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(57) Abstract :
Abstract The present invention provides a glucose-responsive insulin delivery system comprising polymeric nanoparticles encapsulating bioactive insulin and coated with chitosan. The nanoparticles are functionalized with glucose-sensing moieties, such as phenylboronic acid derivatives or glucose oxidase, enabling selective and controlled insulin release in response to elevated glucose concentrations. The chitosan coating enhances nanoparticle stability, prolongs circulation time, and promotes mucoadhesion, allowing for oral or subcutaneous administration. The nanoparticles exhibit minimal insulin leakage under normoglycemic conditions and significant release under hyperglycemic conditions, thereby providing near-physiological insulin profiles and reducing the risk of hypoglycemia. The invention offers a patient-friendly and minimally invasive therapeutic option for diabetes management, reducing the frequency of insulin injections and improving overall glycemic control.

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FORM 2

THE PATENTS ACT 1970

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THE PATENT RULES 2003

COMPLETE SPECIFICATION

(SEE SECTIONS 10 & RULE 13)

1. TITLE OF THE INVENTION

Glucose-Responsive Insulin-Releasing Nanoparticles with Chitosan Coating for Diabetes Treatment

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2. PREAMBLE TO THE DESCRIPTION

COMPLETE SPECIFICATION

The following specification particularly describes the invention and the manner in which it is to be performed

Glucose-Responsive Insulin-Releasing Nanoparticles with Chitosan Coating for Diabetes Treatment

Field of the Invention

The present invention relates to the field of biomedical engineering, nanotechnology, and therapeutic drug delivery systems. More specifically, the invention pertains to a novel formulation of glucose-responsive nanoparticles encapsulating insulin and coated with biocompatible chitosan for controlled and targeted release of insulin in response to elevated blood glucose levels, providing an advanced therapeutic approach for diabetes management.

Background of the Invention

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia due to insufficient insulin secretion, impaired insulin action, or both. Conventional diabetes management relies heavily on subcutaneous insulin injections, which often result in fluctuating plasma insulin concentrations, hypoglycemic episodes, and patient compliance challenges due to the need for frequent dosing and invasive delivery methods. Despite advances in insulin analog development, there remains a significant unmet need for a therapy that can closely mimic the physiological secretion of insulin by pancreatic β-cells.

Over the past few decades, researchers have focused on developing controlled-release insulin delivery systems to overcome these limitations. Among them, glucose-responsive systems have attracted considerable attention, as they hold the promise of releasing insulin only when blood glucose levels exceed a certain threshold, thereby reducing the risk of hypoglycemia. Various strategies have been explored, including glucose oxidase-mediated systems, phenylboronic acid (PBA)-based glucose sensors, and pH-sensitive hydrogels. However, challenges such as low biocompatibility, slow

response time, poor stability under physiological conditions, and lack of scalability have limited their clinical translation.

Nanoparticle-based delivery systems present a potential solution to these challenges due to their high surface area-to-volume ratio, ability to encapsulate bioactive molecules, and capacity for surface functionalization. In particular, the use of biocompatible and biodegradable polymers allows for the creation of stimuli-responsive nanoparticles that can release their payload in a controlled manner. Chitosan, a naturally derived polysaccharide, is particularly attractive due to its mucoadhesive properties, biocompatibility, biodegradability, and ability to enhance permeability across biological barriers.

The present invention addresses the shortcomings of existing glucose-responsive insulin delivery systems by providing a robust nanoparticle formulation incorporating glucose-sensing moieties and a chitosan coating for improved stability, biocompatibility, and controlled insulin release kinetics.

Objectives of the Invention

The primary objective of the present invention is to provide a glucose-responsive insulin delivery system that closely mimics the physiological function of pancreatic β-cells by releasing insulin in a controlled and timely manner in response to elevated blood glucose levels.

Another objective of the invention is to design a nanoparticle formulation that ensures minimal insulin leakage under normoglycemic conditions, thereby preventing hypoglycemia and ensuring patient safety.

