Abstract: The present invention provides methods and compositions for modulating blood glucose levels, and methods and compositions for use in the treatment of diabetes, in particular type 2 diabetes.
MODULATION OF BLOOD GLUCOSE LEVELS

Technical Field

[001] The present invention relates generally to methods and compositions for regulating or modulating blood glucose levels. The invention also relates to methods and compositions for use in the treatment of diabetes, in particular type 2 diabetes. Specifically the invention relates to such treatment involving the oromucosal delivery of an incretin mimetic, more particularly a GLP-1 mimetic such as exenatide, optionally in combination with insulin or an analogue thereof. More particularly, the invention relates to sublingual administration of compositions comprising an incretin mimetic, for example a GLP-1 mimetic such as exenatide, wherein the composition optionally also comprises insulin or an analogue thereof.

Background Art

[002] The hallmark of diabetes mellitus is hyperglycaemia resulting from impaired carbohydrate metabolism. Type 2 diabetes has a complex pathophysiology characterised by deficient insulin activity arising from decreased insulin secretion secondary to beta-cell failure, compromised insulin action in peripheral target tissues (insulin resistance), or a combination of the two abnormalities. This abnormal metabolic state is exacerbated by excess hepatic glucose production and altered metabolism of proteins and lipids, which along with hyperglycaemia, contribute to microvascular and macrovascular complications.

[003] Type 2 diabetes accounts for approximately 85% to 95% of diabetes cases in the developed world. Age and weight are established risk factors for type 2 diabetes and the majority of sufferers are overweight or obese. As such, diet modification and exercise are typically front line treatment for type 2 diabetes. Pharmacologic intervention with an oral antidiabetic agent such as metformin or sulphonylureas or a combination of such agents is often the next step in treatment. Other alternative oral treatments include alpha-glucosidase inhibitors, meglitinides and thiazolidinediones.
In patients who do not achieve acceptable glycaemic control using oral antidiabetic agents, insulin was, until recently, the only viable alternative. However determination of appropriate insulin doses require self-monitoring of blood glucose levels, and insulin use is often associated with weight gain.

Incretins, such as glucagon-like peptide 1 (GLP-1), facilitate insulin secretion following their release from the gut into the circulation in response to food intake. Incretin mimetics have multiple anti-hyperglycaemic actions that mimic some of the effects of GLP-1. Exenatide is one such incretin mimetic, registered for the treatment of type 2 diabetes by injection (Byetta®, by Amylin Pharmaceuticals, Inc.), in combination with metformin, sulphonylureas and thiazolidinediones in adults who have not achieved adequate glycemic control on maximally tolerated doses of oral therapies. Byetta® is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycemic control with these agents.

However a disadvantage of treatment with Byetta® is that it must be administered twice daily by subcutaneous administration (injection). The need for subcutaneous injections can hamper the ability of individuals to self-medicate and manage their own treatment regime. Accordingly there is a need for the development of simple, low cost treatment options that enable sufferers of diabetes to administer their own medication with convenience and without pain or side effect.

**Summary of the Invention**

Embodiments of the present invention provide methods and compositions for the oromucosal, typically sublingual, administration of an incretin mimetic, typically a GLP-1 mimetic. The methods and compositions of the invention offer numerous advantages over current options for treatment using incretin mimetics, typically GLP-1 mimetics such as exenatide, that require administration by injection, thereby providing patients suffering from diabetes or metabolic syndrome, for example, with a safe and effective new treatment option. For example sublingually administered exenatide avoids the fluctuations in blood glucose levels (hyperglycaemia and hypoglycaemia)
typically observed following exenatide injections, providing improved maintenance or regulation of blood glucose levels. Additionally, sublingual administration offers reduced side effects compared to exenatide administration by injection. Severe nausea is a commonly experienced side effect of exenatide injections. As a result, new patients placed on an exenatide injection regime are given a reduced dose (typically 5 \( \mu g \)) for two weeks before the dose is increased to the normal 10 \( \mu g \).

[008] As described and exemplified herein, the inventor has also unexpectedly found that exenatide administered sublingually acts synergistically with insulin administered sublingually, thereby offering further benefits for subjects in terms of improved efficacy.

[009] In a first aspect, the present invention provides a method for the treatment of metabolic syndrome or diabetes in a subject, the method comprising the oromucosal administration of an effective amount of an incretin mimetic to the subject.

[0010] Typically the incretin mimetic is a GLP-1 mimetic. The GLP-1 mimetic may be a GLP-1 analogue. The GLP-1 analogue may be a peptide-based analogue such as, for example, exenatide.

[0011] Typically the oromucosal administration is sublingual or buccal administration. More typically the administration is sublingual.

[0012] In particular embodiments the diabetes is type 2 diabetes.

[0013] The exenatide typically comprises or consists of the amino acid sequence set forth in SEQ ID NO:1.

[0014] The exenatide analogue may be, for example, AC3174. The exenatide analogue AC3174 typically comprises or consists of the amino acid sequence set forth in SEQ ID NO:2.

[0015] The incretin mimetic may be administered in any form suitable for oromucosal
delivery, such as, for example in solid or liquid unit dosage form. The incretin mimetic may be formulated in a gel matrix delivery system.

[0016] The incretin mimetic may be formulated in a composition using a process comprising the following steps:

(i) providing a coating liquid comprising the incretin mimetic, a saccharide and a water-miscible solvent;
(ii) providing particles comprising one or more water-soluble gel-forming compounds;
(iii) fluidising the particles within a processing chamber of an apparatus in such a manner that the particles move in an upward direction within the chamber in a helical path;
(iv) spraying the coating liquid onto the particles so as to provide coated particles; and
(v) allowing the coated particles to dry.

[0017] The method may further comprise the administration of an effective amount of insulin or an analogue thereof. In an embodiment the incretin mimetic and the insulin or analogue thereof provide a synergistic combination.

[0018] The insulin or analogue thereof may be formulated in the same composition as the incretin mimetic, or in a different composition. Where the insulin or analogue thereof and the incretin mimetic are administered in different compositions, the compositions may be administered by the same or different routes, and may be administered simultaneously or sequentially (in either order).

[0019] In a second aspect, the invention provides a method for regulating blood glucose levels in a subject, the method comprising the oromucosal administration of an effective amount of an incretin mimetic to the subject.

[0020] Typically the incretin mimetic is a GLP-1 mimic. The GLP-1 mimic may be a GLP-1 analogue. The GLP-1 analogue may be a peptide-based analogue such as, for example, exenatide.
Regulating blood glucose levels in the subject may comprise normalizing blood glucose levels. The subject may have diabetes, typically type 2 diabetes, or metabolic syndrome. Regulating blood glucose levels may improve glucose in the subject. For example, said regulation may prevent or treat, or assist in preventing or treating hypoglycaemia or hyperglycaemia.

Typically the oromucosal administration is sublingual or buccal administration. More typically the administration is sublingual.

The exenatide typically comprises or consists of the amino acid sequence set forth in SEQ ID NO: 1.

