also typically require refrigerated storage, to ensure the integrity of the insulin. It should also be noted that absorption through the oral and nasal membranes avoids hepatic metabolism.

[00010] Another approach has been to tether the insulin to nanoparticles for oral delivery. Such nanoparticles have previously been made out of biopolymers. In one such example, chitosan which had been functionalised to be in the form of a quaternary ammonium salt was used as the core, and then coated with hyaluronic acid to absorb to the mucus layer of the intestine has been described. However, these nanoparticles are too large (approximate average size of about 120nm) to allow absorption of the nanoparticle *per se*, instead requiring release of the insulin in the intestine for use. In another such example, gold nanoparticles have been described to attach thiol-containing proteins to the gold surface. However, these nanoparticles are most effective as transdermal agents for absorption across the oral and nasal mucous membranes, with poor intestinal absorption recorded. As noted below, sublingual absorption avoids hepatic first pass metabolism.

[00011] While the discussion above relates to insulin as a primary example of a protein- or peptide-based outpatient therapy, the problems existing in the current state of the art relating to insulin delivery also exist for other proteins and peptides that may be therapeutically beneficial to a subject if formulated for oral administration.

[00012] Therefore, there is a need for compositions and methods facilitating the non-invasive administration of therapeutic proteins or peptides (e.g. insulin) which maintain biological activity when absorbed. It is desirable for the compositions and methods to be capable of oral administration allowing absorption by the intestine and entry into intestinal blood vessels. This may provide a means to overcome existing problems encountered during oral delivery of proteins and peptides such as insulin. Furthermore, in some specific applications it can be desirable for such compositions and methods to act primarily on the liver, the primary target for insulin action, which may reduce circulating systemic levels of insulin and limit adverse effects such as hypoglycaemia and weight gain.

Summary

[00013] The present disclosure aims to alleviate at least one existing deficiency in existing approaches for treating conditions arising from insufficient endogenous peptide or protein

production in subjects, and/or orally administering proteins and peptides to treat such conditions.

[00013a] In one aspect, the present disclosure relates to a composition comprising a therapeutic amount of a conjugate, wherein the conjugate comprises an Ag_2S quantum dot, a therapeutically effective peptide or protein and a polymer, wherein the composition is formulated for oral administration.

[00013b] In another aspect, the present disclosure relates to use of a conjugate comprising an Ag_2S quantum dot, insulin and a polymer in the manufacture of a medicament for treating hyperglycemia in a subject in need thereof, wherein the conjugate is formulated to be administered to the subject orally.

[00013c] In another aspect, the present disclosure relates to use of a conjugate comprising an Ag_2S quantum dot, an endogenous peptide or protein and a polymer in the manufacture of a medicament for treating insufficient endogenous peptide production in a subject in need thereof, wherein the conjugate is formulated to be administered to the subject orally.

[00013d] In another aspect, the present disclosure relates to use of a conjugate comprising an Ag_2S quantum dot, a therapeutic exogenous peptide or protein and a polymer in the manufacture of a medicament for treating a subject suffering from a condition, wherein the condition is treatable with administration of a therapeutic exogenous peptide or protein, wherein the conjugate is formulated to be administered to the subject orally.

[00013e] In another aspect, the present disclosure relates to use of a conjugate comprising an Ag_2S quantum dot, insulin and a polymer in the manufacture of a medicament for treating hyperglycemia in a subject, wherein the use comprises that the medicament is to be orally administered to the subject, wherein the quantum dot is an Ag_2S quantum dot between 5nm and 20 nm in diameter, wherein the conjugate is metabolized in a hepatocyte, thereby releasing the insulin into the blood stream of the subject.

[00013f] In another aspect, the present disclosure relates to use of a conjugate comprising an Ag_2S quantum dot, insulin and a polymer in the manufacture of a medicament for treating type I or type II diabetes.

[00013g] In another aspect, the present disclosure relates to a conjugate comprising an Ag_2S quantum dot, a protein or peptide and a polymer for use in therapy.