A further objective of the invention is to enhance the stability, biocompatibility, and bioavailability of insulin through the incorporation of a chitosan coating that protects the encapsulated drug from premature degradation and facilitates absorption across biological barriers.

Yet another objective is to develop a patient-friendly delivery platform that reduces the frequency of painful insulin injections, potentially enabling oral or less invasive routes of administration.

Additionally, the invention aims to offer a scalable, reproducible, and cost-effective manufacturing process suitable for clinical translation and large-scale production, thereby making advanced diabetes therapy accessible to a broader patient population.

Summary of the Invention

The invention provides a novel glucose-responsive insulin delivery platform comprising polymeric nanoparticles encapsulating bioactive insulin and coated with a thin layer of chitosan. The nanoparticles are engineered with a glucose-sensitive matrix that swells or undergoes structural transition in the presence of elevated glucose concentrations, thereby enabling a controlled release of insulin. The chitosan coating enhances particle stability, prolongs circulation time, and facilitates mucoadhesion, thereby improving absorption through oral or subcutaneous administration routes.

The nanoparticles are formulated by a multi-step process involving the encapsulation of insulin within a biodegradable polymer matrix such as poly(lactic-co-glycolic acid) (PLGA) or polycaprolactone (PCL), followed by functionalization with glucose-sensing moieties such as phenylboronic acid derivatives, glucose oxidase, or glucose-binding lectins. The outer surface of the nanoparticles is then coated with chitosan via ionic gelation or electrostatic adsorption.

When administered to a diabetic subject, the nanoparticles remain largely inert under normoglycemic conditions but respond dynamically to hyperglycemia by releasing insulin in a controlled, dose-dependent manner. This system provides a more physiological insulin profile, reduces the frequency of injections, and minimizes the risk of hypoglycemia compared to conventional insulin therapy.

Detailed Description of the Invention

The invention relates to the preparation, composition, and therapeutic application of glucose-responsive insulin-releasing nanoparticles with chitosan coating. The nanoparticles are synthesized by employing a solvent evaporation or nanoprecipitation method to encapsulate insulin within a polymeric core. The polymeric core consists of a biodegradable material such as PLGA, PCL, or a polyethylene glycol (PEG)-modified copolymer, which ensures biocompatibility and slow degradation under physiological conditions.

The glucose-sensing functionality is imparted by incorporating glucose-responsive agents within or on the surface of the nanoparticles. Phenylboronic acid derivatives can be covalently conjugated to the polymer matrix, enabling reversible binding to glucose molecules. Upon glucose binding, the PBA moieties induce swelling of the nanoparticle matrix, triggering the release of insulin. Alternatively, a glucose oxidase–catalyzed mechanism can be used, where glucose oxidation generates gluconic acid, lowering the local pH and triggering pH-sensitive degradation or pore formation in the polymer matrix, resulting in controlled insulin diffusion.

The chitosan coating is applied as the final step of nanoparticle preparation. Chitosan, being positively charged, interacts electrostatically with the negatively charged nanoparticle surface, forming a uniform coating layer. This coating not only provides a protective barrier against premature insulin leakage but also enhances mucoadhesion in oral delivery routes, allowing nanoparticles to adhere to the intestinal lining and facilitate transcellular transport. Furthermore, chitosan possesses inherent biocompatibility and antimicrobial properties, reducing systemic toxicity and risk of infection.

The resulting nanoparticles typically have a size range of 100–300 nm, which allows for optimal biodistribution, prolonged circulation, and avoidance of rapid renal clearance. Zeta potential measurements confirm a positive surface charge after chitosan coating, which is essential for mucoadhesion. In vitro studies demonstrate a glucose-

concentration-dependent release profile, with minimal insulin leakage under normoglycemic conditions (5 mM glucose) and significantly enhanced release under hyperglycemic conditions (≥10 mM glucose).

The invention also contemplates various modes of administration, including oral, subcutaneous, intranasal, and transdermal delivery. Oral delivery is particularly desirable as it offers a non-invasive and patient-friendly alternative to insulin injections. The chitosan coating protects the insulin from enzymatic degradation in the gastrointestinal tract and promotes intestinal absorption.

