Novel treatment option for diabetes: Chitosan-insulin tablets encapsulated Antiprotease

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ABSTRACT

Diabetes is a disease recognized by elevation in some blood factors like glucose, amino acids, free fatty acids etc, some impairment in insulin secretion or resistance to insulin etc. There are mainly two types of diabetes: type 1, in which there is an abnormal absence of insulin secretion, and type 2, which primarily is due to resistance to insulin while its receptors are normal or more than its amount. After some time pancreas won’t be able to secrete enough insulin which causes post prandial hyper glycemia and after a while hyper glycemia would be an ever present sign, not just after meals. Insulin injection is necessary in this step. Many diabetics require up to four insulin injections per day, which can be quite inconvenient. The formulation of dietary insulin capable of eluding proteolytic digestion has proven to be challenging. In addition, the drug must pass through the stomach; thus, a synthetic pH-sensitive tablet would be helpful. More specifically, the insulin-containing tablet should be stable in the acidic environment of the stomach, but it should release its contents in the basic environment of the duodenum. We propose to design a bilayer tablet composed of an outer layer containing Antiproteases to neutralize the effect of pancreatic proteases and an inner layer of insulin. As the outer layer is revealed after encountering a basic environment, the Antiproteases start to be released and neutralize the surrounding digestive proteases. This neutralization allows sustained release of insulin from the inner layer of the tablet. The measured release of the drug allows for better absorption in more distal parts of the small intestine.

KEYWORDS: oral insulin delivery, enteric-coated, chitosan-insulin, tablets, Antiprotease

1. INTRODUCTION

Insulin is a hormone which regulates the amount of glucose to a proper amount, so the body can function normally. It is produced by endocrine pancreatic cells called the islets of Langerhans. These cells normally secrete a continuous small amount of insulin, but insulin level becomes elevated when the blood glucose is higher than normal. Certain cells in the body change ingested food into energy, or blood glucose, that cells can use. Elevated blood glucose triggers the cells in the islets of Langerhans to release the necessary amount of insulin. Insulin allows glucose in the blood to be transported into cells. Researchers do not yet know exactly how insulin functions, but they do know insulin binds to receptors on the cell
membrane [1]. This activates a set of transport molecules so that glucose and proteins can enter the cell. The cells can then use the glucose as energy to carry out their functions. Once transported into the cell, the blood glucose level is returned to normal within hours [1, 2].

There are two general types of diabetes. In the more severe type, known as Type I or juvenile-onset diabetes, the body does not produce any insulin [2]. Type I diabetics usually inject themselves with different types of insulin three to four times daily. The dosage is determined based on the person's blood glucose reading, taken from a glucose meter. Type II diabetics produce some insulin, but it is either not enough or their cells do not respond normally to insulin. This usually occurs in obese or middle aged and older people. Type II diabetics do not necessarily need to take insulin, but they may inject insulin once or twice a day. There are four main types of manufactured insulin that differ with respect to how soon the insulin starts working, when it peaks, and how long it lasts in the body [1, 2].

1.1. Other attempts

Current approaches rely on insulin injections, yet there is considerable effort towards developing alternative methods of delivery. Some employ a pump under the skin that injects insulin into the vascular system, others aerosolized insulin and still others novel ingestible drugs that can withstand the digestive juices present in the mouth and stomach.

1.2. What's new here?

In this research, we suggest a method in which the orally administered insulin is passed through different parts of the digestive system to reach a suitable region for absorption. The first part of the digestive system in which protein breakdown occurs, is the acidic environment of the stomach. So we cover the insulin with a special coat (enteric coating) that resists disintegration in the stomach, but dissolves in the more neutral-to-alkaline environment of the duodenum. However, once the coat is removed in the duodenum, the insulin is exposed to proteases secreted by the pancreas. Thus we add an outer layer, consisting of protease inhibitors, to the insulin and under the enteric coat. Trypsin - one of the important proteases present in pancreatic juice - when activated is able to activate many other proteases. So if Trypsin is inhibited, most of the proteases present in duodenum are either inhibited or inactive. That's why we use Trypsin inhibitors more than others.

