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Research Article

RECENT TRENDS IN DIABETES TREATMENT USING NANOTECHNOLOGY

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Abstract

This review article discusses the potential applications of nanoparticles and BioMEMS as drug delivery systems for diabetes treatment. This manuscript discusses polymeric nanoparticles, oral insulin administration using polysaccharides and polymeric nanoparticles, inhalable insulin nanoparticle formulations, and insulin delivery using BioMEMS. In addition to ceramic and polymeric nanoparticles, studies on gold nanoparticles for insulin delivery and treatment of diabetes-associated symptoms are discussed. There are a few limitations in them use of conventionally available drug delivery systems for diabetes treatment. This article reviews the subject in brief with suitable references to original research articles and review articles on earlier and current research findings about various types of nanoparticles and BioMEMS in diabetes treatment and their limitations.

Introduction

The field of nanotechnology has been undergoing tremendous development in the recentdecade. Nanotechnology is the ability to work at the atomic, molecular, supramolecular levels (on a scale of ~1-100nm) in order to understand, create and use material structures, devices and systems with fundamentally new properties and functions resulting from their small structure.In addition to the developments in scientific disciplines such as electronics, material science, space research and robotics, nanotechnology is expected to make significant advances in mainstream biomedical applications, including the areas of gene therapy, imaging and novel drug discovery and drug delivery in the treatment of diseases like diabetes, cancer, etc. There are a few limitations in the use of conventionally available drug delivery systems. Lack of target specificity, altered effects and diminished potency due to drug metabolism in the body,cytotoxicity of certain anticarcinogenic pharmacological agents, are to mention a few. Biocompatible nanoparticles with optimized physical, chemical and biological properties can overcome these limitations and serve as effective drug delivery systems. These newer generations of drug delivery systems have significant advantages over conventionally available drug delivery systems. This manuscript discusses the need for nanoparticulate drug

delivery systems, their advantages, limitations and recent advances in application of such drug delivery systems in the treatment of diabetes.

Diabetes, types and its etiology

Diabetes mellitus, often referred as diabetes is caused by decrease in insulin secretion by pancreatic islet cells leading to increase in blood glucose level (hyperglycemia). Diabetes insipidus is a condition characterized by excretion of large amounts of severely diluted urine, which cannot be reduced when fluid intake is reduced. This is caused due to deficiency of antidiuretic hormone(ADH) also known as vasopressin secreted by the posterior pituitary gland. Diabetes mellitus is characterised by excessive weight loss, increased urge for urination (polyuria), increased thirst (polydipsia) and an excessive desire to eat (polyphagia). Diabetes mellitus has been classified as Type 1 or insulin dependent diabetes, Type 2 or noninsulin dependent diabetes and Gestational diabetes. Type 1 diabetes mellitus is characterized by loss of insulin-producing beta cells of islets of Langerhans in the pancreas, thereby leading to deficiency of insulin. The main cause of this beta cell loss is T-cell mediated autoimmune attack. Type 1 diabetes in children is termed as juvenile diabetes. Type 2 diabetes mellitus is caused by insulin resistance or reduced insulin sensitivity combined with reduced insulin secretion.Control of blood sugar level through modified dietary sugar intake, physical exercise, insulin therapy and oral medications have been advised for control of Type 1 diabetes mellitus.Nanomedicine research over the past few decades have been aimed at the applications of nanoparticles for Type 1 diabetes mellitus treatment.

Nanoparticles for insulin delivery

The various types of nanoparticles that are currently studied for their use as drug delivery systems are as follows:

• Polymeric biodegradable nanoparticles that include nanospheres and nanocapsules

• Ceramic nanoparticles

• Polymeric micelles

• Dendrimer

• Liposomes.

The applications of various types of nanoparticles and Biomems (bio microelectromechanical system) for insulin delivery in the treatment of diabetes are outlined in the following sections.