The exenatide analogue may be, for example, AC3174. The exenatide analogue AC3174 typically comprises or consists of the amino acid sequence set forth in SEQ ID NO: 2.

The incretin mimetic may be administered in any form suitable for oromucosal delivery, such as, for example in solid or liquid unit dosage form. The incretin mimetic may be formulated in a gel matrix delivery system.

The incretin mimetic may be formulated in a composition using a process comprising the following steps:

(i) providing a coating liquid comprising the incretin mimetic, a saccharide and a water-miscible solvent;
(ii) providing particles comprising one or more water-soluble gel-forming compounds;
(iii) fluidising the particles within a processing chamber of an apparatus in such a manner that the particles move in an upward direction within the chamber in a helical path;
(iv) spraying the coating liquid onto the particles so as to provide coated particles; and
(v) allowing the coated particles to dry.
The method may further comprise the administration of an effective amount of insulin or an analogue thereof. In an embodiment the incretin mimetic and the insulin or analogue thereof provide a synergistic combination.

The insulin or analogue thereof may be formulated in the same composition as the incretin mimetic, or in a different composition. Where the insulin or analogue thereof and the incretin mimetic are administered in different compositions, the compositions may be administered by the same or different routes, and may be administered simultaneously or sequentially (in either order).

In a third aspect, the invention provides a method for reducing the side effects associated with injection of an incretin mimetic, the method comprising oromucosally administering the incretin mimetic to a subject.

In a particular embodiment the incretin mimetic is a GLP-1 mimetic such as exenatide or an analogue thereof.

Typically the oromucosal administration is sublingual or buccal administration. More typically the administration is sublingual.

In a fourth aspect, the invention provides a pharmaceutical composition formulated for oromucosal administration for the treatment of diabetes or metabolic syndrome or for the regulation of blood glucose levels, the composition comprising an incretin mimetic.

Typically the incretin mimetic is a GLP-1 mimetic. The GLP-1 mimetic may be a GLP-1 analogue. The GLP-1 analogue may be a peptide-based analogue such as, for example, exenatide.

The composition may be formulated using a process comprising the following steps:

(i) providing a coating liquid comprising the incretin mimetic, a
saccharide and a water-miscible solvent;
(ii) providing particles comprising one or more water-soluble gel-forming compounds;
(iii) fluidising the particles within a processing chamber of an apparatus in such a manner that the particles move in an upward direction within the chamber in a helical path;
(iv) spraying the coating liquid onto the particles so as to provide coated particles; and
(v) allowing the coated particles to dry.

[0035] Typically the oromucosal administration is sublingual or buccal administration. More typically the administration is sublingual.

[0036] The exenatide typically comprises or consists of the amino acid sequence set forth in SEQ ID NO:1.

[0037] The exenatide analogue may be, for example, AC3174. The exenatide analogue AC3174 typically comprises or consists of the amino acid sequence set forth in SEQ ID NO:2.

[0038] The composition may further comprise insulin or an analogue thereof. The composition may be a synergistic composition comprising the incretin mimetic, optionally a GLP-1 mimetic such as exenatide, and the insulin or an analogue thereof.

[0039] In a fifth aspect, the invention provides the use of an incretin mimetic for the manufacture of a medicament for treating diabetes or metabolic syndrome, and/or for regulating blood glucose levels, wherein the medicament is formulated for oromucosal administration.

[0040] In accordance with the above aspects, where the incretin mimetic is a peptide-based molecule, the mimetic may be administered in the form of a polynucleotide encoding the mimetic. The polynucleotide may be located in a genetic construct, operably linked to a promoter.
Brief Description of the Drawings

[0041] Embodiments of the invention are described herein, by way of example only, with reference to the accompanying drawings.

[0042] **Figure 1.** Blood glucose levels in diabetic mice following administration of exenatide at -60 min, followed by intraperitoneal glucose challenge at 0 min. Circles (top), vehicle delivered sublingually; squares, 50 µg exenatide sublingual; upright triangles, 100 µg exenatide sublingual; diamonds, 150 µg exenatide sublingual; upside down triangles, 200 µg exenatide sublingual; circles, 1 µg exenatide subcutaneous (s.c).

[0043] **Figure 2.** Blood glucose levels at 0 min (A) and 20 min (B) derived from the results shown in Figure 1. ***, p<0.01 versus vehicle.

[0044] **Figure 3.** A. Area under the curve analysis (AUC) of blood glucose levels from 0-120 min, derived from the results shown in Figure 1. ***, p<0.01. B. Percent change in AUC calculated as (AUC[exenatide] - AUC[vehicle]) / AUC[vehicle].

[0045] **Figure 4.** Blood glucose levels in diabetic mice following administration of exenatide at -60 min, followed by intraperitoneal glucose challenge at 0 min. Circles, vehicle delivered sublingually; squares, 2 µg exenatide sublingual; upright triangles, 5 µg exenatide sublingual; upside down triangles, 10 µg exenatide sublingual; diamonds, 25 µg exenatide sublingual; crosses, 50 µg exenatide sublingual; stars, 1 µg exenatide subcutaneous (s.c).

[0046] **Figure 5.** Blood glucose levels at 0 min (A) and 20 min (B) derived from the results shown in Figure 4. ***, p<0.01 versus vehicle.

[0047] **Figure 6.** A. Area under the curve analysis (AUC) of blood glucose levels from 0-120 min, derived from the results shown in Figure 4. ***, p<0.01. B. Percent change in AUC calculated as (AUC[exenatide] - AUC[vehicle]) / AUC[vehicle].
[0048] Figure 7. Blood glucose levels in diabetic mice following administration of exenatide at -60 min, followed by intraperitoneal glucose challenge at 0 min. Circles, vehicle delivered sublingually; squares, 10 µg exenatide sublingual; upright triangles, 15 µg exenatide sublingual; upside down triangles, 20 µg exenatide sublingual; diamonds, 25 µg exenatide sublingual; stars, 1 µg exenatide subcutaneous (s.c).

[0049] Figure 8. Blood glucose levels at 0 min (A) and 20 min (B) derived from the results shown in Figure 7. ***, p<0.01 versus vehicle.

[0050] Figure 9. A. Area under the curve analysis (AUC) of blood glucose levels from 0-120 min, derived from the results shown in Figure 7. ***, p<0.01. B. Percent change in AUC calculated as (AUC[exenatide] - AUC[vehicle]) / AUC[vehicle].

[0051] Figure 10. Relative bioavailability of exenatide in monkeys. Squares, 20 µg exenatide administered sublingually, adjusted to 10 (average from four monkeys); triangles, 5 µg exenatide administered subcutaneously (average from three monkeys).

[0052] Figure 11. Blood serum glucose levels in a diabetic human subject following administration of exenatide at -60 min, followed by intraperitoneal glucose challenge at 0 min. Diamonds, 100 µg exenatide sublingual; squares, placebo sublingual; triangles, 5 µg exenatide (Byetta) subcutaneous.