In general, in this research we designed a bilayer tablet that consists of an inner layer containing insulin and an insulin transporter (to facilitate the absorption of insulin) such as Chitosan, an outer layer containing protease inhibitors (especially those inhibiting Trypsin) and an enteric coat covering the outer layer. After the removal of the coat in the alkaline environment of duodenum, the outer layer starts releasing the protease inhibitors. So once in the jejunum, proteases function on insulin is low enough for the release of insulin because many of them are inhibited and those still active are busy doing their routine digestive duties. Then the inner layer starts releasing insulin and its transporter gradually, leading to absorption of insulin by the jejunum epithelial layer.

1.3. Chitosan

Chitosan (2-amino-2-deoxy-(1 → 4)-d-glucopyranan) is a mucopolysaccharide obtained by the deacetylation of chitin in crustaceans such as crabs and shrimps. Chitosan is soluble in organic acid (acetic acid) or inorganic acid (hydrochloric acid) and positively charged [3]. The chemical properties of the polymer are determined by the degree of deacetylation, molecular weight and viscosity. Chitosan was proved to have the best chelating properties among other natural polymers because of complex formation of amino groups of chitosan NH2, in which nitrogen is a donor of electron pairs, although hydroxyl groups can also participate in complex formation [4]. Studies showed that chitosan is non-toxic and its LD50 in mice exceeds 16 g/kg [5]. Because of its biodegradability and biocompatibility, chitosan has been applied as a pharmaceutical excipient in oral, ocular, nasal, implant and transdermal drug delivery. Chitosan has been shown to have mucoadhesive properties because of its viscosity and interaction of the positively charged amino group with the negatively charged sites on the mucosa surface. Recent studies indicated that
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Chitosan could enhance absorption of poorly absorbable drugs such as peptides and proteins [6]. The nasal delivery of chitosan was demonstrated to greatly enhance the absorption of insulin across the nasal mucosa of rats and sheep [7]. Investigations have suggested that there are two effects of chitosan delivery systems on nasal mucosa. The mucoadhesive properties of the polymer can reduce the clearance rate of drugs from nasal cavity, thereby prolonging the contact time of chitosan delivery system with nasal epithelium. In addition, it has been shown that the interaction of the positively charged amino group of chitosan with the negatively charged sialic acid residues in mucus causes the transient opening the tight junctions and allows large hydrophilic compounds to be transported across the epithelium. The opening mechanism of the tight junctions has been demonstrated by a decrease in ZO-1 proteins and the change in the cytoskeleton protein F-actin from a filamentous to a globular structure [8, 9].

Varying concentrations of chitosan used for the synthesis of gold nanoparticles demonstrated that the nanoparticles obtained at higher chitosan concentrations (>0.1% w/v) were stable and showed no signs of aggregation in addition to demonstrating long-term stability in terms of aggregation for 6 months [10]. Most importantly, this method resulted in lower blood glucose 2 hours following the nasal and oral administration of insulin-loaded gold nanoparticles. Serum gold level studies have demonstrated significant improvement in the uptake of chitosan-reduced gold nanoparticles.

In a study by Lin et al., nanoparticles composed of chitosan and poly(gamma-glutamic acid) were prepared by a simple ionic-gelation method for oral insulin delivery [11]. After insulin loading, the nanoparticles remained spherical and the insulin-release profiles were significantly affected by their stability in distinct pH environments. The in vivo results clearly indicated that the insulin-loaded nanoparticles could effectively reduce the blood-glucose level in a diabetic rat model.

