Review Article

A Shrewd Ingenious Approach of Oral Drug Delivery of Insulin for the Amelioration of Diabetic Patients with better therapeutic Outcomes

Abstract

Hundred years history of Insulin discovery; Since 1922 insulin has helped countless individuals save their lives. However, the challenges of subcutaneous administration, the requirement for routine self-monitoring of glucose, and the non-physiological action profiles of insulin led many doctors and patients to request non-injectable insulin delivery techniques.

Alternative administration techniques without the need for an IV or an injection are widely desired. Since it is simple for patients and doesn't involve injection, the oral route is the preferred way to provide medication. The gastrointestinal stability of protein therapeutics is one of several major obstacles to the effective development of oral protein medication formulations.

An oral formulation for a protein and peptide drug must preserve the drug's structure, protect the drug from proteolysis, and allow for the drug to be absorbed into the bloodstream. A variety of approaches to oral protein delivery have been proposed to meet these needs.

Toxicity is a critical factor to be considered when evaluating the potential of insulin-loaded nanoparticles. Given that nanoparticles are engineered to interact with 527 Oral Insulin Delivery, it is important to ensure that they do not cause any adverse effects or even damage the intestinal epithelium.

Oral insulin delivery has been an interesting and promising research field that promises to revolutionize the way diabetes mellitus is treated.

Overall, the success of oral insulin depends on the ability to manufacture insulin both in sufficient quantities for oral delivery as well as efficiently in a cost-conscious pharmaceutical marketplace. Pharmaceutical companies are on the frontline in developing a system to deliver insulin orally; It is clear that further work needs to be done to bring the first insulin oral delivery system to the market. Addressing the issues successfully will create a new paradigm in diabetes treatment.

Keywords: Insulin, Oral Drug Delivery, Type 1 Diabetes Mellitus, Protein Peptide therapeutic approach

Introduction

Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are metabolic disorders marked by a persistent decline in β-cell function. If left untreated or treated improperly, both diseases can develop serious, fatal consequences and are highly expensive to manage. As a result, keeping blood glucose levels close to normal lowers the chance of developing long-term diabetes consequences such as adult blindness, cardiovascular disease, nontraumatic amputation, and diabetic nephropathy[1].

Insulin became the first FDA-approved recombinant protein medicine that was commercially available. Protein and peptide medications are often given intravenously due to their size and stability. Most require frequent administration or high doses to be effective due to their short serum half-lives.

In fact, T1DM patients with intensive insulin can lower their risk of retinopathy by 50% to 70%, neuropathy by 60%, and nephropathy by 35% to 56%[2].

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Joslin attempted the first oral insulin formulations in 1922 and 1923, but the attempts were unsuccessful. Since then, other researchers have attempted to understand this idea without success[3].

Long-term subcutaneous, intramuscular, or intravenous injection usage is a significant burden that affects patients' comfort, quality of life, and adherence to treatment[4].

Alternative administration techniques without the need for an IV or an injection are widely desired. Since it is simple for patients and doesn't involve injection, the oral route is the preferred way to provide medication. The gastrointestinal stability of protein therapeutics is one of several major obstacles to the effective development of oral protein medication formulations.

The predicted benefits of oral insulin therapy simply seem too great and many to be ignored. Oral treatment, as opposed to subcutaneous insulin injections, is not linked to any (fear of) pain and would allow for more flexibility in the practical application of insulin therapy. Therefore, the availability of oral insulin would not only facilitate insulin therapy but also almost certainly result in higher patient compliance[5].

Oral therapy must ensure that the therapeutic activity must be maintained in Gastro-Intestinal Tract, and the active substance must reach high blood levels to deliver therapeutic effectiveness. In order to release the protein in the protein-neutral environment of the small or large intestine, an oral delivery system must shield the medication from stomach acid and digestive enzymes.

Insulin is usually administered subcutaneously, which greatly lowers morbidity and mortality; but nevertheless, only around 60% of patients successfully maintain long-term glycemic control[6].