[00014] In a first example of the present disclosure, there is provided a composition comprising a therapeutic amount of a conjugate, wherein the conjugate comprises a quantum dot and a therapeutically effective peptide or protein. The peptide or protein may be less than about 30 kDa in size. It may be between 1 and 25 kDa, or between 3 and 25 kDa, 10 and 20 kDa, 5 and 30 kDa, or 15 and 30 kDa, i.e., it may be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 kDa. It may have a primary amine group available for attachment to the QD. It may be selected from the group consisting of insulin, growth hormone, fibroblast growth factor 21 (FGF21), a glucagon-like peptide-1 (GLP-1) agonist, a GLP-2 receptor agonist, a platelet derived growth factor (PDGF) beta receptor modulator, an integrin alpha-4/beta-7 antagonist, a PYY(3-36) analogue, vasopressin, interleukins (less than 30 kDa in size), enkephalins, endorphins or any other suitable protein or peptide, and combinations thereof. The insulin may be a native insulin (such as porcine-origin native insulin) or it may be a long-acting analogue (such as glargine insulin or detemir insulin), an intermediate-acting analogue (such as isophane insulin or Neutral Protamine Hagedorn insulin), or a fast-acting analogue (such as insulin aspart, insulin lispro or insulin glulisine). The GLP-1 agonist may be selected from liraglutide or exenatide or it may be any other suitable GLP-1 agonist. The GLP-2 agonist may be apraglutide or it may be any other suitable GLP-2 agonist. The PDGF beta receptor modulator may be BOT191 (also known as Fibroferon), or it may be any other suitable PDGF beta receptor modulator. The integrin alpha-4/beta-7 antagonist may be PN-10943 or it may be any other suitable integrin alpha-4/beta-7 antagonist. Other suitable peptides and proteins that are less than 30 kDa and comprise at least one primary amine group may be known to the skilled person and would be suitable for QD conjugation.

[00015] The following options may be used in conjunction with either the first or second example, either individually or in any suitable combination.

[00016] The composition may be formulated for oral administration.

[00017] The quantum dot may be an Ag_2S quantum dot. The average diameter of the quantum dot may be between about 1 nm and about 20 nm. It may be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,

12, 13, 14, 15, 16, 17, 18, 19 or 20 nm. The average diameter of the quantum dot may be less than about 10 nm.

[00018] The conjugate may further comprise a polymer. The polymer may be a biopolymer. The biopolymer may cover at least part of the conjugate or it may cover substantially all of the conjugate. The biopolymer may be selected from the group consisting of heparin, gelatin, hyaluronic acid, chitosan, galactose, glucose, and any combination thereof. The polymer or the biopolymer may cover at least part of the conjugate. These polymers or biopolymers may protect the protein or peptide of the conjugate during transit through the gastrointestinal tract or specifically target the hepatocytes in the liver. The conjugate may accumulate in or on the surface of a hepatocyte of the subject after oral administration.

[00019] The composition may be for administration to a subject that may have been diagnosed with a condition related to insufficient endogenous peptide production. The condition may be type I or type II diabetes or another condition related to insufficient endogenous peptide production. The composition may be for administration to a subject that may have been diagnosed with a condition requiring treatment by an exogenous (i.e., not naturally occurring) protein or peptide. The condition may be diabetic nephrology, liver fibrosis, non-alcoholic steatohepatitis (NASH), renal fibrosis, celiac disease, inflammatory bowel disease (IBD), ulcerative colitis or another gastrointestinal disease. The condition may be treated or treatable by delivery of the protein or peptide to the liver, small bowel, kidneys, pancreas or other gastrointestinal organ or tissue.

[00020] The composition may further comprise a pharmaceutically acceptable excipient.

[00021] In a second example of the present disclosure, there is provided a method of treating hyperglycemia in a subject in need thereof, the method comprising administering to the subject a therapeutic amount of a conjugate comprising a quantum dot and insulin.

[00022] In a third example of the present disclosure, there is provided a method of treating insufficient endogenous peptide production in a subject in need thereof, the method comprising administering to the subject a therapeutic amount of a conjugate comprising a quantum dot and a protein or peptide effective in replacing the insufficient endogenous peptide.