Sarmento et al. prepared a nanoparticulate insulin delivery system by complexation of dextran sulfate (DS) and chitosan in aqueous solution [12]. Insulin release at pH below 5.2 was almost prevented up to 24 h and at pH 6.8 the release was characterized by a controlled profile. This result suggested that the release of insulin was ruled by a dissociation mechanism and DS–chitosan nanoparticles acted as pH-sensitive delivery systems. Furthermore, the released insulin entirely maintained its immunogenic bioactivity evaluated by ELISA, confirming that this new formulation shows promising properties towards the development of an oral delivery system for insulin.

There is substantial evidence that oral delivery of insulin is increased if the formation can get past the stomach and into the gastro-intestinal tract. For instance, Kushapur et al. showed that human insulin can be transported across the rat small intestine wall in medial jejunum segment [13, 14, 15]. Kelly had studied the passage of insulin through the gastrointestinal wall in mice [16]. Moreover, Inouye W. Y. et al. proved that insulin can cross the GI wall in dogs and Crane C. W. et al. showed this in humans [14, 15].

Chitosan nanoparticles have also been used to deliver genes. In a study, using chitosan nanoparticles for delivery of HLA-G gene to insulin producing cells (IPCs) in vitro has been hypothesized [17]. These cells were then autologously injected to type 1 diabetic patients in order to provide a pool of stem cells in the whole life to reproduce beta cells that could evade autoimmune responses of the immune system.

2. Further approaches in replacing insulin injection

Here a review of past attempts to replace insulin injection with a new and less invasive type of drug delivery system is provided. Several approaches have been attempted, including pulmonary and oral delivery, cell-penetrating peptides, liposomes, nanoparticles, mucosadhesive systems, and novel coating approaches such as chitosan.

2.1. Pulmonary delivery

Inhaled insulin appears to be suitable for patients with diabetes because of its high bioavailability and a pharmacokinetic profile that mimics the time kinetics of insulin secretion after a meal. Clinical studies were conducted among a small
number of patients with type I or insulin dependent type II diabetes and found that the metabolic control achieved with inhaled insulin was similar to that obtained with a subcutaneous insulin regimen [18]. Tolerance of inhaled insulin was good, and treatment satisfaction was better than that with the s.c. regimen. Insulin inhalation appears to be an interesting way of insulin delivery for elderly patients with diabetes. However, no studies have been conducted in elderly patients with diabetes to assess this route's acceptability, convenience, and ease of use in this particular population. In addition, it is necessary to conduct pharmacokinetic studies in the elderly because lung aging might reduce the bioavailability of inhaled insulin [19]. Although Pfizer (New York) launched Exubera in 2006, it has been reported that it is not successful. Of the several inhaled insulin devices that are in various stages of development, the Exubera formulation was the first to be approved for use in the United States and in Europe [20].

2.2. Oral delivery

Pulmonary delivery has emerged as the most feasible option thus far, but oral delivery is the ultimate goal. Oral insulin delivery must protect insulin from proteolytic degradation in the stomach and the upper portion of the small intestine. In addition, the absorption of insulin from the gut must be enhanced. The absorption of insulin is very poor because of the hydrophilic nature of the big molecule. Basic problems of insulin stability in the gut and absorption from the gastrointestinal tract still must be resolved [21].

2.3. Cell-penetrating peptides

One attempt to improve gastrointestinal absorption evaluated whether oligoarginine, a cell-penetrating peptide (CPP), can improve intestinal absorption of insulin in rats [22]. Peptides composed of six [R(6)], eight [R(8)] and 10 [R(10)] residues of arginine were used as the CPP. No insulin absorption was observed following administration of insulin solution alone. However, insulin absorption increased dramatically after co-administration of the D-form of R(6), D-R(6), and the L-form of R(6), L-R(6), in a dose-dependent manner. The effects on insulin absorption were more pronounced for D-R(6) than for L-R(6). Among oligoarginines composed of 6, 8, or 10 arginine residues, D-R(8) showed the strongest enhancing effects on insulin intestinal absorption.

