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Review

Polymeric hydrogels for oral insulin delivery

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ABSTRACT

The search for an effective and reliable oral insulin delivery system has been a major challenge facing pharmaceutical scientists for over many decades. Even though innumerable carrier systems that protect insulin from degradation in the GIT with improved membrane permeability and biological activity have been developed, yet a clinically acceptable device is not available for human application. Efforts in this direction are continuing at an accelerated speed. One of the preferred systems widely explored is based on polymeric hydrogels that protect insulin from enzymatic degradation in acidic stomach and delivers effectively in the intestine. Swelling and deswelling mechanisms of the hydrogel under varying pH conditions of the body control the release of insulin. The micro and nanoparticle (NP) hydrogel devices based on biopolymers have been widely explored, but their applications in human insulin therapy are still far from satisfactory. The present review highlights the recent findings on hydrogel-based devices for oral delivery of insulin. Literature data are critically assessed and results from different laboratories are compared.

Contents

1. Introduction

The Nobel Prize winning discovery of insulin from the dog's pancreas by Banting, Best and Mcleod in 1923 [1] and its isolation in chemically pure crystalline form in 1926 [2] were the important milestones in the history of biomedical research. Over the past decades, due to the advances in biotechnology, a large number of variants of insulin from different sources have been developed and used for the treatment of diabetes mellitus [3]. The commonly available insulin formulations include rapid, short, intermediate and long-lasting suspensions. However, the most widely practiced method of insulin administration is through parenteral route, since oral administration has several drawbacks associated with insulin inactivation by proteolytic enzymes in the gastrointestinal tract (GIT), low permeability through intestinal membrane [4], hyper-insulinemia, pain, allergic reactions and low patient compliance. In addition, parenteral route may not replicate the normal dynamics of endogenous insulin release, resulting in a failure to achieve long-lasting glycemic control in diabetic patients [5]. On the other hand, portal delivery of insulin, which mimics endogenous insulin release, can be achieved via intestinal administration. Obviously, from this perspective, development of an oral delivery system providing adequate bioavailability of insulin would revolutionize the treatment of diabetes.

In order to circumvent the problems associated with parenteral administration of insulin, alternative strategies have been suggested in the literature including co-administration with absorption enhancers [6] or enzyme inhibitors, chemical modification [7], polymeric micro/

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nano carriers [8], lipid-based carriers as liposomes [9], solid lipid nanoparticles (NPs) [10], etc. Hitherto, each of these developments met with a limited success and no commercially acceptable oral insulin product is available for human use. Nevertheless, accelerated research efforts in the past decades clearly demonstrate the possibility of developing polymeric devices for oral insulin therapy. Even though some of these approaches have shown low bioavailability of insulin and exhibit several negative effects such as irritation of the intestinal mucosal membrane and impairment of the membrane barrier, yet few devices including copolymeric hydrogel microparticle of poly(methacrylic acid) grafted with poly(ethylene glycol) P(MAA-g-EG) have demonstrated [11–13] enhancement of oral insulin absorption in animal experiments up to 4.2% bioavailability in addition to their ability to protect insulin from the enzymes as well as adhesive characteristics on the mucus membrane. In a recent investigation by Sonaje et al. [14] the highest achievement of insulin bioavailability was demonstrated in animal diabetic models.

Due to intense research activities in search of novel polymeric devices to protect insulin from enzymatic degradation and to allow it to reach the intestine unmolested, much work has been reported in recent years. Innumerable review papers have been published covering various aspects of such devices in oral insulin therapy [3,5,15–19]. The present review compiles important and significant reports from 2005 onwards until recently on the development of hydrogel-based devices used in oral insulin therapy. However, some references to earlier citations have also been made where necessary. A search of the literature indicated significant activities in this area and the review is timely. The results from various laboratories are critically discussed on polymeric hydrogel devices used in oral insulin therapy.

2. Barriers to insulin delivery

The major hurdles preventing successful oral insulin delivery are overcoming the enzymatic barrier and acid-catalyzed degradation in the stomach, luminal degradation in the intestine as well as intracellular degradation [5]. The pH variation along the GIT from highly acidic (pH 1.2 to 3.0) of the stomach to slightly basic (pH 6.5 to 8.0) environment in the intestine would lead to oxidation, hydrolysis or deamidation of insulin, thus making it inactive [15]. Enzymatic degradation is caused by proteolytic enzymes such as pepsin in the stomach and trypsin, α-chymotrypsin and carboxypeptidases in the intestine. Higher degradation rate (>10 times) has been observed in the presence of α-chymotrypsin than with trypsin [20]. However, the rate of degradation of insulin depends on its associated state in solution. For instance, insulin is a monomer at low concentration (0.1 mM), which dimerizes in the pH range of 4 to 8. At concentrations >2 mM, hexamer is formed at neutral pH [21] and the associated state affects its rate of degradation. In the presence of bile salts, the rate of degradation may increase nearly six times [22] with the complete dissociation of insulin into monomeric form. In addition, metabolism by cytochrome P450-3A4 and apically polarized efflux mediated by ATP dependent P-glycoproteins is another reason for reduced bioavailability of insulin internally.

