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Review

Applications of mesoporous silica in biosensing and controlled release of insulin

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ABSTRACT

The development of new oral insulin delivery systems could bring significant benefits to insulin-dependent patients due to the simplicity of the method, avoidance of pain caused by parenteral administration and maintenance of optimal therapeutic levels for a longer period. However, administration of such therapeutic proteins orally remains a challenge because insulin (Ins) is a very sensitive molecule and can be easily degraded under the existing pH conditions in the stomach and intestines. Moreover, due to the large size of insulin, intestinal epithelium permeability is very low. This could be improved by immobilizing insulin in the mesoporous silica pores (MSN), acting as a shield to protect the molecule integrity from the proteolytic degradation existing in the stomach and upper part of the small intestine. Due to the high adsorption capacity of insulin, biocompatibility, ease of functionalization with various organic and/or inorganic groups, high mechanical and chemical resistance, adjustable pore size and volume, MSN is considered an ideal candidate for the development of controlled release systems that are sensitive to various stimuli (pH, temperature) as well as to glucose. Modifying MSN surfaces by coating with various mucoadhesive polymers (chitosan, alginate, etc.) will also facilitate interaction with the intestinal mucus and improve intestinal retention time. Moreover, the development of glucose-responsive systems for achieving MSN-based self-regulated insulin delivery, decorated with various components serving as sensors – glucose oxidase (GOD_x) and phenylboronic acid (PBA) that can control the insulin dosage, avoiding overdose leading to serious hypoglycemia. MSN have also been tested for application as biosensors for glucose monitoring.

1. Introduction

Organic-inorganic hybrid nanoparticles represent a class of new biomaterials and can be used as a carrier for delivering a wide range of therapeutic agents such as proteins, vaccines, etc. (Siavashani et al., 2016; Yu et al., 2016) . The human body contains thousands of proteins that fulfill important functions, namely, the growth, development and regulation of metabolism (Carter, 2011). Many diseases occur due to the degradation of intracellular protein functions. Protein therapy is essential for improving human health and especially for the treatment of many diseases, such as cancer and diabetes (Vivero-Escoto, 2013). *Diabetes mellitus* is a metabolic disorder caused by a decrease in insulin secretion by pancreatic islet cells, reflecting in increased blood sugar levels and anomalies of carbohydrate, protein and fat metabolism. Moreover, if diabetes is not treated or controlled timely, it affects various parts of the body such as the nervous system, heart, kidneys, eyes, skin, etc. (Zhang et al., 2013). According to the data provided by the International Diabetes Federation, the number of people affected by diabetes is expected to reach 333 million by 2025, meaning that 90% of these people will have type 2 diabetes. In most Western countries, the overall prevalence of diabetes has reached 4–6%, and of this 10–12% are elderly people, aged between 60 and 70. Annual health costs due to diabetes-related complications account for about 6–12% of total healthcare spending (Surabhi and Mamatha, 2016). Numerous factors are contributing to the development of diabetes, such as: low insulin secretion, inherited or acquired insulin deficiency, inefficiency of

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existing insulin, i.e. high production and low use of glucose. Other risk factors that lead to long-term complications of diabetes are: food, smoking, alcohol consumption, lack of physical exercise, consumption of certain types of drugs, hormones, vascular or cardiovascular diseases, etc. (Riaz, 2015; Kumdhavalli et al., 2016). Diabetes (type 1 – insulin dependent) develops due to low insulin production, whereas type 2 diabetes (non-insulin dependent) develops due to resistance to its effects. Both types lead to hyperglycemia, which indicates acute signs of diabetes, namely: excessive production of urine and, implicitly, high fluid intake, blurred vision, weight loss, lethargy, and changes in metabolism (Varshney et al., 2012; Tiwari, 2015). Other forms of diabetes include: gestational diabetes, maturity-onset diabetes of the young (MODY) and latent autoimmune diabetes in adults (LADA) (Santoro et al., 2014; Poudel, 2012). Gestational diabetes develops during pregnancy due to an inadequate response of the body to insulin, and in most cases this form of diabetes disappears after childbirth (Yu et al., 2016). MODY is a rare early onset monogenic form of diabetes accounting for less than 2% of all diagnosed diabetes cases, frequently misidentified as type 1 or 2 diabetes. MODY is inherited in an autosomal-dominant pattern and is due to a primary defect in β-cell function (Kim, 2015; Kavvoura and Owen, 2012; Tang et al., 2017). LADA is an endocrine disorder characterized by progressive destruction of β-pancreatic cells, by means of an autoimmune mechanism, leading thus to total insulin deficiency (Nawal et al., 2017). LADA is a slow-developing subtype of type 1 diabetes, presenting characteristics of type 1 and type 2 diabetes, which leads to misdiagnosis and faulty treatment. Compared to adult onset type 1 diabetes, LADA patients reach optimal metabolic control with non-insulin antidiabetic drugs for at least 3–6 months, while patients diagnosed with type 1 diabetes require immediate insulin treatment. From this perspective, LADA differs from type 1 diabetes, and its clinical characteristics overlap with type 2 diabetes (Parveen et al., 2015).

Currently, the primary method of treating patients with type 1 diabetes is based on frequent injections of insulin as well as by administering other types of proteins such as glucagon-like peptide 1 (GLP-1) very similar in structure to glucagon (Yu et al., 2016; Heinemann, 2011; Araújo et al., 2016). However, a major disadvantage of subcutaneous insulin administration is associated with inadequate blood glucose control and is manifested by hypoglycemia, weight gain due to intensive therapy, eripheral hyperinsulinemia, lipoatrophy, lipohyperatrophy, etc. Moreover, besides medical treatment, several general rules must be followed by diabetics in order to maintain an optimal blood glucose level, namely, constant monitoring of glucose levels, reduction of sugar intake, exercise, etc. (Zhang et al., 2016).

