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Research review paper

Polymer-based nanoparticles for oral insulin delivery: Revisited approaches

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ABSTRACT

Diabetes *mellitus* is a high prevalence and one of the most severe and lethal diseases in the world. Insulin is commonly used to treat diabetes in order to give patients a better life condition. However, due to bioavailability problems, the most common route of insulin administration is the subcutaneous route, which may present patients compliance problems to treatment. The oral administration is thus considered the most convenient alternative to deliver insulin, but it faces important challenges. The low stability of insulin in the gastrointestinal tract and low intestinal permeation, are problems to overcome. Therefore, the encapsulation of insulin into polymer-based nanoparticles is presented as a good strategy to improve insulin oral bioavailability. In the last years, different strategies and polymers have been used to encapsulate insulin and deliver it orally. Polymers with distinct properties from natural or synthetic sources have been used to achieve this aim, and among them may be found chitosan, dextran, alginate, poly(γ-glutamic acid), hyaluronic acid, poly(lactic acid), poly(lactide-co-glycolic acid), polycaprolactone (PCL), acrylic polymers and polyallylamine. Promising studies have been developed and positive results were obtained, but there is not a polymeric-based nanoparticle system to deliver insulin orally available in the market yet. There is also a lack of long term toxicity studies about the safety of the developed carriers. Thus, the aims of this review are first to provide a deep understanding on the oral delivery of insulin and the possible routes for its uptake, and then to overview the evolution of this field in the last years of research of insulin-loaded polymer-based nanoparticles in the academic and industrial fields. Toxicity concerns of the discussed nanocarriers are also addressed.

Contents

Abbreviations: AE, Association efficiency; ATP, Adenosine triphosphate; CD, Circular dichroism; CSK, C-Src tyrosine kinase; Cys, Cysteine; DEMC, Diethylmethyl chitosan; DMEC, Dimethylethyl chitosan; DTPA, Diethylene triamine pentaacetic acid; HPMCP, Hydroxypropyl methylcellulose phthalate; LCS, Lauryl chitosan; PAA, Poly(acrylic acid); PCL, Polycaprolactone; PEG, Polyethylene glycol; PLA, Poly(lactic acid); PLGA, Poly(lactic-co-glycolic acid); TEC, N,N,N-triethylchitosan; TMC, N,N,N-trimethylchitosan; TPP, Tripolyphosphate; γ-PGA, Poly(γ-glutamic acid)

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1. Introduction

The International Diabetic Federation reported that 366 million people were affected by diabetes in 2011 and estimated that by 2030 this number will raise up to 552 million (Whiting et al., 2011). Due to its high prevalence and secondary effects, diabetes is one of the most lethal diseases and responsible for almost three million deaths per year worldwide, as reported by the World Health Organization (Wild et al., 2004). On average, life expectancy is reduced by more than 20 years in people with type 1 diabetes and by up to 10 years in people with type 2 diabetes (Hosseininasab et al., 2014).

In 1922, the discovery of insulin from dog pancreas was a milestone in the history of diabetes therapy with a Nobel Prize winning, which had a great importance in biomedical research (Banting and Best, 1922). Indeed, insulin is the most used and effective drug to control diabetes. From the time of this discovery, peptides and proteins have been used as biopharmaceuticals due to their advantages such as high activity, specificity and effectiveness compared to conventional drugs (Herrero et al., 2012). However, suitable oral formulations of proteins are still under development, facing countless challenges despite all the efforts, time and money spent on the research (Herrero et al., 2012). Hence, parenteral delivery remains the most common route for insulin administration (Chaturvedi et al., 2013).

The use of biocompatible and biodegradable nanoparticles has been described as a promising strategy toward oral administration of proteins and peptides (Hosseininasab et al., 2014). In order to enhance the oral bioavailability of insulin, as well as to provide a stable and biocompatible environment to the encapsulated drug, polymeric nanoparticles have been claimed to be the perfect candidates for the oral delivery of insulin (Morishita and Peppas, 2006).