[0053] Figure 12. Blood glucose levels over a 12 week period in a diabetic human subject administered 50 µg exenatide sublingually for 12 weeks. Squares, glucose levels at 2 hours postprandial; circles, fasting blood glucose levels.

[0054] Figure 13. Postprandial (2 hrs after meal) plasma glucose levels over 11 days in a diabetic human subject administered 20 µg exenatide plus 500 mg metformin (squares) or 500 mg metformin alone (diamonds).

[0055] Figure 14. Blood glucose levels in diabetic mice following administration of test compounds at -60 min, followed by intraperitoneal glucose challenge at 0 min.
Circles, sublingual blank control; squares, sublingual vehicle; upright triangles, 5 μg sublingual exenatide; diamonds, 5 μg sublingual exenatide plus 10 IU/kg insulin; stars, 1 IU/kg insulin subcutaneous.

**Detailed Description of the Invention**

[0056] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

[0057] The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0058] As used herein the term "effective amount" includes within its meaning a non-toxic but sufficient amount of an agent or compound to provide the desired therapeutic effect. The exact amount required will vary from subject to subject depending on factors such as the species being treated, the age and general condition of the subject, the severity of the condition being treated, the particular agent being administered and the mode of administration and so forth. Thus, it is not possible to specify an exact "effective amount". However, for any given case, an appropriate "effective amount" may be determined by one of ordinary skill in the art using only routine experimentation.

[0059] As used herein the terms "treating" and "treatment" refer to any and all uses which remedy a disease state or symptoms, prevent the establishment of disease, or otherwise prevent, hinder, retard, or reverse the progression of disease or other undesirable symptoms in any way whatsoever. Thus, "treatment" refers not only to treatment designed to cure or remove symptoms in an individual, but also to ongoing therapy designed to control and suppress the occurrence of symptoms. Treatment may
be for a defined period of time, or provided on an ongoing basis depending on the particular circumstances of any given individual.

[0060] As used herein the term "polypeptide" means a polymer made up of amino acids linked together by peptide bonds. The terms "polypeptide" and "protein" are used interchangeably herein, although for the purposes of the present invention a "polypeptide" may constitute a portion of a full length protein. The term "polynucleotide" as used herein refers to a single- or double-stranded polymer of deoxyribonucleotid, ribonucleotide bases or known analogues or natural nucleotides, or mixtures thereof.

[0061] The present invention provides novel therapeutic treatment options for a variety of conditions in which it is desirable to regulate or control blood glucose levels. By way of example, such conditions include metabolic syndrome and diabetes, such as type 2 diabetes. However, those skilled in the art will readily appreciate that the present invention is not limited to those conditions explicitly recited herein, but is applicable to the treatment of any condition wherein it is desirable to regulate or control blood glucose levels.

[0062] Accordingly, particular aspects of the invention provide methods for the treatment of metabolic syndrome or diabetes or for the regulation of blood glucose levels, comprising the oromucosal administration of an effective amount of an incretin mimetic, more particularly a GLP-1 mimetic, to a subject.

[0063] Administration of incretin mimetics by injection can be associated with a variety of side effects. For example exenatide administered by subcutaneous injection has a $T_{\text{max}}$ of approximately 2 hours and typically results in large fluctuations in blood glucose levels (hyperglycaemia and hypoglycaemia). Severe nausea is also a commonly experienced side effect of exenatide injections. As a result, new patients placed on an exenatide injection regime are typically given a reduced dose (typically 5 µg) for two weeks before the dose is increased to the normal 10 µg, to be injected twice daily. The sublingual administration of incretin mimetics such as exenatide, the subject of the present disclosure, can avoid or minimise these side effects. Without wishing to be
bound by theory, the inventor suggests that the delivery system disclosed herein for sublingual administration of peptides such as exenatide reduces the $T_{max}$ and results in a slow and prolonged release of the peptide, which in turn prevents the large fluctuations in blood sugar levels observed following injection. As exemplified herein the sublingual administration of exenatide in both mice and humans maintains blood sugar levels within normal physiological ranges and avoids a drop in blood sugar levels (to as low as 4 mmol/L, being borderline hypoglycaemia) that commonly follows exenatide injections. Accordingly, the sublingual administration of exenatide avoids the need to begin new patient treatment with a half dose regime (5 µg for subcutaneous injection) before moving to a full dose (10 µg for subcutaneous injection).

[0064] Therefore, an aspect of the present invention provides methods for reducing, minimising or avoiding the side effects associated with injection of incretin mimetics such as exenatide or analogues thereof, wherein the methods comprise oromucosal, typically sublingual, administration of the mimetic. Also provided are compositions for reducing, minimising or avoiding the side effects associated with injection of incretin mimetics such as exenatide or analogues thereof, wherein the compositions comprise the mimetic formulated for oromucosal, typically sublingual, administration.

[0065] The GLP-1 mimetic may be, for example, a GLP-1R agonist. The GLP-1R agonist may be resistant to dipeptidyl peptidase-4. The GLP-1R agonist may be, for example, a peptide or small molecule. Exemplary peptide agonists include exenatide, lixisenatide, liraglutide, albiglutide and dulaglutide. The peptide may be conjugated with a polymer, such as exenatide LAR (exenatide incorporated into a poly (D,L-lactic-co-glycolic acid) microsphere suspension). A number of additional GLP-1 mimetics (peptides and small molecules) are currently under investigation or clinical trial, and the skilled addressee will appreciate that the scope of the present disclosure is not limited by reference to any specific mimetic.

[0066] In particular embodiments of the invention the mimetic is exenatide or an analogue thereof. For use in accordance with the present invention the exenatide may comprise or consist of the amino acid sequence set forth in SEQ ID NO:1. Further, the present invention contemplates not only use of the exenatide polypeptide, but also
polynucleotides encoding the same. Those skilled in the art will appreciate that one or more modifications, including amino acid deletions, insertions or substitutions (such as conservative amino acid substitutions), may be made to the exenatide without departing from the scope of the present invention, providing the exenatide polypeptide so modified retains glucoregulatory activity in common with exenatide prior to the modification. The modification may increase, improve or otherwise alter one or more biological activities of exenatide.

[0067] The term "conservative amino acid substitution" refers to a substitution or replacement of one amino acid for another amino acid with similar properties within a polypeptide chain (primary sequence of a protein). For example, the substitution of the charged amino acid glutamic acid (Glu) for the similarly charged amino acid aspartic acid (Asp) would be a conservative amino acid substitution. Amino acid insertional derivatives also include amino and/or carboxylic terminal fusions as well as intrasequence insertions of single or multiple amino acids. Insertional amino acid sequence variants are those in which one or more amino acid residues are introduced into a predetermined site in the protein although random insertion is also possible with suitable screening of the resulting product. Deletional variants are characterised by the removal of one or more amino acids from the sequence. Substitutional amino acid variants are those in which at least one residue in a sequence has been removed and a different residue inserted in its place.

[0068] Encompassed within the scope of the invention are derivatives, homologs, functional fragments and variants of incretin mimetics such as exenatide, which possess qualitative glucoregulatory activity in common with the mimetic.