[00023] In a fourth example of the present disclosure, there is provided a method of treating a subject suffering from a condition, wherein the condition is treatable with administration of a therapeutic exogenous peptide or protein, the method comprising administering to the subject a therapeutic amount of a conjugate comprising a quantum dot and the therapeutic exogenous peptide or protein.

[00024] The following options may be used in conjunction with either the second, third or fourth, either individually or in any suitable combination.

[00025] The conjugate may be administered to the subject orally. The subject may have been diagnosed with diabetes or another condition resulting in insufficient amounts of an endogenous peptide or protein in the tissues of the subject. The diabetes being treated in the subject may be type I or type II diabetes.

[00026] The quantum dot may be an Ag_2S quantum dot. The average diameter of the quantum dot is between about 5nm and about 20nm, or it may be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 nm.

[00027] The conjugate may further comprise a polymer. The polymer may be a biopolymer. The biopolymer may at least partially coat the conjugate, or it may substantially coat the conjugate. The biopolymer may be selected from the group consisting of heparin, gelatin, hyaluronic acid, chitosan, galactose, glucose, and any combination thereof.

[00028] In a fifth example of the present disclosure, there is provided a method of delivering a peptide or protein to an organ of a subject, the method comprising orally administering a conjugate comprising a quantum dot and the peptide or protein to the subject, wherein the organ is selected from the liver, pancreas, small bowel or kidneys.

[00029] The following options may be used in conjunction with the fifth example, either individually or in any suitable combination.

[00030] The quantum dot may be a Ag_2S quantum dot. The Ag_2S quantum dot may be between about 5nm and about 20 nm in diameter.

[00031] The conjugate may optionally comprise a polymer. The polymer may be a biopolymer. The biopolymer may be selected from the group consisting of gelatin, chitosan, galactose, glucose, and any combination thereof.

[00032] In a sixth example of the present disclosure, there is provided a method of lowering blood glucose in a subject, the method comprising orally administering a conjugate comprising a quantum dot and insulin as described herein to the subject, wherein the quantum dot is an Ag_2S quantum dot between about 5nm and about 20 nm, and wherein the conjugate is metabolized in or bound to the surface of a hepatocyte, thereby releasing the insulin into the blood stream of the subject

[00033] In a seventh example of the present disclosure, there is provided use of a conjugate comprising a quantum dot and insulin as described herein for the manufacture of a medicament for the treatment of type I and type II diabetes. The medicament may be formulated for oral administration. The medicament may further comprise a polymer or a biopolymer.

[00034] In an eighth example of the present disclosure, there is provided use of a conjugate comprising a quantum dot and a protein or peptide in the preparation of a medicament. The medicament may be for treating insufficient endogenous production of the peptide or protein in a subject or it may be for providing a therapeutically active exogenous peptide or protein. The medicament may be formulated for oral administration. The medicament may further comprise a polymer or a biopolymer.

Brief Description of Drawings

[00035] Preferred embodiments of the present invention will now be described, by way of example only, with reference to the accompanying figures, wherein:

[00036] Figure 1 shows a schematic representation of a method for synthesizing and characterising water soluble Ag_2S quantum dots of the present invention. Specifically: (a) Schematic illustrating production of cyclohexane soluble QDs. (b) NIR II emission at 1175 nm from 658 nm excitation. (c) FTIR spectra demonstrating dodecane C-H chains on the surface of QDs. (d) TEM images of QDs showing arrangement, size and lattice structure. (e) schematic of phase transfer of COOH capped QDs with representative samples of 1 mM QDs in organic

CLAIMS

1. A composition comprising a therapeutic amount of a conjugate, wherein the conjugate comprises an Ag_2S quantum dot, a therapeutically effective peptide or protein and a polymer, wherein the composition is formulated for oral administration.