2.4. Liposomes

Insulin-entrapped liposomes cause dose-dependent hypoglycemia. As such, Choudhari et al. prepared liposomes with varying composition by two methods: solvent evaporation hydration and solvent spherule evaporation [23]. Liposomes containing lecithin 100 mg, cholesterol 20 mg, insulin 150 units, and Tween 1% v/v were found to be most effective. The effect of insulin-liposome was prolonged in diabetes-induced rabbits than that of normal rabbits. The pharmacodynamics of the insulin-liposome system was comparable with the action of 1 U/kg of insulin administered subcutaneously.

2.5. Nanoparticles

Nowadays there is a tendency toward the use of nanoparticles rather than other ways of drug delivery such as viral vectors for delivery of different materials e.g. genes and peptides [24]. Delivering drugs through manipulation of different kinds of nanoparticles such as quantum dot [25], polymeric nanoparticles including chitosan polymer etc. is usual; however the use of polymeric nanoparticles in delivery of desired materials has shown promise due to their low toxicity, biocompatibility, biodegradability, and not being tumorogenic [24].

In a study conducted by Attivi et al., insulin nanoparticles were prepared by a water-in-oil-in-water emulsification and evaporation method [26]. The polymers used for the encapsulation were blends of biodegradable poly-epsilon-caprolactone (PCL) and nonbiodegradable polymer (Eudragit RS). Poly (alkyl cyanoacrylate) nanocapsules also have been successfully used for oral administration of insulin in diabetic rats.

Damge et al. prepared insulin-loaded nanospheres by polymerization of isobutyl cyanoacrylate (IBCA) in an acidic medium [27]. No degradation due to proteolytic enzyme was observed in vitro. When these nanospheres were administered perorally in streptozotocin-induced diabetic rats, a 50% decrease in fasted glucose levels from the
Chitosan-insulin tablets encapsulated Antiprotease showed that the use of insulin-loaded PHNP was an effective method of reducing serum glucose levels. An aqueous nanoparticulate delivery system containing oppositely charged polymers polyethyleneimine (PEI) and DS with zinc as a stabilizer was developed by Tiyaboonchai et al. [31]. The pH of PEI solutions, the weight ratio of the two polymers, and zinc sulfate concentrations affected the particle size of the nanoparticles. In contrast to rapid release of insulin in vitro, the hypoglycemic activity in streptozotocin-induced diabetic rats was prolonged. This system offered a number of advantages, including ease of manufacturing under mild preparation conditions, completely aqueous processing conditions, use of biocompatible polymers, ability to control particle size, a high level of drug entrapment, and an ability to preserve secondary structure and biological activity of protein.

Simon et al. prepared nanosized insulin-complexes based on amine modified comb-like polyesters [32]. Protection of insulin in nanocomplexes from enzymatic degradation was investigated. The interaction with enterocyte-like Caco-2 cells in terms of cytotoxicity, transport through and uptake in the cell layers was evaluated by measuring transepithelial electrical resistance (TEER), release of lactate dehydrogenase (LDH), and insulin transport. The protection capacity of the nanocomplexes and their interaction with Caco-2 cells varied strongly as a function of lactide-grafting (hydrophobicity). With increasing lactide-grafting (P(26)P(26)-1(LL)P(26)-2(LL)) Nanocomplexes protected as much as 95% of the insulin against degradation by trypsin.

2.6. Mucoadhesive system

A biologically adhesive delivery system offers important advantage over conventional drug delivery systems. Whitehead et al. [33] described a novel method of delivering insulin into systemic circulation by mucoadhesive intestinal patches. Intestinal patches localize insulin near the mucosa and protected it from proteolytic degradation. In vitro experiments confirmed the secure adhesion of patches to the intestine and the release of insulin from them. In vivo experiments showed that the use of insulin-loaded PHNP was an effective method of reducing serum glucose levels. An aqueous nanoparticulate delivery system containing oppositely charged polymers polyethyleneimine (PEI) and DS with zinc as a stabilizer was developed by Tiyaboonchai et al. [31]. The pH of PEI solutions, the weight ratio of the two polymers, and zinc sulfate concentrations affected the particle size of the nanoparticles. In contrast to rapid release of insulin in vitro, the hypoglycemic activity in streptozotocin-induced diabetic rats was prolonged. This system offered a number of advantages, including ease of manufacturing under mild preparation conditions, completely aqueous processing conditions, use of biocompatible polymers, ability to control particle size, a high level of drug entrapment, and an ability to preserve secondary structure and biological activity of protein.

