JOURNAL OF FOOD AND DRUG ANALYSIS 23 (2015) 351–358

Available online at www.sciencedirect.com

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journal homepage: www.jfda-online.com

Review Article

Application of polymeric nanoparticles and micelles in insulin oral delivery

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ARTICLE INFO

Article history:
Received 21 September 2014
Received in revised form
29 January 2015
Accepted 29 January 2015
Available online 31 March 2015

Keywords:
diabetes mellitus
insulin
micelles
nanoparticles
oral delivery

ABSTRACT

Diabetes mellitus is an endocrine disease in which the pancreas does not produce sufficient insulin or the body cannot effectively use the insulin it produces. Insulin therapy has been the best choice for the clinical management of diabetes mellitus. The current insulin therapy is via subcutaneous injection, which often fails to mimic the glucose homeostasis that occurs in normal individuals. This provokes numerous attempts to develop a safe and effective noninvasive route for insulin delivery. Oral delivery is the most convenient administration route. However, insulin cannot be well absorbed orally because of its rapid enzymatic degradation in the gastrointestinal tract. Therefore, nanoparticulate carriers such as polymeric nanoparticles and micelles are employed for the oral delivery of insulin. These nanocarriers protect insulin from degradation and facilitate insulin uptake via a transcellular and/or paracellular pathway. This review article focuses on the application of nanoparticles and micelles in insulin oral delivery. The recent advances in this topic are also reviewed.

1. Introduction

Diabetes mellitus is an endocrine disease in which the pancreas does not produce sufficient insulin or the body cannot efficiently use the insulin it produces [1,2]. There are two basic types of diabetes: type I and type II. In type I diabetes, patients produce very little or no insulin. In type II diabetes, patients cannot use insulin efficiently. The number of diabetics will increase to 438 million worldwide by the year 2030, according to the World Health Organization (WHO) [3]. The primary goal for the treatment of type I and type II diabetes is to cure the symptoms related to hyperglycemia [4]. Insulin has an important role in diabetes treatment. Patients with type I diabetes require daily injections of insulin to survive. Patients with type II diabetes may or may not require exogenous insulin for treatment.

Human insulin is composed of 51 amino acid residues. Its molecular formula is $C_{257}H_{387}N_{65}O_{77}S_6$ and the corresponding molecular weight is 5808 daltons. Human insulin consists of

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http://dx.doi.org/10.1016/j.jfda.2015.01.007

two amino acid chains (an A chain and a B chain) that are linked by disulfide bonds, which contain 21 amino acid residues and 30 amino acid residues, respectively. Insulin can be isolated from human, porcine, bovine or sheep sources [5]. The blood glucose level in diabetic patients typically ranges 14–50 mmol/L [6]. By using exogenous insulin, the blood glucose level is reduced and maintained within a narrow range of 3.5–7.0 mmol/L. Insulin promotes the cellular uptake of glucose and increases the synthesis of glycogen, fatty acids, and proteins. Thus, the role of insulin is to convert excess glucose into two storage forms—namely, glycogen and triglycerols—and maintain glucose homeostasis [2]. Insulin cannot be orally administered because it is unstable and degraded by proteolytic enzymes in the gastrointestinal tract [7]. The current insulin therapy is administered by subcutaneous injection, and the major adverse effects of this therapy include hypoglycemia, allergy, insulin resistance, and edema [8]. Multiple and frequent injections of insulin are necessary but burdensome, which leads to poor patient compliance. In addition, there is a risk of infection at the injection site, especially for diabetic patients [6,9]. All of these events have provoked numerous attempts to develop a safe and effective noninvasive route for insulin delivery.

