BIODEGRADABLE NANOPARTICLES

TECHNICAL FIELD

The present invention relates to biodegradable nanoparticles which are particularly useful in the treatment of disorders such as diabetes, oral dosage forms containing such nanoparticles and methods of making the nanoparticles.

BACKGROUND ART

The vast majority of peptide biopharmaceuticals such as insulin are administered by intravenous or subcutaneous injection. These routes of administration are often inconvenient and painful, particularly when multiple daily injections are required.

Attempts have therefore been made to provide oral administration of peptide biopharmaceuticals such as insulin to overcome these drawbacks.

Oral administration of peptide biopharmaceuticals is challenging since the therapeutically active peptides are subject to degradation and/or destabilisation in the acidic conditions of the stomach. Another obstacle is the permeability of the intestinal mucosa to peptides, which determines the extent of intestinal absorption and the efficiency of therapeutic action.

Sophisticated strategies are therefore required to preserve the therapeutically active peptides in the stomach and to enhance intestinal absorption.

A well-known approach is the encapsulation in polymeric nanoparticles. However, this strategy may not be suitable for oral administration of therapeutically active peptides due to the difficulty of encapsulation with acceptable drug loading.

For example, the article "Peptide-Polymer Interactions during Polymerisation of Polyalkyl Cyanoacrylate Nanoparticles" (Journal of Controlled Release, March 2015),

herein referred to as D2, polyethyl cyanoacrylate and poly-n-butyl cyanoacrylate nanoparticles are formed including bioactive peptides including insulin. The nanoparticles in D2 are prepared by anionic polymerisation and it is observed that covalent peptide-polymer bonds form in nanoparticles for some bioactive peptides, but not for insulin.

The covalent bonds impair bioactivity, and D2 investigates the effect of lowering the pH of polymerisation on the nanoparticles. They find that at low pH (pH 1.9) stable, well-shaped nanoparticles comprising insulin cannot be formed, and the insulin loading is unacceptably low at 4%.

D1 (WO 91/00XXX) describes polymeric nanoparticles based on polyisobutyl cyanoacrylate comprising entrapped insulin, prepared by interfacial polymerisation. D1 suggests that further substances may be present in the nanoparticles, such as pharmaceutically acceptable stabilisers.

The problem addressed by the present invention is to provide nanoparticles which are not only stable and well-shaped with acceptable insulin loading, but also provide a significant reduction in blood glucose levels which can be maintained over a prolonged period of time after oral administration.

The present invention solves this problem by providing biodegradable nanoparticles as defined in claim 1. Surprisingly, these nanoparticles provide the advantages of providing therapeutically effective insulin concentrations in the blood for longer periods, as described herein. Furthermore, the nanoparticles are stable and well-shaped with acceptable levels of insulin loading.

Neither D1 nor D2 teach this solution to the above problem.

SUMMARY OF THE INVENTION

In a first aspect, the invention provides biodegradable nanoparticles according to claim 1.

Such nanoparticles which entrap insulin in the form of a non-covalent complex provide the advantage of releasing insulin over a prolonged period of time after oral administration, and provides enhanced intestinal absorption.

Furthermore the use of a C_2-C_6 monomer ensures physical stability of the nanoparticles and good insulin loading, without which the enhanced effect of prolonged release would not be possible.

In a second aspect, the invention provides an oral dosage form according to claim 5 comprising nanoparticles of the first aspect.

In this way, the nanoparticles can be easily administered orally in order to treat a particular disease.

In a third aspect, the invention provides nanoparticles or oral dosage form for use as a medicament, according to claim 8.

In a fourth aspect, the invention provides nanoparticles or an oral dosage form for use in a method of treatment of a disorder associated with elevated blood glucose levels, according to claim 9.

In a fifth aspect, the invention provides a method of manufacturing biodegradable nanoparticles according to claim 11.

The claimed method provides biodegradable nanoparticles including a non-covalent insulin complex and a pharmaceutically acceptable stabiliser, thereby demonstrating good physical stability, morphology and insulin loading and allowing insulin to be released over a long period and more effectively absorbed by the intestine.

It is believed that this is due to the physiochemical properties of insulin and to the mechanism of anionic polymerisation. Insulin has an isoelectric point of 5.3. At a pH below 5.3, it is capable of being positively charged. At a pH of 2 or less, insulin has a strong positive net charge and therefore, it can form a non-covalent complex with the negatively charged PACA chains during the polymerisation reaction.

DETAILED DESCRIPTION

Preferably, at least 90% of the nanoparticles have a hydrodynamic diameter between 100 nm and 300 nm more preferably 120 nm to 280 nm as measured by dynamic light scattering. This ensures good intestinal absorption.

