Advancement of nanoparticle-based insulin delivery systems in treatment of diabetes

H. Kubra Elcioglu

Marmara Üniversitesi Recep TayyipErdoğan Külliyesi, Eczacılık Fakültesi, Başıbüyük Yolu, 4D, Maltepe-İstanbul,

E-mail: krishanthikaru@gmail.com

Abstract

Insulin injections remain to be preferred approach for the treatment of insulin-dependent diabetes mellitus (type I) and for many patients non-insulin-dependent diabetes mellitus (type II). The subcutaneous injection of insulin decreases the quality of life of many people and causes suboptimal control of blood glucose levels. It would be beneficial if insulin could be administered orally, buccal, nasal, pulmonary, ocular and rectal in order to replace parenteral therapy because different routes of insulin could mimic the physiological fate of endogenously secreted insulin and might provide a better glucose homeostasis. When considering poor patient compliance and difficulties of administration in using parenteral insulin this makes the oral route the most preferred and safest if it?s available. In order to obtain adequate bioavailability, oral route of insulin should overcome various gastrointestinal tract (GIT) barriers such as chemical, enzymatic and absorption barriers. Polymeric nano and/ or microparticles have been used as matrices for the delivery of oral route of insulin. Nanoparticles; have a large specific surface area and protection power against gastrointestinal environment, are thought to be the most promising solution for oral delivery of insulin.

Diabetic cases have increased rapidly in recent years throughout the world. Currently, for type-1 diabetes mellitus (T1DM), multiple daily insulin (MDI) injections is the most popular treatment throughout the world. At this juncture, researchers are trying to develop different insulin delivery systems, especially through oral and pulmonary route using nanocarrier based delivery system. This next generation efficient therapy for T1DM may help to improve the quality of life of diabetic patients who routinely employ insulin by the subcutaneous route. In this paper, we have depicted various next generation nanocarrier based insulin delivery systems such as chitosan-insulin nanoparticles, PLGA-insulin nanoparticles, dextran-insulin nanoparticles, polyalkylcyanoacrylated-insulin nanoparticles and solid lipid-insulin nanoparticles. Modulation of these insulin nanocarriers may lead to successful oral or pulmonary insulin nanoformulations in future clinical settings. Therefore, applications and limitations of these nanoparticles in delivering insulin to the targeted site have been thoroughly discussed.

Diabetes mellitus (hyperglycemia), a metabolic disorder, is caused either due to lower insulin secretion by the cells or due to lower binding efficiency of insulin on their cell surface receptors resulting in high blood glucose level. According to the survey in low- and middle-income countries there are 366 million people living with diabetes and the count is expected to rise to 552 million by 2030 [1]. Especially in the developing countries, diabetes has increased rapidly during the last decade. In 21st century, this diseases have the possibility to become a new epidemic in the Middle East, Sub-Saharan Africa, Latin America, India, and the rest of Asia [2]. Symptoms of diabetes include excessive weight loss, polyuria, polydipsia and polyphagia [3]. Diabetes has been categorized as Type 1 and Type 2. Type 1 diabetes is insulin dependent condition, characterized by deficiency of insulin due to destruction of insulin-producing beta cells of islets of Langerhans by autoimmune system in pancreas.

Treatment of diabetes need constant monitoring of blood glucose level, regulating it through modified dietary sugar intake, physical exercise and insulin therapy (subcutaneous administration) to attain normoglycemia [6]. Disadvantages of subcutaneous administration of insulin are hypoglycemia [7], peripheral hyperinsulinemia [8], lipoatrophy, lipohyperatrophy [9], obesity due to intensive therapy [10], insulin neuropathy and insulin presbyopia. Current dosage of injectable insulin, required to maintain acceptable serum glucose level, comprise of up to four subcutaneous injections per day [11] which can cause psychological stress leading to poor patient compliance. Thus, focusing on the alternative route of administration (oral or pulmonary) or reducing the injection doses are beneficial to reduce the inconvenience and drawbacks associated with this conventional method [12–15]. Furthermore, orally delivered insulin reaches systemic circulation after passing through liver similar to physiological insulin secretion while injected insulin may result in peripheral hyperinsulinemia and associated complications. However, major obstructions in developing oral or pulmonary insulin

formulations are either enzymatic barriers or physical barriers (i.e. intestinal epithelium), which oral insulin has to overcome [11, 16]. Insulin, 51 amino acid protein, can get deteriorated by gastric pH and intestinal enzymes, and even intestinal epithelial cell membranes serve as absorption barrier for intact peptide structure resulting in less than 1 % bioavailabity of total insulin taken orally [17]. Taken together, restrictions like; fragile nature and short half-lives of proteins may serve as extra barriers in the formulation of oral dosage forms. In this context, over past few decades attempts have been made to develop suitable alternative formulations. Some of the methods include the use of permeation enhancers [18, 19]; protease inhibitors [20, 21], hydrogels [22, 23], and protein–ligand conjugates [24, 25]. Although, significant advancement has been made worldwide in attaining the general objective for a convenient and equally effective oral insulin delivery [15], still sufficient commercial development has not been achieved. As a solution to these challenges, nanocarriers have been considered as the best suited vehicle for oral delivery of insulin [26, 27]. Various nanocarriers, like polymeric or micelles, have granted a promising advancement to acquire desirable biopharmaceutical and pharmacokinetic properties for insulin. Therefore, in this review we have tried to highlight several nanocarrier formulations for insulin delivery related to chitosan coated nanoparticles, PLGA-insulin nanoparticles, dextran-insulin nanoparticles, PACA-insulin nanoparticles and solid lipid-insulin nanoparticles. Moreover, limitations associated with these nanocarriers for insulin delivery has also been discussed.

Biography

H. K**?**bra Elcioglu has completed his Ph.D. at the age of 31 years from Marmara University and postdoctoral studies from Marmara University School of Pharmacy, Department of Pharmacology. She is the associated professor in Pharmacology and also Vice Dean of Marmara University School of Pharmacy. She has published more than 13 papers in reputed journals. She is the member of Turkish Pharmacological and Clinical Pharmacy Societies.