[0069] "Derivatives" of include analogues, functional fragments, parts, portions or variants from either natural or non-natural sources. Non-natural sources include, for example, recombinant or synthetic sources. By "recombinant sources" is meant that the cellular source from which the subject molecule is harvested has been genetically altered.
[0070] Where the following disclosure refers to the GLP-1 mimetic exenatide, it should be understood that this is exemplary only. Those skilled in the art will appreciate that this disclosure is also applicable to other incretin mimetics, in particular peptide-based mimetics.

[0071] "Analogue" means a polypeptide that is a derivative of, for example, exenatide, which derivative comprises addition, deletion, substitution of one or more amino acids, such that the polypeptide retains substantially the same function as the exenatide from which it is derived, in particular having substantially the same or similar glucoregulatory properties of exenatide. One exemplary analogue is AC3174 in which the methionine residue at position 14 of exenatide is replaced by a leucine residue. The sequence of AC3174 typically comprises or consists of the amino acid sequence set forth in SEQ ID NO:2.

[0072] The term "fragment" refers to a polypeptide that is a constituent of, for example, a full-length exenatide or analogue thereof. The fragment typically possesses qualitative biological activity in common with the full-length polypeptide. The fragment may be derived from the full-length polypeptide or alternatively may be synthesised by some other means, for example chemical synthesis. As used herein a "variant" of exenatide means a molecule of substantially similar sequence to the exenatide or analogue of which it is a variant and which exhibits at least some of the functional activity of the molecule of which it is a variant. A variant may take any form and may be naturally or non-naturally occurring. Generally, variant polypeptides may share at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity.

[0073] A peptide-based mimetic such as exenatide or analogue thereof can also be further modified, for instance, by glycosylation, amidation, carboxylation, or phosphorylation, or by the creation of acid addition salts, amides, esters, in particular C-terminal esters, and N-acyl derivatives. The molecules can also be further modified to create peptide derivatives by forming covalent or non-covalent complexes with other moieties. Covalently-bound complexes can be prepared by cross-linking the chemical moieties to functional groups on the side chains of amino acids comprising the peptides,
or at the N-or C terminus. For example, a modified polypeptide may be generated with a polyethylene moiety conjugated at one or more locations (PEGylation) to increase in vivo half life. Those skilled in the art will appreciate that a number of other well known approaches exist to extend the in vivo half life of polypeptides, such as for example the addition of albumin affinity tags, and the present disclosure is not limited by reference to the exemplary means specifically discussed herein.

[0074] The peptide-based mimetic such as exenatide or analogue thereof may be synthesised by standard methods of liquid or solid phase chemistry well known to those of ordinary skill in the art. For example synthesis may follow the solid phase chemistry procedures of Steward and Young (Steward, J. M. & Young, J. D., Solid Phase Peptide Synthesis. (2nd Edn.) Pierce Chemical Co., Illinois, USA (1984), or . Howl (ed.) Peptide Synthesis and Applications, Methods in Molecule Biology (Volume 298), 2005. In general, such synthesis methods comprise the sequential addition of one or more amino acids or suitably protected amino acids to a growing peptide chain. Typically, either the amino or carboxyl group of the first amino acid is protected by a suitable protecting group. The protected amino acid is then either attached to an inert solid support or utilised in solution by adding the next amino acid in the sequence having the complimentary (amino or carboxyl) group suitably protected and under conditions suitable for forming the amide linkage. The protecting group is then removed from this newly added amino acid residue and the next (protected) amino acid is added, and so forth. After all the desired amino acids have been linked, any remaining protecting groups, and if necessary any solid support, is removed sequentially or concurrently to produce the final polypeptide.

[0075] The peptide-based mimetic such as exenatide or analogue thereof may also be produced using standard techniques of recombinant DNA and molecular biology that are well known to those skilled in the art. Guidance may be obtained, for example, from standard texts such as Sambrook et al., Molecular Cloning : A Laboratory Manual, Cold Spring Harbor, New York, 1989 and Ausubel et al., Current Protocols in Molecular Biology, Greene Pubb. Assoc. and Wiley-Intersciences, 1992. Methods described in Morton et al. 2000 [Immunol Cell Biol 78:603-607], Ryan et al., 1995 (J Biol Chem 270:22037-22043) and Johnson et al, 2005 (J Biol Chem 280:4037-4047)
are examples of suitable purification methods, although the skilled addressee will appreciate that the present invention is not limited by the method of purification or production used and any other method may be used to produce molecules for use in accordance with the methods and compositions of the present invention.

[0076] Embodiments of the present invention also provide for the administration of, for example, exenatide or analogue thereof in the form of a polynucleotide encoding the exenatide or analogue thereof. The polynucleotide may be administered in a vector. The vector may be a plasmid vector, a viral vector, or any other suitable vehicle adapted for the insertion and foreign sequences and introduction into eukaryotic cells. Typically the vector is an expression vector capable of directing the transcription of the DNA sequence of the polynucleotide encoding the desired polypeptide into mRNA. The vector may include expression control and processing sequences such as a promoter, an enhancer, ribosome binding sites, polyadenylation signals and transcription termination sequences. Examples of suitable viral expression vectors include for example Epstein-barr virus-, bovine papilloma virus-, adenovirus- and adeno-associated virus-based vectors. The vector may be episomal.

[0077] The present invention provides methods and compositions for the oromucosal delivery of incretin mimetics. Typically the oromucosal administration comprises sublingual or buccal administration whereby the composition is placed into contact with the buccal mucosa either under the tongue or in the cheek pouch allowing entry of the active agent directly to the bloodstream by absorption. Suitable forms for oromucosal administration include solid, liquid, emulsion, gel and suspension. In a particular embodiment, a composition of the invention is administered in solid unit dosage form, for example in the form of a tablet, capsule, caplet, or lozenge. In one embodiment, the administration may comprise a gel administered to the buccal or sublingual area.

[0078] Suitable solid compositions may comprise a rapid or slow disintegrating composition comprising the incretin mimetic in a pharmaceutically acceptable water soluble or water dispersible carrier material. Such compositions may disintegrate or dissolve in the mouth upon placement under the tongue or insertion into the buccal pouch. Compositions may be formulated for rapid or immediate release of the incretin
mimetic, or alternatively for delayed or controlled release. Techniques and processes for achieving delayed or controlled release of active agents are well known to those skilled in the art.

[0079] In general, suitable compositions may be prepared according to methods that are known to those of ordinary skill in the art and may include a pharmaceutically acceptable diluent, adjuvant and/or excipient. The diluents, adjuvants and excipients must be “acceptable” in terms of being compatible with the other ingredients of the composition, and not deleterious to the recipient thereof.