Preferably C_2-C_6 alkyl 2-cyanoacrylate monomers are selected from ethyl 2-cyanoacrylate and n-butyl 2-cyanoacrylate. Such monomers provide nanoparticles with good stability, morphology and insulin loading.

Preferably, the pharmaceutically acceptable stabiliser is selected from dextran, chitosan and pectin. Such stabilisers ensure nanoparticles have good physical stability and morphology and high insulin loading. Dextran is particularly preferred.

Preferably, the insulin loading, i.e. the amount of insulin relative to the total weight of nanoparticles, of 15-30 wt %.

Preferably, the oral dosage form is a capsule or tablet, for ease of administration.

Preferably, the oral dosage form further comprises a coating. This provides additional protection while the dosage form passes through the stomach.

Preferably, the disorder associated with elevated blood glucose levels is diabetes, more preferably type-2 diabetes. In this way, the nanoparticles provide an effective treatment for these diseases.

In the method according to the fifth aspect, preferably the organic solvent is chloroform.

Preferably, the oil is eythl oleate.

Preferably, the noionic surfactant is selected from sorbitan monolaureate and polyvinyl alcohol.

Preferably, the C_2-C_6 alkyl 2-cyanocrylate monomer and insulin are in a weight ratio of 2:1.

Preferably, the pharmaceutically acceptable stabiliser is present in an amount of 0.5 to 1 % relative to the weight of insulin.

The invention will now be demonstrated in more detail by the following examples.

CLAIMS

1. Biodegradable nanoparticles based on a biodegradable homopolymer of C_2 – C_6 alkyl 2-cyanoacrylate monomers, comprising a non-covalent insulin complex encapsulated or entrapped therein along with a pharmaceutically acceptable stabiliser, wherein;

    the nanoparticles have a hydrodynamic diameter of 300 nm or less as measured by dynamic light scattering and comprise 10 to 30 % by weight of insulin relative to the total weight of the nanoparticles.

2. Biodegradable nanoparticles according to claim 1, wherein at least 90 % of the nanoparticles have a hydrodynamic diameter between 100 nm and 300 nm.

3. Biodegradable nanoparticles according to claims 1 or 2, wherein the C_2-C_6 alkyl 2-cyanoacrylate monomers are selected from ethyl 2-cyanoacrylate and n-butyl 2-cyanoacrylate.

4. Biodegradable nanoparticles according to any one of claims 1 to 3, wherein the pharmaceutically acceptable stabiliser is selected from dextran, chitosan and pectin, preferably dextran.

5. An oral dosage form comprising biodegradable nanoparticles according to any one of claims 1 to 4.

6. An oral dosage form according to claim 5, which is a tablet or capsule.

7. An oral dosage form according to claim 5 or 6, further comprising a coating.

8. Biodegradable nanoparticles according to any one of claims 1 to 4 or an oral dosage form according to any one of claims 5 to 7, for use as a medicament.

9. Biodegradable nanoparticles according to any one of claims 1 to 4, or oral dosage form according to any one of claims 5 to 7, for use in a method of treatment of a disorder associated with elevated blood glucose levels.

10. Biodegradable nanoparticles or oral dosage form for use according to claim 9, characterised in that the disorder is diabetes, in particular type-2 diabetes.

11. A method manufacturing the biodegradable nanoparticles of claim 1 by anionic polymerisation, comprising the steps of:

   a. Dissolving a therapeutically effective amount of insulin in an aqueous solution of pH less than or equal to 2 comprising a pharmaceutically acceptable stabiliser;
   b. Mixing the aqueous solution with an oil and a non-ionic surfactant and stirring to form a water-in-oil emulsion;
   c. Dissolving a C_2-C_6 alkyl 2-cyanoacrylate monomer in an organic solvent;
   d. Slowly adding the organic solution of the monomer from step c to the nanoemulsion from step b under continuous stirring thereby spontaneously initiating polymerisation;
   e. Allowing polymerisation to progress and the organic solvent to evaporate, thereby producing nanoparticles; and
   f. Separating the nanoparticles from the nanoemulsion and purifying them.

12. A method according to claim 11 wherein the pharmaceutically acceptable stabiliser is selected from dextran, chitosan and pectin.

13. A method according to claim 12, wherein the stabiliser is dextran.

14. A method according to any one of claims 11 to 13, wherein the organic solvent is chloroform and/or the oil is ethyl oleate.

15. A method according to any one of claims 11 to 14, wherein the nonionic surfactant is selected from sorbitan monolaurate and polyvinyl alcohol.

Category		Max. possible	Marks Marker	Marker
Independent claims	Product claim	32	32	32
Independent claims	Method for preparing the nanoparticles	24	24	24
Independent claims	Oral dosage and medical use	14	12	12
Dependent claims	Dependent claims	15	11	12
Description	Description	15	13	13
Total			**92**	**93**

Examination Committee I agrees on 93 points and recommends the grade PASS