Due to the use of needles and the intricacy of the insulin treatment regimen, the late stage at which insulin may be delivered, and patient anxiety over hypoglycemia episodes and weight gain, this may be the case. Different insulin injection routes are being studied as a solution to these issues. Because it is non-invasive, the oral route is still the recommended method for drug administration[7].

However, due to their inherent lack of permeability through the intestinal epithelium, proteins like insulin have low oral bioavailability. Therefore, expertise in the mucosal microenvironment and intestinal physiology is necessary to develop a delivery system intended to deliver insulin orally.

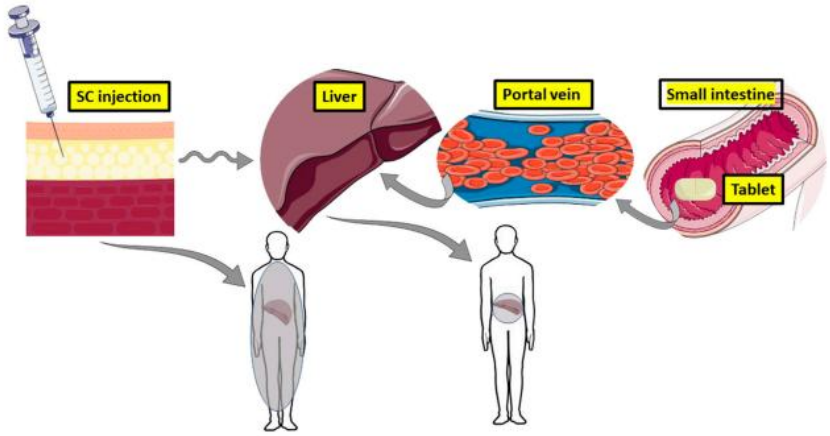

Fig1: The theoretic advantage of oral insulin versus subcutaneous (SC) injection[8].

Insulin administered orally mimics the physiological secretion of insulin from pancreatic beta cells to the liver's portal vein. Little insulin reaches the periphery because it is inactivated at the liver target by 50%; instead, it concentrates in the liver (grey). Insulin administered subcutaneously (SC) floods the periphery, resulting in hyperlipidemia and hypoglycemia. The liver receives only 10% of it, which explains the lack of targeting (diffuse gray throughout the body).

Attack by intestinal peptidases and innately low epithelial permeability brought on by large molecular weight and hydrophilicity cause instability in the intestinal tract and hinder the successful oral delivery of peptides.

Over the past few years, different drug delivery strategies have been introduced to overcome the low oral bioavailability of insulin.

Proteins' high molecular weight and hydrophilicity prevent them from being absorbed through the intestine, which results in low oral bioavailability, insignificant plasma levels, and high variability. As a result, therapeutic proteins are frequently administered via parenteral routes; insulin, for example, is given subcutaneously to treat diabetes mellitus[9].

Oral administration, on the other hand, is regarded as a superior route of administration due to its affordability and widespread acceptance, particularly because it allows for avoiding the use of needles and other injection materials.

Therefore, numerous attempts have been made to create an oral carrier that can deliver insulin continuously and effectively, thereby eliminating the risk of contamination, localized pain, and immune reactions, as well as patient compliance issues. Additionally, oral administration of insulin more closely resembles the body's natural insulin pathway after endogenous secretion, resulting in improved glucose homeostasis[10].

Numerous studies have highlighted the link between conventional subcutaneous injections and patient non-adherence, and it is estimated that more than half of adult patients who are insulin dependent purposefully avoid injections[11].