[0080] Examples of pharmaceutically acceptable diluents are demineralised or distilled water; saline solution; vegetable based oils such as peanut oil, safflower oil, olive oil, cottonseed oil, maize oil, sesame oils, vitamin E oil, arachis oil or coconut oil; silicone oils, including polysiloxanes, such as methyl polysiloxane, phenyl polysiloxane and methylphenyl polysilosxane; volatile silicones; mineral oils such as liquid paraffin, soft paraffin or squalane; lower alkanols, for example ethanol or iso-propanol; lower aralkanols; lower polyalkylene glycols or lower alkylene glycols, for example polyethylene glycol, polypropylene glycol, ethylene glycol, propylene glycol, 1,3-butylene glycol or glycerin; fatty acid esters such as isopropyl palmitate, isopropyl myristate or ethyl oleate; polyvinylpyrridone; and petroleum jelly and propylene glycol. The diluent may be dextran, dextrin, dextrose, sucrose, maltose, mannitol, gelatin, pregel starch, starch, amino acids trehalose, carboxymethylcellulose, cellulose, methyl cellulose, ethyl cellulose, albumin agar; carrageenan; gum tragacanth or gum acacia. Typically, the carrier or carriers will form from 0.1% to 99.9% by weight of the compositions.

[0081] A broad range of processes for the preparation of dosage forms suitable for sublingual administration are well known to those skilled in the art and are contemplated by the present invention. For example, suitable formulations may be prepared by processes including freeze drying under vacuum, supercritical fluid drying, spray drying using heat, and fluid bed spray drying. Of particular application in the context of particular embodiments of the present invention is a process involving microencapsulation whereby the active ingredient is coated onto granules, tablets or
microparticles, typically using solvents. One particularly suitable process involves the use of a fluidised bed spray process facilitating the coating onto granules at room temperature of actives including polypeptides with a water solubilising coat, as disclosed in International Patent Application Publication No. WO 02/058735 (the disclosure of which is incorporated herein in its entirety by reference). Microparticles such as water soluble sugars or gel forming particles may be thus coated, or alternatively a blank tablet, lozenge or capsule core may be spray coated. Also known in the art are means for the preparation of oral compositions incorporating an effervescent agent as a penetration enhancer to increase the permeability of the active agent across the buccal and sublingual mucosa (see for example US Patent No. 6,974,590, the disclosure of which is incorporated herein in its entirety by reference). Other delivery modes contemplated by the present invention include the use of bioadhesives, mucoadhesives and liposomes.

[0082] Briefly, the incretin mimetic may be formulated in a composition using a process comprising the following steps:

(i) providing a coating liquid comprising the incretin mimetic, a saccharide and a water-miscible solvent;
(ii) providing particles comprising one or more water-soluble gel-forming compounds;
(iii) fluidising the particles within a processing chamber of an apparatus in such a manner that the particles move in an upward direction within the chamber in a helical path;
(iv) spraying the coating liquid onto the particles so as to provide coated particles; and
(v) allowing the coated particles to dry.

[0083] The compositions of the invention may also be administered in the form of liposomes. Liposomes may be derived from phospholipids or other lipid substances, and are formed by mono- or multi-lamellar hydrated liquid crystals dispersed in aqueous medium. Specific examples of liposomes used in administering or delivering a composition to target cells are DODMA, synthetic cholesterol, DSPC, PEG-cDMA, DLinDMA, tocotrienols, tocopheniols, or any other non-toxic, physiologically
acceptable and metabolisable lipid capable of forming liposomes. The compositions in liposome form may contain stabilisers, preservatives and/or excipients. Methods for preparing liposomes are well known in the art, for example see Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 ff., the contents of which are incorporated herein by reference.

[0084] The compositions of the invention may also be administered in the form of microparticles. Biodegradable microparticles formed from polylactide (PLA), polylactide-co-glycolide (PLGA), and epsilon-caprolactone (ε-caprolactone) may be used.

[0085] The compositions of the invention may incorporate a controlled release matrix that is composed of sucrose acetate isobutyrate (SAIB) and an organic solvent or mixture of organic solvents. Polymer additives may be added to further increase the viscosity so as to decrease the release rate.

[0086] Those skilled in the art will readily appreciate that a number of suitable processes and techniques exist for the manufacture of suitable oral compositions in accordance with the present invention and that the invention is not limited by reference to any one particular process or technique.

[0087] Solid forms for oral administration may contain binders acceptable in human and pharmaceutical practice, sweeteners, disintegrating agents, diluents, flavourings, colouring, coating agents, preservatives, lubricants and/or time delay agents. Suitable binders include gum acacia, gelatine, corn starch, pregel starch, gum tragacanth, sodium alginate, carboxymethylcellulose or polyethylene glycol. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, guar gum, xanthan gum, bentonite, alginic acid or agar. Suitable diluents include lactose, sorbitol, mannitol, dextrose, kaolin, cellulose, calcium carbonate, calcium silicate or dicalcium phosphate. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein,
shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E alpha-tocopherol, tocotrienols which also act as anti-oxidant and colouring agents, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

[0088] Liquid forms for oral administration may contain, in addition to the above agents, a liquid carrier. Suitable liquid carriers include water, oils such as olive oil, peanut oil, sesame oil, sunflower oil, safflower oil, arachis oil, coconut oil, liquid paraffin, ethylene glycol, propylene glycol, polyethylene glycol, ethanol, propanol, isopropanol, glycerol, fatty alcohols, triglycerides or mixtures thereof.

[0089] Suspensions for oral administration may further comprise dispersing agents and/or suspending agents. Suitable suspending agents include sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, poly-vinyl-pyrrolidone, sodium alginate or acetyl alcohol. Suitable dispersing agents include lecithin, polyoxyethylene esters of fatty acids such as stearic acid, polyoxyethylene sorbitol mono- or di-oleate, -stearate or -laurate, polyoxyethylene sorbitan mono- or di-oleate, -stearate or -laurate and the like.

[0090] Emulsions for oral administration may further comprise one or more emulsifying agents. Suitable emulsifying agents include dispersing agents as exemplified above or natural gums such as guar gum, gum acacia or gum tragacanth.

[0091] The therapeutically effective dose level of a composition of the present invention for any particular patient will depend upon a variety of factors including any one or more of: the nature of condition being treated and the stage of the condition; the activity of the active agent employed; the composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of sequestration of compounds; the duration of the treatment; drugs used in combination or coincidental with the treatment, together with other related factors well known in medicine. One skilled in the art would be able, by routine experimentation, to
determine an effective, non-toxic dosage. These will most often be determined on a case-by-case basis.

[0092] By way of example, for sublingual administration of the exenatide or analogue thereof, individual doses of, for example, about 5 µg to about 200 µg may be used. Typically the dose employed in accordance with the invention is between about 5 µg and about 200 µg, between about 10 µg and about 200 µg, between about 50 µg and about 200 µg, between about 75 µg and about 200 µg between about 100 µg and about 200 µg, between about 125 µg and about 200 µg, between about 150 µg and about 200 µg, or between about 175 µg and about 200 µg. The dose may be in the order of about 5 µg, 10 µg, 15 µg, 20 µg, 25 µg, 30 µg, 35 µg, 40 µg, 45 µg, 50 µg, 55 µg, 60 µg, 65 µg, 70 µg, 75 µg, 80 µg, 85 µg, 90 µg, 95 µg, 100 µg, 110 µg, 120 µg, 130 µg, 140 µg, 150 µg, 160 µg, 170 µg, 180 µg, 190 µg, 200 µg, 220 µg, 240 µg, 260 µg, 280 µg, 300 µg, 350 µg, 400 µg, 450 µg and 500 µg. In particular embodiments the dose may be about 100 µg to about 200 µg, optionally administered twice daily, and optionally administered about 30-120 minutes (typically 60 minutes) before a meal.