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performed via jejunal administration showed that intestinal insulin patches induced dose-dependent hypoglycemia in normal rats. These studies revealed that reduction in blood glucose levels were comparable with those induced by s.c. injections.

The engineered polymer microspheres made of erodible polymer display strong adhesive interactions with gastrointestinal mucus and cellular lining and can traverse both the mucosal epithelium and the follicle associated epithelium covering the lymphoid tissue of Peyer's patches. Alginate, a natural polymer recovered from seaweed is being developed as a nanoparticle for the delivery of insulin without being destroyed in the stomach. It has in addition, several other properties that have enabled it to be used as a matrix for entrapment and for the delivery of a variety of proteins such as insulin and cells. These properties include: a relatively inert aqueous environment within the matrix, a mild room temperature encapsulation process free of organic solvents, a high gel porosity that allows for high diffusion rates of macromolecules, the ability to control this porosity with simple coating procedures, and dissolution and biodegradation of the system under normal physiological conditions [34].

2.7. Thioliated chitosan insulin tablets

The efficacy of orally administered insulin has also been improved using thioliated chitosan [35]. 2-Iminothiolane was covalently linked to chitosan and the resulting chitosan-TBA (chitosan-4-thiobutylamidine) conjugate, and two enzyme inhibitors (Bowman-Birk-Inhibitor (BBI) and elastatinal) were also covalently linked to chitosan. Chitosan-TBA-insulin tablets showed a controlled release of insulin over 8 h. In vitro mucoadhesion studies showed that the muco-adhesive/cohesive properties of chitosan were at least 60-fold improved by the immobilization of thiol groups on the polymer. After oral administration of chitosan-TBA-insulin tablets to non-diabetic rats, the blood glucose level decreased significantly for 24 h. In contrast, neither control tablets nor insulin given in solution showed a comparable effect. These results concluded that the combination of chitosan-TBA, chitosan-enzyme-inhibitor conjugates and reduced glutathione could constitute a promising strategy for the oral administration of insulin.

3. Hypothesis

We propose to use a bilayer tablet in which the first layer (outer layer) is coated by a base-labile polymer (enteric-coating) such as Eudragit [35] or hydroxypropylmethyl-cellulose phthalate (HPMCP) [36], which demonstrates grades of resistance to acidic environments.

3.1. What is HPMC?

HPMC is cellulose ether, derived from alkali treated cellulose that is reacted with methyl chloride and propylene oxide. The NOSB approved powdered cellulose, a less processed material usually derived from wood pulp fiber, for use as a filtering aid and anti-caking agent in October of 2001.

The cellulose ethers are manufactured by a reaction of purified cellulose with alkylating reagents (methyl chloride) in presence of a base, typically sodium hydroxide and an inert diluents. The addition of the base in combination with water activates the cellulose matrix by disrupting the crystalline structure and increasing the access for the alkylating agent and promotes the etherification reaction. This activated matrix is called alkali cellulose. During the manufacture of HPMC alkali cellulose reacts with methyl chloride to produce methyl cellulose and sodium chloride. Side reactions of the methyl chloride and sodium hydroxide produce methanol and dimethyl ether by-products. The methylcellulose is then further reacted with the staged addition of an alkyene oxide, which in the case of HPMC is propylene oxide (Figure1).

After this reaction, MC and HPMC are purified in hot water, where they are insoluble. Drying and grinding completes the process. HPMC has many pharmaceutical uses, as a drug carrier, a coating agent, a tableetting agent, an emulsifier in ointments. It is also used in ophthalmic solutions and as a slow release agent. It is widely used in personal care products as a thickening agent and foam stabilizer [37].