Discussion:

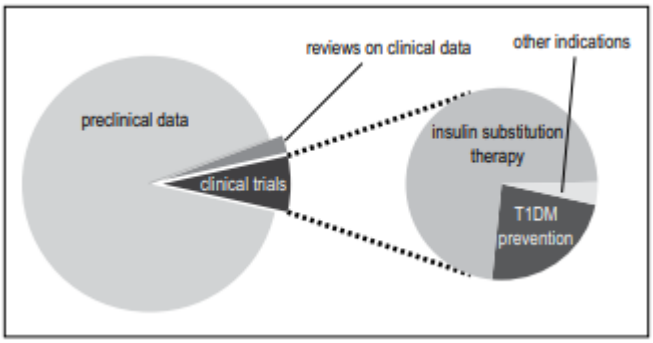

Fig 2: The results of a systematic literature review. The graph shows the distribution of indications across clinical studies as well as the overall percentage of preclinical and clinical data reported on oral insulin. Oral insulin has also been researched as a pharmaceutical preventative for type 1 diabetes as well as for a different non-diabetic ailment (pediatric short bowel disease). This is in addition to insulin replacement therapy.

An oral formulation for a protein and peptide drug must maintain the drug's structural integrity, guard against proteolysis, and enable bloodstream absorption. To satisfy these needs, a number of strategies for oral protein administration have been suggested. The co-administration of extra substances to change the physiology of the GI tract, medication modification, and carrier delivery are some of the most common methods for oral protein delivery. Table 2 provides an overview of each strategy's primary benefits and significant drawbacks. Protein drugs' inability to diffuse across GI tract tissues is hampered by their size, which ranges from 10 to 100 k Da.

Approaches As Oral Protein And Peptide Delivery	Common Example	Advantages	Major Challenges
Permeation enhancers	Surfactants, fatty acids, medium chain glycerides, steroidal detergents, acylcarnitines and alkanoylcholines, N-acetylated-a-amino acids and N-acetylated non-a-amino acids, chitosans	• Enhanced intestinal • permeability by disrupting the epithelium's tight junctions • Relatively easy co-administration	• Potential to damage the intestinal epithelium • Diminished immunoprotective function of the intestinal epithelium in preventing pathogen entry
Protease inhibitors	Serpin, aprotinin and soybean trypsin inhibitors, camostat mesilate, chromostatin, ovomucoids, polymer inhibitor conjugates (such as carboxymethyl cellulose-elastinal)	• Reduced degradation of protein drugs in the GI tract • Maintained stability and bioactivity of more of the drug.	• Variability in enzyme presence and activity between the small and large intestine • Concerns over predictable dosing and patient-to-patient variability in absorption • Long term effects to food digestion have not been fully investigated(enzyme deficiency)
Conjugation of protein and peptide drugs	PEG, transferrin, vitamin B-12, FcRn receptor molecules	• Improved resistance to degradation • Extended half-life in the bloodstream • Potential for cell receptomediated transport	• With large conjugates such as PEG, increased size may inhibit transcellular transport • Long term effects of chronic administration still need to be evaluated
Enteric coatings	Eudragit® systems, hypromellose phthalate	• Protect the protein drug from degradation in the stomach • Controlled release(pH triggered)	• Do not facilitate the absorption process • Need to use protease Inhibitors and permeation enhancers in conjunction
Degradable polymer matrices	Poly(lactide-co-glycolide), poly(epsilon-caprolactone)	• Protect the protein drug from degradation in the stomach • Controlled release(enzyme or pH triggered) • Enhanced stability over non cross linked systems	• Variability in enzyme presence and activity between the small and large intestine • Drug diffusion Out Of • The carrieris dependent on the exten to fdegradation and susceptible to patient-to-patient variability • Need to characterize of the effect of degradation products on the GI tract
Mucoadhesive carriers	PEG-grafted polymers, thiomers, chitosan, lectin, sodium alginate, pectin, cellulose derivatives	• Protect the protein drug from degradation in the stomach • Prolonged residence time of carriers at the site of absorption (increase in drug bioavailabilty) • Increased drug concentration gradient at the epithelial barrier	• Limited diffusion of the protein drug out of the carrier,which typically necessitates adegradable or environmentally responsive component • Concernsover Adhesion and localization of delivery systems with in aspecific GI-segment,ideally where the drug has its ‘absorption window’
Complexation hydrogel carriers	Poly(methacrylicacid-g-ethylene glycol), poly(methacrylicacid-co-N-vinyl pyrrolidone), poly((methacrylic acid-co-N-vinyl pyrrolidone) -g-ethylene glycol),poly (itaconic acid-co-N-vinyl pyrrolidone)	• Protect the protein drug from degradation in the stomach • Controlled release (pH triggered) • Enhanced stability over non cross linked systems • Amenable forco-delivery of permeation enhancers,etc. • Amenable for conjugation with or inclusion of mucoadhesive tethers	• Potential for variation in fasted and fed states