[0093] It will also be apparent to one of ordinary skill in the art that the optimal quantity and spacing of individual dosages will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the nature of the particular individual being treated. Also, such optimum conditions can be determined by conventional techniques known to those skilled in the art. For example, a subject may be administered the desired daily dose in a single unit dosage form once per day, or in two unit dosage forms administered twice a day.

[0094] It will also be apparent to one of ordinary skill in the art that the optimal course of treatment, such as, the number of doses of the composition given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

[0095] Embodiments of the present invention contemplate the administration of one or more additional compounds or molecules together with the incretin mimetic. Such
additional compounds or molecules may be formulated together with the incretin mimetic in a single composition. For example, the studies exemplified herein demonstrate the unexpected synergy resulting from the oromucosal administration of both exenatide and insulin.

[0096] As described above in relation to incretin mimetics such as exenatide, the present invention contemplates various modifications to the insulin molecule without departing from the scope of the invention and thus the disclosure above in relation to exenatide is equally applicable to insulin and should be regarded as applying thereto. Thus, analogues of insulin are also contemplated herein, including for example insulin aspart, insulin lispro, insulin glulisine, insulin glargine and insulin detemir.

[0097] The insulin or analogue thereof may be administered at a dose of between about 1 IU and about 200 IU, between about 1 IU and about 100 IU, or between about 5 IU and 100 IU. For example the dose may be about 5 IU, 10 IU, 15 IU, 20 IU, 25 IU, 30 IU, 35 IU, 40 IU, 45 IU, 50 IU, 55 IU, 60 IU, 65 IU, 70 IU, 75 IU, 80 IU, 85 IU, 90 IU, 95 IU, or 100 IU. Typically the insulin may be administered twice daily (or up to four times daily depending on the severity of the condition suffered) about 60 minutes before meals.

[0098] Those skilled in the art will appreciate that in view of the synergy observed between exenatide and insulin, the coformulation and/or coadministration of exenatide and insulin, or analogues thereof, may allow reduced amounts or doses of each to be used in order to achieve the desired therapeutic effect compared to the amount or dose of each that would be required if administered alone.

[0099] Methods and compositions of the present invention may be employed in combination with other therapies for the regulation of blood glucose levels and/or for the treatment of conditions such as diabetes and metabolic syndrome. Suitable agents or therapies which may be used in combination with the compositions of the present invention will be known to those of ordinary skill in the art. For such combination therapies, each component of the combination may be administered at the same time, or sequentially in any order, or at different times, so as to provide the desired therapeutic
effect. When administered separately, it may be preferred for the components to be administered by the same route of administration, although it is not necessary for this to be so. Alternatively, the components may be formulated together in a single dosage unit as a combination product.

[00100] All publications mentioned in this specification are herein incorporated by reference. The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

[00101] It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

[00102] The present invention will now be further described in greater detail by reference to the following specific examples, which should not be construed as in any way limiting the scope of the invention.

Examples

Example 1 - Sublingual administration of exenatide to diabetic mice

[00103] 200mg standard placebo tablets containing sugars, amino acids, buffering agents and gel formers were manufactured using the inventor's microencapsulation technology as described in WO 2012/109694 (the disclosure of which is incorporated by reference herein in its entirety). Tablets were dissolved in 1 ml of water and homogenised lightly to form a smooth gel. This gel was used as a standard delivery vehicle, with or without exenatide (Vitapharm Technology Development Co. Ltd.).

[00104] Male diabetic mice (strain C57/BL6) were sourced from Shanghai SLAC Laboratory Animal Co. Ltd. (Shanghai, China). For the experiments described below,
mice of approximately 60g were used. Mice were fasted for six hours prior to administration of exenatide or placebo (-60 min). One hour later (0 min), an intraperitoneal glucose challenge was administered, and blood glucose measured at -60 min, 0 min, 30 min, 40 min, 60 min and 120 min. For administration, 5 µl gel containing various doses of exenatide or placebo were placed under the tongue of the mice using a micropipette.

[00105] In experiment 1, six groups of five mice were treated. In four treatment groups mice were administered 50 µg, 100 µg, 150 µg or 200 µg exenatide sublingually. These were compared to 1 µg subcutaneously administered exenatide and sublingual placebo. The results of experiment 1 are shown in Figure 1. Blood glucose levels in each treatment group at 0 min and at 20 min are shown in Figure 2. Area under the curve analysis of blood glucose levels between 0-120 min (AUCo-i20min) for each treatment group are shown in Figure 3.

[00106] In experiment 2, seven groups of five mice were treated. In five treatment groups mice were administered 2 µg, 5 µg, 10 µg, 25 µg or 50 µg exenatide sublingually. These were compared to 1 µg subcutaneously administered exenatide and sublingual placebo. The results of experiment 2 are shown in Figure 4. Blood glucose levels in each treatment group at 0 min and at 20 min are shown in Figure 5. Area under the curve analysis of blood glucose levels between 0-120 min (AUCo-no_m in) for each treatment group are shown in Figure 6.

[00107] Experiment 3 included four treatment groups, comprising sublingual administration of 10 µg (five mice), 15 µg (ten mice), 20 µg (ten mice) or 25 µg (five mice) exenatide. These were compared to 1 µg subcutaneously administered exenatide (five mice) and sublingual placebo (five mice). The results of experiment 3 are shown in Figure 7. Blood glucose levels in each treatment group at 0 min and at 20 min are shown in Figure 8. Area under the curve analysis of blood glucose levels between 0-120 min (AUCo-no_m in) for each treatment group are shown in Figure 9.

[00108] The results of these experiments demonstrate that sublingual delivery of exenatide is viable and effective. As determined by area under the curve analysis,
subcutaneous exenatide at 1 µg significantly lowered blood glucose levels compared to vehicle (placebo) between 0 - 120 min. Similarly, sublingually administered exenatide at 10 µg, 15 µg, 20 µg and 25 µg also significantly lowered blood glucose levels compared to vehicle (placebo) between 0 - 120 min, the efficacy being comparable between the doses upon statistical calculation. Sublingually administered exenatide at 10 µg, 15 µg, 20 µg and 25 µg significantly decreased the fasting glucose levels (i.e. without glucose challenge, at 60 min post exenatide administration).