In this review, the benefits and drawbacks on the oral insulin delivery as well as the different pathways of insulin-loaded nanoparticle uptake through intestinal epithelium will be discussed. The different polymeric nanoparticles developed so far for oral delivery of insulin will be presented. In addition, the efforts of the pharmaceutical industry to develop an insulin oral delivery system and the toxicity concerns about the use of polymer-based nanoparticles will be reviewed.

2. Benefits and drawbacks on oral insulin delivery

Despite all the successes achieved after insulin discovery, diabetes therapy tends to fail in long-lasting treatments followed by a number of side-effects. Thus, more than a few improvements are urgently needed, especially regarding the administration route of insulin. On one hand, parenteral delivery of insulin is hindered by the lack of patient compliance to treatment due to the uncomfortable use of injections with needles. On the other hand, oral administration is the most accepted delivery route of insulin due to its convenience, and it is painless and easy for self-medication. Based on efficacy and toxicity, it is possible to tune the dosing schedule of insulin to the responses of individual patients (Plapied et al., 2011). Moreover, the oral route mimics the endogenous pathway of insulin after secretion, as it suffers the first pass to the liver instead of going to the systemic bloodstream (Chaturvedi et al., 2013; Herrero et al., 2012). Owing to its role in blood glucose level control, the liver is the first and foremost important target of pancreas-secreted insulin (Rekha and Sharma, 2013). Indeed, only a small amount (approximately 20%) of subcutaneously administrated insulin reaches the liver (Still, 2002). Reproducing the physiological mechanisms of glucose metabolism as faithfully as possible, allows the control and/or decrease of the side effects that are commonly described by patients under insulin therapy. Encountered first in the liver, insulin levels are reduced in systemic circulation, which minimizes the risk of hypoglycemia episodes, immune responses as well as insulin resistance in type 2 diabetic patients (Rekha and Sharma, 2013). Other problems such as allergic reactions, lipodystrophy around the injection site and risk of infectious disease transmission, can also be avoided with oral administration of insulin (Hosseininasab et al., 2014). Finally, the oral route is more cost-effective since there is no need of specialized people for the administration, decreasing the number of visits to the hospital and avoiding costs in injection materials (Pridgen et al., 2014).

However, the path is not straightforward and achieving an effective oral formulation for delivery of insulin is still a goal to pursue. Along the gastrointestinal tract there are several barriers that must be overcome to increase the bioavailability of insulin. For instance, the harsh pH conditions in the stomach, the enzymatic activity, the presence of mucus and the poor permeability across the intestinal epithelium are the main concerns for the activity and effectiveness of the protein (Chaturvedi et al., 2013; Chen et al., 2011; Hosseininasab et al., 2014). Besides the physiological features of the gastrointestinal tract, a better knowledge of the differences between animal models and humans would also guarantee a more reliable extrapolation of the results obtained from preclinical to clinical studies, as well as a better understanding of how diet, fasting states, patient-to-patient variability and disease states affect the protein absorption (des Rieux et al., 2006; Hunter et al., 2012; Pridgen et al., 2014).

3. Mechanisms of the intestinal uptake of polymeric nanoparticles

Regardless of the conferred protection of insulin by nanoparticles from the hostile conditions of the gastrointestinal tract, the transport across the intestinal epithelium still remains a barrier to overcome. As a gatekeeper, the epithelium acts by thwarting proteins from being absorbed, making it the major restrictive barrier to the nanoparticle passage from the lumen to the *lamina propria* (Pridgen et al., 2014). The epithelial cells maintain this protection because of the tight junctions between adjacent cells (Hochman and Artursson, 1994). Thus, the transport and the absorption mechanisms may either be paracellular (between the cells) or transcellular (through the cells), and are mainly regulated by the characteristics of the mucosa and by the physicochemical properties of the nanoparticles such as size, charge and lipophilicity (Choonara et al., 2014; des Rieux et al., 2013).

It is commonly accepted that due to the features of the paracellular route, which has a small surface area (less than 1% of the total intestine) and a limited space owing to the tightness of the junctions between cells (3 and 10 Å in diameter), this is not the most common mechanism of nanoparticle uptake (des Rieux et al., 2013; Plapied et al., 2011; Rekha and Sharma, 2013). However, it has been described that some natural