Table 1: Summary of Common Approaches to Enable Oral Protein and Peptide Delivery

Fig 3. Intestinal epithelial permeability has been found to be lowest in the colon and higher in the upper small intestine. Although over 90% of nutrients are absorbed in the upper small intestine, where the intestinal epithelium is most permeable, protein drug absorption is still lower than that of drugs with lower molecular weights.

Oral Insulin Administration Delivery Systems

In order to develop an efficient oral delivery method, consideration must be given to the maintenance of insulin biological stability in the GIT and in the cytosol of enterocytes. Several insulin delivery techniques, such as tablets, capsules, intestinal patches, hydrogels, microparticles, and nanoparticles, have been researched to deliver insulin by paracellular and/or transcellular transport throughout the ileum and colon. Excipients may be used in the delivery techniques used to shield insulin from aggregation and enzymatic breakdown, prolong its duration in the GIT, and enhance intestinal uptake.

This section will examine several oral insulin delivery techniques with an emphasis on nanoparticles, which can enter the colon in a number of ways.

Where Oral Insulin Developments Stand Today

Standard Dosage Forms Because it is more convenient and patients are more likely to comply, many research groups around the world are working to develop an oral delivery system, primarily in the form of tablets or capsules. These studies are discussed because they are well-known and have a lot of applications in both the academic and professional worlds. A Bowman-Birk inhibitor, insulin, and lactational enzyme inhibitors covalently bonded to chitosan were added to chitosan-4-thiobutylamidine tablets. The enzyme inhibitors are concentrated in the tablets due to their covalent connection, which prevents their release in the GIT and reduces local and systemic side effects. Additionally, chitosan and mucus glycoprotein combine to create a mucoadhesive matrix that can deliver insulin and significantly lower blood glucose levels in normoglycemic rats over the course of 24 hours. A core tablet coated with three distinct polymeric layers makes up the CODESTM colon-specific medication delivery system12. These pills of sodium glycocholate, citric acid, lactulose, meglumine, polyethylene oxide, and insulin were created[13]. Thus, meglumine and citric acid are used as pH adjusters and insulin solubilizers, respectively, and sodium glycocholate is used as an absorption enhancer. Lactulose is used to promote the start of drug release in the colon. They work to create a gel barrier, which, when combined with polyethylene oxide in the tablet core, enables a prolonged release of insulin in the dog's colon. Due to its capacity to remain insoluble up to pH 6 in an aqueous media and in the acidic conditions of the stomach, the anionic polymer Eudragit S1000 is utilized for drug delivery through the intestine. In hyperglycemic beagle dogs, the hypoglycemic effect of enteric-coated Eudragit S100 capsules manufactured in polyethylene glycol (PEG) 4000 or Witepsol W35 bases or as a physical mixture containing sodium salicylate as an absorption enhancer was investigated[15]. The results showed that Witepsol W35 (1 g) with sodium salicylate (50 mg) placed in hard gelatin capsules covered with Eudragit S100 was the best insulin formulation. In comparison to subcutaneous insulin, this system was able to reduce plasma glucose levels by about 25–30% and produce relative hypoglycemia of about 12.5%. Insulin can also be given orally by intestinal patches, which can be formed of insulin, Carbopol 934, sodium carboxymethyl cellulose, and ethyl cellulose on one side of the disc. These discs can have a diameter of 1-4 mm and a thickness of 400 m. To prevent the release of insulin in the stomach, the discs might also be enteric-coated or put inside

enteric-coated capsules[16]. Various pharmaceutical companies are also working to create a suitable system for oral insulin delivery.