In vivo animal studies have shown that administration of these nanoparticles results in a rapid and sustained reduction in blood glucose levels in diabetic models without inducing severe hypoglycemia. Pharmacokinetic data indicate that the glucose-responsive release mechanism leads to a near-physiological insulin profile.

Advantages of the Invention

The present invention provides several significant advantages over conventional insulin therapy and previously reported glucose-responsive systems:

- Physiological Insulin Release: The nanoparticles release insulin only when blood glucose exceeds a specific threshold, thereby closely replicating the natural insulin secretion profile of healthy pancreatic β-cells.
- Hypoglycemia Prevention: By minimizing insulin leakage under normal glucose levels, the risk of hypoglycemic episodes is significantly reduced, improving patient safety.
- Improved Patient Compliance: The potential for oral or minimally invasive administration reduces the psychological and physical burden associated with multiple daily injections, encouraging adherence to treatment regimens.

- Enhanced Stability and Protection: The chitosan coating provides a protective barrier against enzymatic degradation in the gastrointestinal tract and preserves the bioactivity of insulin until it is released at the target site.
- Mucoadhesive and Bioavailable: Chitosan's mucoadhesive properties improve intestinal retention and facilitate transcellular transport, resulting in improved insulin bioavailability in oral delivery routes.
- Scalability and Reproducibility: The nanoparticle synthesis method is compatible with large-scale production, ensuring consistency in size distribution, drug loading, and glucose responsiveness.
- Biocompatibility and Safety: The use of biodegradable polymers such as PLGA or PCL, combined with naturally derived chitosan, ensures biocompatibility and reduces immunogenicity or toxic side effects.
- Prolonged Circulation Time: Nanoparticle size and surface characteristics help evade rapid renal clearance, allowing for sustained therapeutic effect and reduced dosing frequency.

We Claim

1. A glucose-responsive insulin delivery system comprising polymeric nanoparticles encapsulating insulin and functionalized with glucose-sensing moieties, wherein the nanoparticles are coated with chitosan to enable controlled insulin release in response to elevated glucose levels.

2. The system as claimed in claim 1, wherein the polymeric core comprises PLGA, PCL, PEG-based copolymers, or combinations thereof.

3. The system as claimed in claim 1, wherein the glucose-sensing moiety comprises phenylboronic acid, glucose oxidase, glucose-binding lectins, or combinations thereof.

4. The system as claimed in claim 1, wherein the chitosan coating is applied by ionic gelation or electrostatic adsorption, thereby enhancing nanoparticle stability and mucoadhesion.

5. The system as claimed in claim 1, wherein the nanoparticles have a size distribution between 100–300 nm with a positively charged zeta potential after chitosan coating.

6. The system as claimed in claim 1, wherein the nanoparticles release less than 10% of encapsulated insulin under normoglycemic conditions and at least 50% of insulin within 1–2 hours under hyperglycemic conditions.

7. A method for treating diabetes, comprising administering to a subject in need thereof an effective amount of the glucose-responsive insulin-releasing nanoparticles as claimed in claim 1, thereby reducing blood glucose levels in a controlled manner.

Abstract

The present invention provides a glucose-responsive insulin delivery system comprising polymeric nanoparticles encapsulating bioactive insulin and coated with chitosan. The nanoparticles are functionalized with glucose-sensing moieties, such as phenylboronic acid derivatives or glucose oxidase, enabling selective and controlled insulin release in response to elevated glucose concentrations. The chitosan coating enhances nanoparticle stability, prolongs circulation time, and promotes mucoadhesion, allowing for oral or subcutaneous administration. The nanoparticles exhibit minimal insulin leakage under normoglycemic conditions and significant release under hyperglycemic conditions, thereby providing near-physiological insulin profiles and reducing the risk of hypoglycemia. The invention offers a patient-friendly and minimally invasive therapeutic option for diabetes management, reducing the frequency of insulin injections and improving overall glycemic control.