2. The composition of claim 1, wherein the peptide or protein is less than 30 kDa in size.

3. The composition of claim 1 or claim 2, wherein the peptide or protein is selected from the group consisting of insulin, growth hormone, fibroblast growth factor 21 (FGF21) a glucagon-like peptide-1 (GLP-1) agonist, a glucagon-like peptide-2 (GLP-2) agonist, a platelet derived growth factor (PDGF) beta receptor modulator, and an integrin alpha-4/beta-7 antagonist, a PYY(3-36) analogue, vasopressin, interleukins (less than 30 kDa in size), enkephalins, endorphins and combinations thereof.

4. The composition of claim 3, wherein:
   the GLP-1 agonist is liraglutide or exenatide; and/or
   the GLP-2 agonist is apraglutide; and/or
   the PDGF beta receptor modulator is BOT191; and/or
   the integrin alpha-4/beta-7 antagonist is PN-10943.

5. The composition of any one of claims 1 to 4, wherein the average diameter of the Ag_2S quantum dot is between 1 nm and 10 nm and/or the average hydrodynamic diameter of the conjugate is between 30 nm and 100 nm.

6. The composition of any one of claims 1 to 5, wherein the polymer is a biopolymer that comprises any two or more selected from the group consisting of chitosan, galactose and glucose.

7. The composition of any one of claims 1 to 6, wherein the polymer or the biopolymer covers at least part of the conjugate.

8. The composition of any one of claims 1 to 7, wherein the conjugate accumulates on/in a hepatocyte of the subject after oral administration.

9. The composition of any one of claims 1 to 8, wherein the composition comprises a pharmaceutically acceptable excipient.

10. Use of a conjugate comprising an Ag_2S quantum dot, insulin and a polymer in the manufacture of a medicament for treating hyperglycemia in a subject in need thereof, wherein the conjugate is formulated to be administered to the subject orally.

11. Use of a conjugate comprising an Ag_2S quantum dot, an endogenous peptide or protein and a polymer in the manufacture of a medicament for treating insufficient endogenous peptide production in a subject in need thereof, wherein the conjugate is formulated to be administered to the subject orally.

12. Use of a conjugate comprising an Ag_2S quantum dot, a therapeutic exogenous peptide or protein and a polymer in the manufacture of a medicament for treating a subject suffering from a condition, wherein the condition is treatable with administration of a therapeutic exogenous peptide or protein, wherein the conjugate is formulated to be administered to the subject orally.

13. The use of claim 12, wherein the condition is selected from diabetic nephrology, liver fibrosis, non-alcoholic steatohepatitis (NASH), renal fibrosis, celiac disease, inflammatory bowel disease (IBD), ulcerative colitis or another gastrointestinal disease.

14. The use of claim 12, wherein the condition is type I or type II diabetes.

15. The use of any one of claims 10 to 14, wherein the polymer is a biopolymer that comprises any two or more selected from chitosan, galactose and glucose.

16. The use of claim 15, wherein the biopolymer at least partially coats the conjugate.

17. The use of any one of claims 10 to 16, wherein the average diameter of the Ag_2S quantum dot is between 5nm and 10 nm in diameter and/or the average hydrodynamic diameter of the conjugate is between 30 nm and 100 nm.

18. Use of a conjugate comprising an Ag_2S quantum dot, insulin and a polymer in the manufacture of a medicament for treating hyperglycemia in a subject, wherein the use comprises

that the medicament is to be orally administered to the subject, wherein the quantum dot is an Ag_2S quantum dot between 5nm and 20 nm in diameter, wherein the conjugate is metabolized in a hepatocyte, thereby releasing the insulin into the blood stream of the subject.

19. Use of a conjugate comprising an Ag_2S quantum dot, insulin and a polymer in the manufacture of a medicament for treating type I or type II diabetes.

20. A conjugate comprising an Ag_2S quantum dot, a protein or peptide and a polymer for use in therapy.

21. The conjugate of claim 20, wherein the therapy comprises insufficient endogenous production of the peptide or protein in a subject.

22. The use of claim 19 or the conjugate of claim 20 or 21, wherein the medicament or conjugate is to be formulated for oral administration.

23. The use of claim 19 or 22 or the conjugate of any one of claims 20 to 22, wherein the polymer is a biopolymer.