PRODUCT NAME	COMPANY	TECHNOLOGY	STATUS
Capsulin	Diabetology (Jersey, UK)	Axcess™; enteric-coated capsule filled with a mixture of insulin, an absorption enhancer, and a solubilizer	Phase IIa in T1DM and phase II in T2DM completed; agreement with USV Limited(Mumbai India) to complete for the Indian market
ORMD-0801	Oramed (Jerusalem, Israel)	Enteric-coated capsule containing insulin and adjuvants to protect the protein and promote it's intestinal uptake	Phase IIa in T1DM and phase IIb in T2DM
ORA2	BOWS Pharmaceuticals AG (Zug, Switzerland)	Capsule containing insulin in dextran Matrix	Phase II in T2DM; agreement with Orin pharmaceuticals AG(Stockholm, Sweden) for the development
-	Emisphere Technologies (Cedar knolls,NJ)	Eligen; capsule containing insulin and an absorption enhancer that facilitates the passive transcellular transport	Phase II in T2DM suspended
NN1952	Novo Nordisk (Bagsvaerd, Denmark)	GIPET from Merrion pharmaceuticals (Dublin, Ireland); capsule or tablet containing absorption enhancers that activate micelle formation, facilitating	Cancelled after phase II

		transport of insulin	
NN1953;NN1954	Novo Nordisk (Bagsvaerd, Denmark	Tablet of long-acting insulin analog	Phase I in T1DM and T2DM
IN-105	Biocon (Bangalore, India)	Insulin modified with a small PEG	Phase II; searching for other company to pursue development
HDV-1	Diasome (Conshohocken, PA)	Liposomal insulin, which is hepatic-directed vesicles-insulin, HDV-I in orally administered forms	Phase III
-	Biolaxy (Shanghai, China)	NOD Technology; insulin-loaded bioadhesive nanoparticles	Phase I
-	Access Pharmaceuticals (Dallas,TX)	Cobacyte™, nanoparticle or polymer containing insulin, coated with vitamin B_{12} for targeted delivery	Phase I

Table 2: List of Orally tested Insulin Formulations

Actrapid®, a subcutaneous form of ordinary human insulin, and CapsulinTM were examined for their pharmacokinetic and pharmacodynamic characteristics by the biopharmaceutical company Diabetology. In a phase 2 trial, it was discovered that either Actrapid or Capsulin (150 and 300 U) increased the rate of glucose infusion, with maximal values being reached between 280 and 330 minutes. Actrapid had higher maximum glucose infusion rates than any dose of Capsulin. No variations were seen between 150 and 300 U of Capsulin, and a strong hypoglycemic effect over 6 h was confirmed following its administration. Capsulin (150 and 300 U) appeared to be safe and well tolerated in a phase 2a study using male volunteers with T1DM. It was also able to cause consistent increases in blood insulin levels within 30-120 minutes of dose and manage blood glucose levels for a longer period of time. Additionally, it was discovered that the control of glucose levels and increases in insulin levels were dose-dependent.

Discussions and Future Expectations

Diabetes patients continue to find oral insulin replacement therapy to be an appealing alternative to subcutaneous injections. However, it appears that finding a suitable insulin formulation will be much

more challenging than initially anticipated. In the last ten years, technological advancement and increased desire have driven the pharmaceutical industry to try again to develop oral treatments after decades of unsuccessful attempts to make an insulin pill.

