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Review

Strategies for effective oral insulin delivery with modified chitosan nanoparticles: A review

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ABSTRACT

Over the last few decades, various natural polymers have been applied to the problem of oral insulin delivery using advanced nanotechnology. Parenteral administration of insulin is widely accepted, but administration via the oral route could overcome the poor patient compliance with repeated injection. Polymers from natural as well as synthetic sources have recently been used in the synthesis of insulin delivery vehicles suitable for oral administration. The biopolymer chitosan has been widely studied in oral insulin delivery due to its favorable properties such as biocompatibility, biodegradability, non-immunogenicity and non-toxicity.

This review focuses on progress in the synthesis of chitosan and modified chitosan nanoparticles for efficient oral insulin delivery, with an emphasis on the biological efficacy of the nanoparticles. Obstacles to oral delivery and possible remedies are also brought into focus. Modifications to protect insulin from the harsh acidic environment of the gastrointestinal (GI) tract are described. Chemical barriers such as the acidic gastric pH and the presence of proteolytic enzymes in the stomach and intestine limit the effective absorption of external insulin within the GI tract. Absorption of insulin is physically hindered by the absorption barrier consisting of a single layer of columnar epithelial cells joined at the apical surface by a tight junction complex. The presence of negative charges in the junction complex leads to segregation of the apical layer from the basolateral compartment of the epithelial cells, making the intestinal environment selective for particles based on size and charge. Nanoparticles are able to overcome these barriers and deliver insulin. While this technology still has some drawbacks, chitosan and modified chitosan nanoparticles are highly promising agents for oral insulin delivery.

Abbreviations: ADA, American Diabetes Association; AE, association efficiency; BBI, Bowman–Birk inhibitor; CD, cyclodextrin; β-CD, β-cyclodextrin; CMC, carboxymethyl cellulose; CP-β-CD, cationic-β-CD polymer; DD, degree of deacetylation; DM, diabetes mellitus; DMEC, dimethylethyl chitosan; DS, dextran sulfate; EDTA, ethylene diamine tetraacetic acid; GI, gastro-intestinal; GSH, glutathione; HNF, hepatocyte nuclear factor; HP-β-CD-I, hydroxypropyl-β-cyclodextrin–insulin; IU, international unit; LADA, latent autoimmune diabetes of the adult; LD50, lethal dose 50; LSC, lauryl-succinyl chitosan; MODY, maturity onset diabetes of the young; mv, millivolt; nm, nanometer; NPH, neutral protamine hagedorn; PA, pharmacological availability; PBS, phosphate buffered saline; PCP, poly(methacrylic acid)–chitosan–PEG; PEC, polyelectrolyte complex; PEG, poly(ethylene glycol); PGA, poly(γ-glutamic acid); pHEMA, poly(hydroxyl ethyl methacrylate); PI, isoelectric point; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; TEC, triethyl chitosan; TMC, trimethyl chitosan; TMC–Cys, trimethyl chitosan–cysteine conjugate; TEER, transepithelial electrical resistance; WHO, World Health Organization.

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Contents

1. Introduction

While insulin has been available for ninety years, it is not yet able to combat the diabetes pandemic that has developed in this century. Considering a predicted doubling in diabetes-related deaths between 2005 and 2030 [1] and the fact that the economic burden of diabetes represents approximately 6% of the total health budget of developed countries [2], it is surprising that insulin, the most effective diabetes treatment, has not gained widespread use. While insulin can be used alone in the therapy of diabetes without any oral antidiabetic drug, the reverse is not true [3]. Insulin therapy is commonly delayed despite the dire consequences, partly due to the inconvenience and complications associated with insulin administration by injection. Thus, in the last decade, the focus has shifted from the development of insulin alternatives to the development of alternative delivery methods.

Invasive parenteral (injected) insulin suffers from poor patient compliance due to needle phobia, pain, skin bulges, allergic reactions, common infections, and stress generated from the difficult long-term regimen of insulin therapy [4,5]. Moreover, many patients still experience hypoglycemic episodes despite easier glucose monitoring options. Parenteral insulin is also associated with non-physiological delivery to the wrong target tissues, poor pharmacodynamics, non-ideal initiation and weight gain [3,6]. Developments in biotechnology have led to the development of alternatives to parenteral delivery, although these developments have not been rapid enough to meet the pressing demand.

The goal of an alternative delivery route is to reach the bloodstream by noninvasive means, which is inaccessible for a protein drug due to the multiple physicochemical barriers. Including those arising in the innate immune system. Scientists are trying to evade these barriers efficiently through ocular, vaginal, rectal, oral (buccal, gastro-intestinal (GI), and sublingual), nasal, and other routes [7,8]. The barriers to reaching the bloodstream are either physical, such as poor absorption at barrier surfaces, or chemical, such as pH inactivation and enzymatic degradation. Fig. 1 presents possible hurdles for oral insulin delivery. Lassmann-Vague and Raccah [7] reviewed the obstacles present for different delivery routes. Delivery of insulin via the ocular route was tested in animal models in combination with different absorption enhancers, with particular attention given to toxicity as polymers were added to overcome low absorption. Vaginal and rectal routes have also been investigated, but the absorption rate and bioavailability are poor due to the thick mucosal layers in these tissues. The use of absorption enhancers (bile salts, chelating agents, surfactants, cyclodextrins, and dihydrofusidate) does not help as they may cause local reactions with severe complications. Nasal delivery has also been evaluated because of the easy access, high vascularity and large absorption area associated with this route. Unfortunately, highly active mucociliary clearance in the nose hindered prolonged drug action resulting in poor bioavailability. Buccal and sublingual insulin administration provide better results due to the low levels of proteolytic enzyme activity, the high vascularization of the tissue, the large surface area for absorption and the ease of administration. However, the multiple layers of oral epithelial cells represent a significant barrier to drug penetration, which, coupled with the continuous flow of saliva, leads to poor efficacy. Taking all of this into account, the oral route is considered to be the most feasible and convenient method of drug administration to improve compliance among diabetic patients. In addition to the large surface available for absorption, orally administered insulin can mimic the physiological fate of insulin in the body [8], providing better glucose homeostasis [9,10].

Orally administered insulin is absorbed directly from the intestine and then transported to the liver via portal circulation, where it inhibits hepatic glucose production [9]. Unlike other delivery routes, the gut is the natural route of nutrient absorption into the circulation. The fact that the gut presents the largest absorption surface of all routes provides better efficacy. However, the oral delivery of peptide drugs is hindered by the structural instability of proteins and peptide drugs in the harsh environment of the gut, i.e., the highly acidic environment in the stomach and the presence of proteolytic enzymes [11]. Fig. 2 presents a schematic diagram of the possible mechanisms by which chitosan nanoparticles improve insulin absorption. Both natural and synthetic polymers have been applied to the design of delivery vehicles capable of overcoming absorption barriers in the form of hydrogels, beads, microspheres, nanoparticles, and other formulations. Natural polymers such as agar, agarose, alginate, and chitosan and synthetic polymers including poly(lactic acid), poly(lactic-co-glycolic acid), poly(phosphoesters), and poly(€-caprolactone) have demonstrated efficacy as protein carriers [12–14]. Polymeric carrier systems for