Oral, buccal, rectal, ocular, transdermal, intravaginal, pulmonary, and nasal routes have been explored as noninvasive routes for insulin delivery [6]. Among these delivery routes, the administration of insulin by the oral route has been the goal for many researchers because it minimizes the risk of hypoglycemia while obtaining high patient compliance. However, the delivery of insulin via the oral route is a challenge because of enzymatic instability and the poor absorption of insulin. Among the possible strategies to achieve acceptable bioavailability, polymeric nanoparticles and micelles have immense potential for insulin oral delivery because of their nanosized feature and feasibility for surface modification [9,10]. These nanocarriers possess several advantages over other conventional delivery systems (e.g., tablets, capsules, beads, microparticles, and microemulsions) [11]. The updates on the most promising advances of nanoparticles and micelles in insulin oral delivery are reviewed.

2. Gastrointestinal hurdles in insulin oral delivery

The administration of insulin by the oral route has been the goal of many researchers. However, the oral bioavailability of insulin is very poor. Macromolecular proteins normally cannot cross the intestinal epithelium. They will instead be degraded in the gastrointestinal tract before absorption [12]. Three main obstacles of insulin oral delivery need to be considered: (1) the enzymes present in the gastrointestinal tract, (2) the physiological barrier of the gastrointestinal tract, and (3) the physicochemical property of insulin.

2.1. *Enzymatic barrier*

The gastrointestinal tract has a variety of enzymatic barriers for insulin oral delivery. The insulin can be degraded by intracellular enzymes (e.g., cathepsins), bacterial flora in the mucus layer and in the epithelial cells of the intestine, and proteolytic enzymes in the stomach and in the intestinal lumen (e.g., pepsin, trypsin, and chymotrypsin) at the brush border membrane (e.g., endopeptidases). These enzymes denature protein drugs. Enzyme inhibitors can slow the insulin degradation rate and increase the insulin that is available for absorption. Sodium cholate and aprotinin reportedly act as enzyme inhibitors and improve insulin absorption in rats [12,13]. However, the use of enzyme inhibitors in long-term diabetic therapy remains questionable because of possible toxicity.

2.2. *Physiological barrier*

The epithelial cells of the gastrointestinal tract are tightly bound by tight junctions (i.e., the zonulae occludentes) in which the outer surface of the intestinal epithelium is coated by mucus and glycocalyx layers, and thus inhibits the passage of insulin and its subsequent absorption [14]. Absorption may be enhanced by using absorption enhancers such as bile salts, trisodium citrates, EDTA, labrasol, and polymeric materials (e.g., chitosan), which help to open the tight junctions of the intestinal epithelium [13,15,16].

2.3. *Physicochemical properties of insulin*

The pore radius of the intestinal mucosa ranges 7–15 Å, which is an important barrier for macromolecular insulin translocation. The insulin molecules tend to aggregate at concentrations above 100nM. The transformation of the insulin monomer with a molecular dimension of approximately 12–14 Å into a hexameric conformation impairs its transport across the intestinal epithelium [7]. Temperature, solvents, and additives may disrupt the primary amino acid sequence and tertiary structure of insulin. The alteration in the functional moiety or native charge of insulin has an impact on its intestinal transport. At physiological pH, the carboxylic and amino groups of insulin are entirely ionized, which results in a zwitterionic configuration. It is likely to preclude insulin absorption from transcellular diffusion, unless the charges are neutralized through ion pairs [7]. The large molecular size of insulin nevertheless remains an obstacle to its absorption. Modification of insulin chemical structure against possible enzymatic degradation is an approach to raise its bioavailability. A diacyl derivative of insulin has been shown to maintain insulin biological activity and to increase its intestinal absorption [17]. However, the application of this approach to insulin is very challenged because of the structural complexity of proteins.

3. Delivery systems for insulin oral delivery

The successful oral delivery of insulin requires considering the physiological and biological stability of insulin in formulations, in the gastrointestinal tract, and in the cytosol of enterocytes. The barriers occurring principally in the oral delivery of insulin can be overcome via incorporating functional excipients in the dosage forms. The functional excipients act as a stabilizer, a protease inhibitor, a mucoadhesive