To prevent unpleasantness caused by parenteral administration of insulin (pain, itching, edema, etc.) (Mazzucchelli and Corsi, 2017) as well as due to inadequate blood glucose control, research efforts have been focused in recent years on new methods of administration of therapeutic proteins (oral, intranasal, pulmonary, transdermal, ocular administration, etc.) (Yogendraji et al., 2011; Cefalu, 2004; Kristensen et al., 2016; El-Sherbiny et al., 2015). Insulin administration directly to the lung, as aerosols using a nebulizer was thought to reduce the glycemia. This route of administration has some competitive advantages such as vast and well perfused absorptive surface, absence of those peptidases that are present in the gastrointestinal (GI) tract and can destroy the insulin molecules, and the ability to bypass the “first pass metabolism”. However, the exact mechanism of adsorption at the pulmonary level is not clear but it is supposed to be via transcytotic and paracellular mechanisms. The first “inhaled powder product” – Exubera (recombinant insulin human [rDNA original]), was developed by Pfizer Inc., and got the approval of Food and Drug Administration (FDA) in 2006, being used for adult patients diagnosed with type 1 and 2 of diabetes. FDA approval was granted based on a clinical trial involving ~2500 adult patients, based on these studies, the maximal concentration using Exubera was reached after only 49 min comparing with 105 min in the case of injection administration (FDA, 2006). For the smokers group, contraindications were reported because in their case the risk of hypoglycemia was significant, at least comparing with the other patients. Moreover, the patients starting the treatment were forced to make pulmonary function tests before the treatment, after 6 months and annually thereafter (Shah et al., 2016). Even if FDA considered this route of administration safe, several papers reported that Exubera can induce pulmonary cancer. In 2007, Pfizer retracted the product from the marker and recorded huge loss, over 2.5 milion dollars along with reporting 6 cases of lung cancer for 6 patients who used Exubera (Shantha, 2016; Pfizer Statement on Exubera Labeling Update in the United States). Another powdered formulation based on insulin was developed by *MannKind Corporation* and reported higher insulin absorption at the pulmonary level (www.afrezza.com). The product, Afrezza (Technosphere insulin), appears to have overcome some of the barriers that contributed to the withdrawal of Exubera and is currently under review by the FDA. Afrezza Technosphere is a drug delivery system made up of microparticles of fumaryl diketopiperazine (FDKP) which forms microspheres of 2–5 μm via hydrogen bonds in slightly acidic conditions. Technosphere insulin delivered by inhaler has a relative bioavailability of 21–25% compared to regular insulin and is quickly eliminated.

Afrezza is considered a unique insulin formulation with a rapid onset of only 15 min and highlights a short duration of action of about 2–3 h, significantly reducing the occurrence of hypoglycaemia as compared to subcutaneous administration of regular human and rapid-acting insulins. The tests performed show that insulin adsorption in this formulation is not significantly influenced by smokers and does not show any major changes in lung function over one year of administration. However, the most common side effects were: hypoglycaemia, cough episodes were common in the first week of treatment but diminished after 6 weeks, amyloid deposits in the lung, insignificant changes in forced volume vital capacity (FVC), DLF (diffusing lung function for lung monoxide (DLCO)) in the groups treated with Technosphere insulin, reversible after 3 months upon cessation of treatment (Sarala et al., 2012). Currently, this formulation is in Phase 3 Clinical Trial (Clinical Identification Number: NCT03324776) and Afrezza is intended to be used for the treatment of T2DM patients with an HbA1c index ranging between 7.5 and 11.5% for 6 months (https://www.clinicaltrials.gov). Another type of inhaled insulin – Aerodose was tested in 15 patients (non-smokers, of whom 10 men) with T2DM and was compared the intra-patient variability of insulin inhaled responses was compared using a clinical Aerodose insulin inhaler (2 doses of 240 units) compared to that administered subcutaneously (2 doses per 24 units) under euglycemic clamp conditions on four separate study days. The results of studies in the Phase 2 clinical trial showed a relative bioavailability of inhaled insulin of about 16% (0–8 h postdosing) and a bio-potency of 13% compared to that administered subcutaneously. Maximum serum insulin levels and associated metabolic effects were achieved much faster with inhaled insulin comparing to subcutaneous injection. There were no clinically significant changes in pulmonary function and no drug-related or inhalatory adverse events (Aerogen Inc) were reported (Perera et al., 2002). However, the route of administration of insulin by the lung is considered noninvasive, it is limited to technical problems associated with inhalation devices, higher cost and long-term safety, especially pulmonary function.

However, oral administration of insulin remains the most beneficial method because it is directly delivered to the liver. A major drawback of therapeutic proteins is that they are highly sensitive molecules and therefore oral administration is extremely difficult due to their unfavorable physico-chemical properties, namely, high molecular size, susceptibility to enzymatic degradation, short plasma half-life, ion permeability, immunogenicity, and the tendency to undergo aggregation, adsorption, and denaturation (Araújo et al., 2016; Pérez et al., 2016; Soudry-Kochavi et al., 2015). Moreover, it is well known that most proteins are therapeutically active only when administered parenterally. To overcome these drawbacks, in recent years, huge research