lauroyl glycinate, N-dodecanoyl-L-glycine, sodium lauroyl histidinate, N-dodecanoyl-L-histidine, sodium lauroyl isoleucinate, N-dodecanoyl-L-isoleucine, sodium lauroyl leucinate, N-dodecanoyl-L-leucine, sodium lauroyl methinoninate, N-dodecanoyl-L-methionine, sodium lauroyl phenylalaninate, N-dodecanoyl-L-phenylalanine, sodium lauroyl prolinate, N-dodecanoyl-L-proline, sodium lauroyl serinate, N-dodecanoyl-L-serine, sodium lauroyl threoninate, N-dodecanoyl-L-threonine, sodium lauroyl tryptophanate, N-dodecanoyl-L-tryptophane, sodium lauroyl tyrosinate, N-dodecanoyl-L-tyrosine, sodium lauroyl valinate, N-dodecanoyl-L-valine, N-dodecanoyl-L-sarcosine, sodium capric alaninate, N-decanoyl-L-alanine, sodium capric asparaginate, N-decanoyl-L-asparagine, sodium capric aspartic acid, N-decanoyl-L-aspartic acid, Sodium capric cysteinate, N-decanoyl-L-cysteine, sodium capric glutamic acid, N-decanoyl-L-glutamic acid, sodium capric glutaminate, N-decanoyl-L-glutamine, sodium capric glycinate, N-decanoyl-L-glycine, sodium capric histidinate, N-decanoyl-L-histidine, sodium capric isoleucinate, N-decanoyl-L-isoleucine, sodium capric leucinate, N-decanoyl-L-leucine, sodium capric methioninate, N-decanoyl-L-methionine, sodium capric phenylalaninate, N-decanoyl-L-phenylalanine, sodium capric prolinate, N-decanoyl-L-proline, sodium capric serinate, N-decanoyl-L-serine, sodium capric threoninate, N-decanoyl-L-threonine, sodium capric tryptophanate, N-decanoyl-L-tryptophane, sodium capric tyrosinate, N-decanoyl-L-tyrosine, sodium capric valinate, N-decanoyl-L-valine, sodium capric sarcosinate, sodium oleoyl sarcosinate, and pharmaceutically acceptable salts thereof.

46. The use of claim 43 or the method of claim 43, wherein said absorption enhancer is sodium N-[8-(2-hydroxybenzoyl)amino]caprylate.