The viscous layer of mucus along the entire GIT presents another hurdle for insulin absorption. The epithelial lining of GIT consists of a tightly bound single layer of columnar epithelial cells supported by *lamina propria* and *muscularis mucosa*. Three types of junctions exist in the epithelial lining: desmosomes or *zonulae adherens*, tight junctions (TJs) or *zonulae occludens*, and gap junctions. TJs provide the mechanical strength to cell lining by holding cells tightly bound to one another and constitute the major barrier for large molecular weight drug permeation between the cells (paracellular transport). The large molecular weight and hydrophilic nature of the peptides restricts their absorption through transcellular or paracellular pathway, leading to poor bioavailability. However, receptor mediated transcytosis mechanism can be exploited for the absorption of insulin [23].

Ziv and Bendayan [24] showed that insulin can be absorbed from the intestinal lumen through transcytotic pathway that involves the binding of insulin to specific receptors on apical plasma membrane followed by internalization through deep invaginations of the luminal plasma membrane and vesicular structures. The insulin is then transferred to basolateral membrane of enterocytes and released into the interstitial spaces without being degraded. This transfer is characterized by the low transport rates and must be enhanced to allow significant absorption of insulin. Trancellular and paracellular are the two major pathways for the absorption of insulin from intestine to systemic circulation. Transcellular absorption involves passive or active absorption through intestinal epithelial cells and M cells of the Peyer's patches, whereas paracellular absorption is concerned with the absorption by a passage through the space between epithelial cells [16]. One of the most widely used approaches is receptor mediated transcytosis mechanism that is much more efficient than pinocytosis, which employs the use of ligands like transferrin (Tf), lectins, vitamin B12, etc., which can bind to the respective receptors at the apical plasma membrane to enable targeting. This approach has been utilized in a number of targeted NP preparations [25].

3. Polymeric hydrogel devices for oral delivery of insulin

Advances in the field of polymer science and modifications of the backbone structures of biopolymers as copolymers, grafted copolymers, interpenetrating polymeric network (IPN) hydrogels, polymeric micro-/nano-devices, all have contributed to the development of devices for oral insulin delivery. However, their long-term efficacy must be demonstrated in larger animals as well as in humans. These systems should withstand the variable pH environment of the GIT before delivering insulin through different pathways in the intestine. Moreover, insulin also acts as a growth hormone and hence, high doses of insulin through peroral route may induce mitogenic changes in the GI epithelium in long-term use. In any case, maintaining the physicochemical and biological stability of insulin in the GIT is of priority concern while using such systems with prolonged retention in the small intestine.

Combining enzyme inhibitors within polymeric systems represents the potential to increase the potency of orally administered insulin. Several insulin derivatives with increased physicochemical and biological stability such as alkylated/acylated insulin, PEGylated and polysialylated insulins have been the most promising candidates for oral administration. A schematic representation of the release and absorption of insulin from the intestine following the oral administration of hydrogel based systems is depicted in Fig. 1.

3.1. Chitosan and its analogs

Chitosan (CS), is a well known naturally occurring biopolymer that is widely used in biomedical area [26]. CS and its chemically modified analogs have been extensively used in insulin therapy, since these have proven to be nontoxic, biodegradable, non-allergic, easily absorbable, and their properties can be easily tailor-made for specific applications [27]. The mucoadhesion property of the cationic CS helps to prolong the residence time of the device in small intestine due to the interaction between the positive charge of CS and the negative charge of sialic-acid groups in mucin, a peptide present in the intestinal wall [28]. The CS facilitates reversible opening of TJs in Caco-2 cell monolayers to decrease the trans-epithelial electrical resistance (TEER) and increase its paracellular permeability [29]. The underlying mechanism and outcome of TJ opening in Caco-2 cells treated with CS has been recently discussed by Yeh et al. [30]. This study demonstrated the increase in claudin-4 (Cldn4) gene