Objectives

One of the main causes of clinical inertia and failure to meet target glycemic objectives has been identified as resistance to injectable insulin. Physicians and patients alike are concerned about the complexities of insulin regimens, the risk of hypoglycemia, the possibility of weight gain, and the requirement for a needle prick with insulin therapy. Due to the requirement that conventional insulins be administered prior to meals, insulin is thought to have a high index of intrusion[17]. Patients look forward to the early development of oral insulin because it will be simple to use, less intrusive, more convenient, and have higher patient compliance or adherence, which will ultimately result in better glycemic control and the prevention of complications from diabetes[18]. Oral insulin may improve b-cell activity by providing them a rest[19]. It may also induce "oral tolerance" or immunomodulation, which may help prevent diabetes[20,21]. Oral insulin can create a significant portosystemic gradient because it travels through the gastrointestinal tract before reaching the liver. This minimizes the body's exposure to systemic insulin and may prevent the sometimes-severe weight gain linked to subcutaneous insulin. Furthermore, blunting of insulin[22] first-phase release, making it difficult with conventional subcutaneous insulins, may be treated by oral insulin.

Limitations:

Toxicological concerns should be directed upon the binomial insulin carrier. When assessing the potential of insulin-loaded nanoparticles, toxicity is a crucial factor to take into account. Nanoparticles must be checked to make sure they don't have any negative impacts or even harm the intestinal epithelium because they are designed to interact with 527 Oral Insulin Delivery. The crucial point is that nanoparticles will degrade in the presence of cells and may influence cellular responses whether they are coated or uncoated. For example, biodegradable nanoparticles can build up inside cells and produce highly hazardous intracellular changes including loss of organelle integrity or gene mutations. The cytotoxicity test is a sensitive, quick, and affordable way to determine whether nanoparticles have the potential to cause sublethal or lethal effects in cells. Cell immunological response may also be impacted, therefore cytotoxicity may not be the only negative effect[23]. Additionally, from a toxicological standpoint, oral insulin delivery may be uncertain because molecules delivered to unnatural locations in inappropriate quantities are likely to behave in unanticipated ways. This may not be a problem if insulin is retained and not released from carrier systems until it enters the systemic circulation, although this strategy is dubious because insulin may result in gastroparesis[24]. Surfactants and absorption enhancers both have the potential to harm the intestinal epithelium over the long run. In fact, when given continuously, absorption enhancers may also encourage the penetration of infections and toxins[25]. Protease inhibitors may interfere with the digestion of dietary proteins, which raises some safety questions about their use. The physiology of the intestinal barrier may also be altered by mucoadhesive systems, which may also impact mucus turnover[26].

Conclusion

A fascinating and appealing area of research, oral insulin delivery has the potential to completely change how diabetes is managed. A number of studies have produced some positive outcomes, and

several delivery systems are currently undergoing advanced development. The fact that the delivery systems created since the 1980s have not demonstrated a definite clinical advantage over the subcutaneous insulin route suggests that there has not been any advancement made despite all of the efforts made since then. It's important to appropriately address a number of issues. Through adequately powered studies in various patient populations across the diabetes spectrum, long-term efficacy and safety must be proven. For a medicine that must be taken continuously throughout life, it is particularly crucial to understand how the drug is absorbed during meals and to make it replicable. Clinical studies must also clearly show that they are superior to oral hypoglycemic medicines and parenteral insulin formulations, particularly by having a better hypoglycemic profile, preventing weight gain, and achieving better disease progression results in long-term investigations. It is important to thoroughly evaluate the toxicological profile of the established delivery systems. Overall, the success of oral insulin relies on the ability to produce insulin effectively in a pharmaceutical market where cost-consciousness is a priority as well as in sufficient amounts for oral delivery. Pharmaceutical companies are leading the charge in creating an oral insulin delivery system, but the majority of them give up during the early stages of development. If they were to make clear what went wrong in those studies, that would be really interesting. To get the first insulin oral delivery device on the market, more work obviously needs to be done. Successfully addressing these problems will usher in a new era of diabetes care.

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