[00109] Based on the above-described experiments, the bioavailability of the sublingually administered exenatide, produced using the inventor's gel matrix delivery system was 10%. Further, similar experiments revealed a bioavailability of approximately 20% using 5 µg exenatide (data not shown). These values compare very favourably (25 to 55 times greater) to the reported bioavailability of only 0.37% for exenatide administered sublingually at a dose of 210 µg (Gedullin et al, 2008, Int J Pharm 356:231-238).

Example 2 - Sublingual administration of exenatide in primates

Monkey study

[00110] A study of the relative bioavailability of sublingually administered exenatide compared to subcutaneous administration was conducted in monkeys. The exenatide was prepared as described in Example 1. Three monkeys were administered 5 µg exenatide subcutaneously and four monkeys were administered 20 µg exenatide sublingually and blood serum glucose levels determined by ELISA at regular intervals up to 2 hours after administration. As shown in Figure 10 sublingual administration results in improved regulation of serum glucose levels (steadier, less variable) compared to subcutaneously administered exenatide.

Human study

[00111] Studies of the effects of sublingually administered exenatide were then conducted in human subjects. The studies were similar to those conducted on mice (Example 1). Briefly, subjects were fasted overnight (11 hours) prior to administration of exenatide or placebo at 9:00 am (-60 min). One hour later (0 min), an intraperitoneal
glucose challenge was administered (75 g in 250 ml water), and blood glucose measured at -60 min, 0 min, 30 min, 40 min, 60 min and 120 min. For administration, tablets containing 100 µg exenatide (prepared using the same composition and in the same manner as the gel used in the mouse studies described above) or placebo were placed under the tongue of the subjects. For comparison, 5 µg exenatide (Byetta) was administered subcutaneously. The study comprised nine healthy (non-diabetic) subjects and two diabetic subjects (referred to below as diabetic subjects #1 and #2).

[00112] 100 µg exenatide administered sublingually had no adverse side effects in the healthy subjects or diabetic subjects. Serum glucose levels over a 2 hour period post administration in healthy subjects administered exenatide sublingually were entirely consistent with levels in subjects that received the sublingual placebo, increasing at 30 min post-administration before slowly reducing thereafter (data not shown). In contrast, in healthy subjects that received subcutaneous exenatide serum glucose levels remained essentially unchanged (data not shown).

[00113] Serum glucose levels in diabetic subject #1 are shown in Figure 11. It can be seen that compared to levels in a subject that received placebo or subcutaneously administered exenatide, the serum glucose levels in subject #1, who received exenatide sublingually, remained relatively constant over the 2 hour period post administration.

[00114] Diabetic subject #2 received 50 µg exenatide sublingually for three months (12 weeks). As shown in Figure 12, both fasting and post prandial blood glucose levels remained quite constant throughout treatment. At the start of treatment subject #2's haemoglobin Ale (HbAlc) levels were borderline high at 6.5, indicative of poor blood sugar control. After 12 weeks exenatide treatment HbAlc levels dropped to 6.3, within the normal range of 4 to 6.5. The subject suffered no side effects from the exenatide treatment and reported feeling significantly healthier and better after the 12 weeks of treatment.

[00115] Postprandial (+2 hours) plasma glucose levels were also followed over 11 days in a diabetic subject that received 20 µg exenatide sublingually and 500 mg metformin, as opposed to 500 mg metformin alone. As can be seen in Figure 13,
postprandial plasma glucose levels remained essentially constant over the 11 day period during the treatment using sublingual exenatide plus metformin, whereas levels were extremely variable on a daily basis during the treatment with metformin alone.

**Example 3 - Sublingual administration of exenatide and insulin to diabetic mice**

[00116] Experiments were conducted in diabetic mice using a combination sublingual therapy of 5 µg exenatide, demonstrated to be sub-therapeutic in Example 1, and 10 IU/kg of insulin (NovoLog®, Novo Nordisk), also demonstrated to be sub-therapeutic when administered sublingually alone (data not shown). The exenatide and the insulin were each prepared using the inventor's microencapsulation technology, as described in Example 1.

[00117] Diabetic mice were administered the combination in experiments carried out as described above in Example 1. As shown in Figure 14, the combination of sub-therapeutic amounts of exenatide and insulin administered sublingually had a significant synergistic effect.
Claims

1. A method for the treatment of metabolic syndrome or diabetes in a subject, the method comprising the oromucosal administration of an effective amount of an incretin mimetic to the subject.

2. The method of claim 1, wherein the incretin mimetic is a GLP-1 mimetic.

3. The method of claim 2, wherein the GLP-1 mimetic is exenatide or an analogue thereof.

4. The method of any one of claims 1 to 3, wherein the oromucosal administration is sublingual or buccal administration.

5. The method of any one of claims 1 to 4, wherein the oromucosal administration is sublingual.

6. The method of any one of claims 1 to 5 wherein the diabetes is type 2 diabetes.

7. The method of claim 3 wherein the exenatide comprises or consists of the amino acid sequence set forth in SEQ ID NO:1.

8. The method of claim 3 wherein the exenatide analogue is AC3174.

9. The method of claim 8 wherein the exenatide analogue AC3174 comprises or consists of the amino acid sequence set forth in SEQ ID NO:2.

10. The method of any one of claims 1 to 9 wherein the incretin mimetic is administered in solid or liquid unit dosage form.

11. The method of any one of claims 1 to 10 wherein the incretin mimetic is formulated in a gel matrix delivery system.

12. The method of any one of claims 1 to 11 wherein the incretin mimetic is
formulated in a composition using a process comprising the following steps:
(i) providing a coating liquid comprising the incretin mimetic, a saccharide and a water-
miscible solvent;
(ii) providing particles comprising one or more water-soluble gel-forming compounds;
(iii) fluidising the particles within a processing chamber of an apparatus in such a
manner that the particles move in an upward direction within the chamber in a helical
path;
(iv) spraying the coating liquid onto the particles so as to provide coated particles; and
(v) allowing the coated particles to dry.

13. The method according to any one of claims 1 to 12, further comprising the
administration of an effective amount of insulin or an analogue thereof.

14. The method of claim 13, wherein the insulin or analogue thereof is formulated in
the same composition as the incretin mimetic.

15. A method for regulating blood glucose levels in a subject, the method comprising
the oromucosal administration of an effective amount of an incretin mimetic to the
subject.

16. The method of claim 15, wherein the incretin mimetic is a GLP-1 mimetic.

17. The method of claim 16, wherein the GLP-1 mimetic is exenatide or an analogue
thereof.

18. The method of any one of claims 15 to 17, wherein the oromucosal administration
is sublingual or buccal administration.

19. The method of any one of claims 15 to 18, wherein the oromucosal administration
is sublingual.

20. The method of any one of claims 15 to 19, wherein the subject has diabetes,
typically type 2 diabetes, or metabolic syndrome.
21. The method of any one of claims 15 to 20, wherein regulating blood glucose levels in the subject comprises normalizing blood glucose levels.

22. The method of any one of claims 15 to 21, wherein regulating blood glucose levels in the subject prevents or treats, or assists in preventing or treating, hypoglycaemia or hyperglycaemia.