Polymeric nanoparticles

These are solid, colloidal particles consist of macromolecular substances that vary in size from 10 nm to 1000 nm. Depending on the methods of preparation nanoparticles can be of two types, nanosphere or nanocapsule. These nanostructures have completely different properties and release characteristics for the encapsulated drug. A nanosphere is a matrix system in which the drug is physically and uniformly dispersed and nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane. (Fig. 2)These particles degrade into biologically acceptable compounds by hydrolysis thus delivering the encapsulated medication to the target tissue.. (a) Scanning electron microscopy image of a hollow nanosphere obtained by spray drying of hydroxyl propyl cellulose and (b) a magnified view of the particle surface. Schematics of different nanotechnology-based drug delivery systems. Nanoparticles are small polymeric colloidal particles with a therapeutic agent either dispersed in polymer matrix or encapsulated in polymer. Polymeric micelles are self-assembled block co-polymers, which in aqueous solution arrange to form an outer hydrophilic layer and an inner hydrophobic core. The miceller core can be loaded with a water insoluble therapeutic agent. Liposomes are lipid structures that can be made ‘stealth’ by PEGylation and further conjugated to antibodies for targeting. Dendrimers aremonodispersed symmetric macromolecules built around a small molecule with an internal cavity surrounded by a large number of reactive end groups**.**Polymeric nanoparticles have been used as carriers of insulin . These are biodegradable polymers with the polymer-insulin matrix surrounded by nanoporous membrane containing grafted glucose oxidase. A rise in blood glucose level triggers a change in the surrounding nanoporous membrane resulting in biodegradation and subsequent insulin delivery. The glucose/glucoseoxidase reaction causes a lowering of the pH in the delivery system's microenvironment. This can cause an increase in the swelling of the polymer system, leading to an increased release of insulin. The polymer swells in size at normal body pH (pH = 7.4)and it shrinks at low pH (pH = 4) when the blood glucose level increases, thus opening the gates and releasing the insulin from the nanoparticle (Fig. 3) [14].These systems release insulin by swelling caused due to changes in blood pH. control of the insulin delivery depends on size of the gates, the concentration of insulin, and the rate of gates opening or

closing (response rate). Schematic representation of polymeric nanoparticles with pH sensitive molecular gates for controlled insulin release triggered by the presence of glucose in blood.

Oral insulin delivery through polysaccharide conjugated polymeric nanoparticles

Development of improved oral insulin administration is very essential for the treatment of diabetes mellitus in order to overcome the problem of daily subcutaneous injections. Insulin when administered orally undergoes degradation in the stomach due to gastric enzymes. Therefore insulin should be enveloped in a matrix like system to protect it from gastric enzymes. This can be achieved by encapsulating the insulin molecules in polymeric nanoparticles. The casein coating protects the insulin from the gastric enzymes. Due to casein's muco-adhesive property, the formulation remained concentrated in the small intestine for a longer period resulting in slower absorption and longer availability in blood stream.

Ceramic nanoparticles

Ceramic nanoparticles are made from calcium phosphate, silica, alumina or titanium. These ceramic nanoparticles have certain advantages like easier preparative processes, high biocompatibility, ultra-low size (less than 50 nm) and good dimensional stability. These particles effectively protect the doped drug molecules against denaturation caused by changes in external pH and temperature.

BioMEMS

Implantable Bio Micro Electro Mechanical Systems (BioMEMS) can be used as insulin pumps for controlled release of insulin when there is an increase in blood glucose level. Another proposed BioMEMS device has a drug reservoir compartment filled with insulin molecules. Biosensors and nonporous membranes with pores of 6 nm in diameter are located in the exterior to detect the changes in blood glucose level and for insulin release.

Other nanoparticulate systems for insulin delivery and for the treatment of diabetes associated symptoms

Other than the ceramic and polymeric nanoparticles, gold nanoparticles have also been tested as insulin carriers. Gold nanoparticles synthesized with chitosan as a reducing agent were tested as a carrier for insulin. The nanoparticles showed long term stability in terms of aggregation and good insulin loading of 53%. Use of chitosan served dual purpose by acting as a reducing agent in the synthesis of gold nanoparticles and also promoted the penetration and uptake of insulin across the oral and nasal mucosa in diabetic rats.

Types of nanoparticles Advantages Limitations

Polymeric nanoparticles Degrade into biologically acceptable compounds by hydrolysis; lesser cytotoxicity;higher targetspecificity; high level of insulin entrapment and ability to preserve insulin structure and biological activity;bypassing of the enzymatic degradation in stomach. Mucoadhesive polymeric nanoparticles may adhere nonspecifically to surfaces they are not intended to (gastric mucosa,gut content) or remain trapped within the mucus.

Ceramic nanoparticles Easy preparative processes; high biocompatibility; ultra-low size(less than 50 nm); good dimensional stability; protect the doped drug molecule against denaturation caused by changes in external pH and temperature; can be manufactured with desired size,shape and porosity; do not undergo swelling or porosity changes. Poor permeability across the mucosal membrane and rapid mucociliary clearance mechanism of nonmucoadhesive formulations for nasally administered insulin.

Gold nanoparticles Long term stability in terms of aggregation and good insulin Widespread distribution in organs like liver, lung, loading; higher uptake of insulin across oral and nasal mucosa;improvedpharmacodynamic activity of insulin. spleen,kidney, brain, heart, stomach and joints. Liposomes Biodegradable, non-toxic and non-immunogenic. Post treatment accumulation in skin.

Conclusions

The science and knowledge that the scientific community has today about nanotechnology and its potential versatile applications is only based on the research work done in the laboratories.Due to their minute size these drug carriers can be cleared away form the body by the body's excretory pathways. When these are not excreted, larger nanoparticles can accumulate in vital organs causing toxicity leading to organ failure.

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