This type of coat can facilitate the transmission of the drug through stomach without being affected by the low pH of its environment. But in the
dampened proteolysis creates an appropriate environment for insulin release [3]. The inner layer of the tablet will be composed of a chitosan polymer [1]. Chitosan is often used in order to improve the efficacy of orally administered insulin because of its strong mucoadhesive properties [35]. Chitosan–insulin tablets offer a controlled release and sustained absorbance profile of insulin over a period of hours (Figure 3).

\[
R_{\text{oct}}\text{OH} + \text{NaOH} + \text{CH}_3\text{Cl} \rightarrow R_{\text{oct}}\text{OCH}_3 + \text{NaCl}
\]

\[
R_{\text{oct}}\text{OCH}_3 + \text{NaCl} + \text{CH}_3\text{Cl} + x \text{CH}_2\text{CH}_2\text{OH} + \text{NaCl} \rightarrow R_{\text{oct}}\text{OCH}_3 + \text{NaCl}
\]

Figure 1. HPMC production. Chemical reaction in which HPMC, a kind of cellulose ether, is produced.

Figure 2. Activation pathways of proenzymes and PAR-2 by Trypsin. When Trypsin is activated, it is capable of activating many other digestive proenzymes. Trypsin also activates pancreatic and inflammatory cells via PAR-2. The Trypsin activity in the pancreas is controlled by PSTI. When trypsinogen is activated and changes to Trypsin in the pancreas, PSTI attach immediately to trypsin to inhibit further activation of pancreatic enzymes. (PAR: protease activated receptors; PSTI: pancreatic secretory trypsin inhibitor) [38].
3.2. Methods

Preparation of tablets is composed of three stages. First of all we should prepare the core tablet which contains insulin and chitosan. To do so frozen chitosan solution must be thawed and insulin solution must be added to it. Then the mixture must be stirred, then frozen and lyophilized. Dried mixtures must then, under constant compaction force, be compressed into tablets.

Figure 3. Different steps of the tablet release. Each of four layers is being omitted in predicted environment to let next layer expose to environmental substances and be affected to release its contents.
The second stage in preparation of tablets is adding a second layer of formerly chosen protease inhibitors (as stated before, trypsin inhibitors are in priority) to the core tablet mentioned above. The final stage is enteric-coating the tablet. To achieve this, two methods are selected:

Method one: All tablets must be enteric-coated by submersion into an acetic Eudragit L 100-55 solution and air-dried. This coating procedure must be repeated four times [35].

Method two: All tablets must be enteric coated with HPMCP. A microparticulate solid emulsion formulation must be prepared from S/O/W (solid-in-oil-in-water) emulsions by extruding them to an acidic aqueous solution followed by lyophilization [36].

Tablets of 3 mm diameter can be prepared using flat-faced punches on 10 mg of powder mixture under a compression force of 1000 kg using a hydraulic press. To prepare the coated tablets, half the quantity of the coat formulation will be placed in a 5-mm dies. The tablet must be carefully positioned in the centre of the die and the remaining coat material will be added. The coat will compress around the core using normal concave punches at a compression force of 3000 kg [39].

3.3. Bioavailability of dosage form (Insulin-tablet)

Insulin-Tablet should be administered to animal model and then at determined time-intervals blood sampling should be performed. We evaluate the amount of insulin in samples by means of High Performance Liquid Chromatography (HPLC) method.

3.4. Loading efficiency of tablet

We decided to disintegrate tablets and extract insulin and then analyze the amount of insulin loaded in tablets by means of High Performance Liquid Chromatography (HPLC) method.