23. A method for preventing or treating hypoglycaemia or hyperglycaemia in a subject, the method comprising the oromucosal administration of an effective amount of an incretin mimetic to the subject.

24. The method of claim 23, wherein the incretin mimetic is a GLP-1 mimetic.

25. The method of claim 24, wherein the GLP-1 mimetic is exenatide or an analogue thereof.

26. The method of any one of claims 23 to 25, wherein the oromucosal administration is sublingual or buccal administration.

27. The method of any one of claims 23 to 26, wherein the oromucosal administration is sublingual.

28. The method of any one of claims 23 to 27, wherein the subject has diabetes, typically type 2 diabetes, or metabolic syndrome.

29. A pharmaceutical composition formulated for oromucosal administration for the treatment of diabetes or metabolic syndrome or for the regulation of blood glucose levels, the composition comprising an incretin mimetic.

30. The composition of claim 29 formulated using a process comprising the following steps:
(i) providing a coating liquid comprising the incretin mimetic, a saccharide and a water-
miscible solvent;
(ii) providing particles comprising one or more water-soluble gel-forming compounds;
(iii) fluidising the particles within a processing chamber of an apparatus in such a manner that the particles move in an upward direction within the chamber in a helical path;
(iv) spraying the coating liquid onto the particles so as to provide coated particles; and
(v) allowing the coated particles to dry.

31. The composition of claim 29 or 30, wherein the incretin mimetic is a GLP-1 mimetic.

32. The composition of claim 31, wherein the GLP-1 mimetic is exenatide or an analogue thereof.

33. The composition of any one of claims 29 to 32, further comprising insulin or an analogue thereof.

34. The composition of any one of claims 29 to 33, wherein the composition is a synergistic composition of exenatide and insulin.

35. Use of an incretin mimetic, and optionally insulin or an analogue thereof, for the manufacture of a medicament for treating diabetes or metabolic syndrome, and/or for regulating blood glucose levels, wherein the medicament is formulated for oromucosal administration.
FIGURE 1

IPGTT

- SL Vehicle
- SL 50ug CSSR Exenatide
- SL 100ug CSSR Exenatide
- SL 150ug CSSR Exenatide
- SL 200ug CSSR Exenatide
- SC 1ug Exenatide

Blood glucose (mmol/L)

Time (min)

Graph showing blood glucose levels over time with different treatments indicated.
**FIGURE 2**

A. Blood Glucose (0min)

B. Blood Glucose (20min)

***p<0.01 VS vehicle

*** P<0.01 vs Vehicle
FIGURE 3

A

IPGTT Glucose AUC<sub>0-120min</sub>

![Graph showing Blood Glucose AUC with different treatments and significance levels.]

**P < 0.01 vs Vehicle**

B

IPGTT Glucose AUC<sub>0-120min</sub>

![Bar chart showing percentage change in Blood Glucose AUC with different treatments.]

Change rate = (AUC<sub>cpd</sub> - AUC<sub>vehicle</sub>) / AUC<sub>vehicle</sub>
FIGURE 4

IPGTT

Blood glucose (mmol/L)

Time (min)

-60  0  60  120

SL Vehicle
SL 2ug CSSR Exenatide
SL 5ug CSSR Exenatide
SL 10ug CSSR Exenatide
SL 25ug CSSR Exenatide
SL 50ug CSSR Exenatide
SC 1ug Exenatide

test article
Glucose
FIGURE 5

A

**Blood Glucose (0min)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Blood Glucose (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>10</td>
</tr>
<tr>
<td>2ug CSSR</td>
<td>8.5</td>
</tr>
<tr>
<td>5ug CSSR</td>
<td>7.5</td>
</tr>
<tr>
<td>10ug CSSR</td>
<td>6.5</td>
</tr>
<tr>
<td>25ug CSSR</td>
<td>5.5</td>
</tr>
<tr>
<td>50ug CSSR</td>
<td>4.5</td>
</tr>
<tr>
<td>1ug Exenatide S.C.</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*p<0.01 VS vehicle

B

**Blood Glucose (20min)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Blood Glucose (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>20</td>
</tr>
<tr>
<td>2ug CSSR</td>
<td>18.5</td>
</tr>
<tr>
<td>5ug CSSR</td>
<td>17.5</td>
</tr>
<tr>
<td>10ug CSSR</td>
<td>16.5</td>
</tr>
<tr>
<td>25ug CSSR</td>
<td>15.5</td>
</tr>
<tr>
<td>50ug CSSR</td>
<td>14.5</td>
</tr>
<tr>
<td>1ug Exenatide S.C.</td>
<td>13.5</td>
</tr>
</tbody>
</table>

# P<0.05, * P<0.01 vs Vehicle
**FIGURE 6**

A

**IPGTT Glucose AUC<sub>0-120min</sub>**

<table>
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<tr>
<th></th>
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</tbody>
</table>

*** P<0.01 vs Vehicle

B

**IPGTT Glucose AUC<sub>0-120min</sub>**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>-8.7%</td>
<td>-33.0%</td>
<td>-42.1%</td>
<td>-51.2%</td>
<td>-55.0%</td>
<td>-59.7%</td>
</tr>
</tbody>
</table>

Change rate = (AUC<sub>cpd</sub>-AUC<sub>vehicle</sub>)/AUC<sub>vehicle</sub>
FIGURE 7

[Graph showing Blood glucose (mmol/L) vs. Time (min) with different treatments:
- SL Vehicle
- SL 10ug CSSR Exenatide
- SL 15ug CSSR Exenatide
- SL 20ug CSSR Exenatide
- SL 25ug CSSR Exenatide
- SC 1ug Exenatide]

Test article
Glucose
**FIGURE 8**

**A**

**Blood Glucose (0min)**

![Graph showing blood glucose levels at 0 minutes with vehicle, 10ug CSSR, 15ug CSSR, 20ug CSSR, 25ug CSSR, and 1ug Exenatide S.C. The bars are labeled with symbols indicating statistical significance: ***p<0.01 VS vehicle.]

**B**

**Blood Glucose (20min)**

![Graph showing blood glucose levels at 20 minutes with vehicle, 10ug CSSR, 15ug CSSR, 20ug CSSR, 25ug CSSR, and 1ug Exenatide S.C. The bars are labeled with symbols indicating statistical significance: # P<0.05, * P<0.01 vs Vehicle.]

# P<0.05 , * P<0.01 vs Vehicle
FIGURE 9

A

IPGTT Glucose AUC$_{0-120\text{min}}$

Blood Glucose AUC

Vehicle
10ug CSSR
15ug CSSR
20ug CSSR
25ug CSSR
1ug Exenatide S.C.

*** P<0.01 vs Vehicle

B

IPGTT Glucose AUC$_{0-120\text{min}}$

Blood Glucose AUC

10ug CSSR
15ug CSSR
20ug CSSR
25ug CSSR
1ug Exenatide S.C.

Change rate = (AUC_{cpd}-AUC_{vehicle})/AUC_{vehicle}