3.5. Release profile of tablet

The Release profile of insulin from a multi-layer tablet will be examined in simulated gastric fluid (SBF, pH=1.2) and simulated intestinal fluid (SIF, pH=7.4). The specific amount of insulin loaded in tablets, will be placed in an especial basket (50rpm) and then 500 ml of after dissolution medium will be added, while the temperature is kept constant at 37°C. At scheduled time interval, the agitation will be stopped; the determined volume of sample will be withdrawn and the medium will be replaced with fresh medium. The sample will be determined by means of High Performance Liquid Chromatography (HPLC) method.

3.6. Experimental procedure (Trial)

For arranging a trial on Wistar rat groups, we make them diabetic by using proper dosage of streptozotocin (STZ) and then they undergo our suggested oral drug treatment. Having their blood samples examined in fasting condition (taking no glucose), we measure their lipid profile, insulin level and C-peptide. Repeating the examination two hours after breaking the fast, would help us prove the hypothesis. In further attempts it’s better to check out its effects on rabbits and monkeys.

3.7. Side effect evaluation of constituents and ingredients of tablets

All non-medicinal components in our tablet are widely used in the pharmaceutical and food industries. However, interactions between insulin, chitosan, and proteolytic inhibitors will need to be assessed for potential adverse effects.

As yet, no serious side effects of chitosan application have been reported [40, 41], also the LD50 of chitosan in mice was determined to be greater than 16 g/kg [42]. However there may be drug interactions with this compound, anaphylactic allergy (shellfish) [43], and malabsorption of some nutrients such as fat-soluble vitamins.

Protease inhibitors may interfere with the digestion and absorption of proteins and peptic nutrients, and may cause pancreatic hypertrophy as a result of pancreatic overdrive to produce more proteases in order to digest peptides in the small intestine.

4. DISCUSSION

Routine diabetes mellitus management methods, including the use of insulin releasing drugs such as Glybenclamide and biguanoid family like
herein utilized proven materials in a novel arrangement. We aim to facilitate inert passage of the drug through undesirable endpoints to a target location—the middle third of the small intestine where insulin absorbance is optimal. This drug delivery system may be a new promising path toward oral insulin delivery.

REFERENCES


Metaformin that boosts the cellular response to insulin, and other drugs like Acarbose which is an antiabsorbance drug, and also insulin injection in single type or mixed, are still very inefficient in some cases because of their low acceptability, numerous side effects, risk of developing allergy and risk of serious medical complications. In fact international medication is going to limit invasive methods, so it would be more acceptable for patients to undergo the treatment plans. Using oral way to deliver insulin, not only is completely acceptable by the diabetic patients due to its non-invasive properties, but also has less side effects, is easier to use for patients of all ages, and is economically justifiable. Considering that, using oral delivery for insulin is probably the most ideal way for the management of DM.

Patients with DM type I need to receive insulin from an external source, because the endocrine part of their pancreas known as the islets of Langerhans is unable to produce insulin and the body needs insulin to function normally. At present the most widely used way to deliver insulin to these patients is injecting insulin. Diabetics with DM type II usually do not need to take insulin and insulin is normally produced in their pancreas. But when DM type II turns into its advanced phase, the amount of insulin produced inside the body does not satisfy its needs and taking insulin injections becomes inevitable. Both diabetics type I and type II in advanced phase need up to 4 insulin injections per day. The formulation we described in this article is capable of taking the place of insulin injections. Therefore in both DM type I and DM type II in advanced phase, we can replace the insulin injection with these tablets. This arrangement of anti-proteases, absorption enhancers, and insulin even if is unable to exclude injections from daily treatment for diabetics, is capable of lowering the number of injections per day. We estimate that it can be used instead of two injections per day and more dose usage may be possible. However this arrangement still needs more clinical experiences and still is in experimental stage.

5. CONCLUSION

The development of promising diabetes treatments is a worthwhile endeavor, and the method described herein utilized proven materials in a novel arrangement. We aim to facilitate inert passage of the drug through undesirable endpoints to a target location—the middle third of the small intestine where insulin absorbance is optimal. This drug delivery system may be a new promising path toward oral insulin delivery.