Review Article

The New Emerging of Diabetes Treatment: A Review of Oral Insulin

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ABSTRACT

Diabetes patients typically get daily subcutaneous insulin injections; however, due to the discomfort of these injections, patient compliance is difficult to maintain; hence, several delivery methods, including oral administration, are being investigated. The emerging field of oral insulin administration is summarised in this overview. There are many formulations to develop oral insulin, such as PEGylation of insulin, targeting moieties-mediated transport strategy, cell penetrating peptides (cpps)-assisted permeation strategy, smart oral robotics-associated traverse strategy, hydrogels for insulin: microenvironment-responsive hydrogels, and zwitterionic micelles. Future oral insulin development will be resolved by non-erratic absorption and bioavailability. One method to deliver the therapeutic ingredient to the colon, improve insulin bioavailability, and eliminate small intestine absorption variation is to include compatible and appropriate excipients in an insulin tablet, such as an acid-resistant enteric coating, enzyme inhibitor, absorption enhancer, and muco-adhesive polymer.

Keywords: antidiabetics, diabetes mellitus, insulin, review

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1.0 Introduction

Pancreatic-cells continuously produce and release the peptide hormone insulin. Insulin fine-tunes the metabolism of carbohydrates, lipids, and protein by stimulating glucose uptake into fat, liver, and skeletal muscles. When insulin's normal function is impaired, hyperglycaemia results, which is the primary cause of the group of metabolic illnesses, or diabetes mellitus (1, 2). The pathophysiology of hyperglycaemia in type 2 diabetes is characterized by three major defects: insulin deficiency due to inadequate pancreatic insulin release, excess hepatic glucose output, and insulin resistance (decreased glucose uptake) in peripheral tissues (including muscle and fat) and the liver (2, 3). Consequently, the discovery of insulin played a crucial role (2, 4).

Sir Edward Albert Sharpey Schafer (1850–1935) demonstrated in 1910 and 1916 that the pancreatic islands can secrete a chemical capable of regulating glucose metabolism, which he named "insulin" from the Latin word for "island," insulin (1, 2). Four Canadian scientists—Frederick Grant Banting, Charles Herbert Best, John James Rickard Macleod, and James Bertrand Collip—overcame the last barriers. In March 1921, the orthopaedic surgeon Banting carried out research on the operation of pancreatic islets under Barron's inspiration. Macleod, the head of Toronto's physiology department, gave him an office, dogs, and a student helper. Banting and his student Charles Best discovered that pancreatic duct ligation led to exocrine pancreas atrophy, islet preservation, and normal glucose levels. Banting et al. demonstrated that alcohol extraction of fresh pancreatic tissue improved glucose control in diabetic dogs without has emerged as a promising solution. By bypassing the discomfort associated with injections, oral insulin could potentially enhance patient adherence and overall ligation or deterioration. The biochemist-pharmacist Collip developed and purified the extraction procedure to create the first safe and effective human pancreatic extract. In January 1922, Leonard Thompson was brought back from the brink of death after receiving the group's extract and survived for thirteen more years (2).

Insulin technology is continuously developed to optimize individualized insulin therapy. The optimal individualized insulin therapy can enhance glucose control by lowering hypoglycaemia risk and adverse effects, accommodating patient preferences, and boosting medication adherence. The subcutaneous route is the most common technique for administering insulin. It is handy because the patient can self-administer the medication, thereby avoiding numerous doctor visits. Subcutaneous delivery requires self-injection by the patient at least 2–4 times daily, although studies indicate that blood glucose cannot be controlled with a single daily injection (5, 6). The repetitive injection of insulin can induce discomfort, necrosis, and infection. It can result in poor patient compliance due to significant discomfort at the injection site, loss of fat tissues at the delivery site, or aberrant accumulation of fat under the skin surface at the subcutaneous delivery site as a result of several injections (5, 7). Therefore, alternative insulin delivery or other routes of insulin, including oral insulin, have been studied to overcome these issues (5, 8).

Recognizing the limitations of injectable insulin therapies, researchers have been exploring innovative approaches to improve the delivery of insulin. Among these approaches, oral insulin administration
diabetes management. Oral insulin administration mimics physiological (endogenous) insulin production by raising portal insulin concentration through

intestinal absorption (5, 9). It has been discovered that oral insulin absorption by nanocarriers such as polymers, lipids, inorganic nanoparticles, etc. generates a strong portal-systemic gradient. Oral insulin therapy is more affordable because it does not require aseptic conditions, and it is met with a high level of patient acceptability and compliance due to the reduced pain and discomfort associated with injection administration. However, breakdown due to gastric juice, enzymes, and first-pass metabolism results in poor bioavailability when insulin is administered orally (5, 8, 10). Oral-Lyn was the first buccal spray rapid-acting insulin approved in Ecuador and promoted by Generex. It uses Rapidmist technology to deliver a mixture of insulin, surfactants, and lipids to the buccal mucosa (1, 2, 11).

However, the successful development and implementation of oral insulin delivery systems require a deep understanding of the complex interplay between drug formulation, absorption kinetics, and physiological barriers within the human body. Consequently, it is crucial to examine the current research landscape surrounding oral insulin delivery. This overview not only sheds light on the advancements made in this field but also highlights the significance of oral insulin administration in revolutionizing diabetes care.

In this context, this study aims to explore the recent developments in oral insulin delivery methods, examining their efficacy, safety, and potential impact on patient outcomes. By synthesizing existing knowledge and addressing gaps in research, this investigation contributes to the ongoing efforts to improve diabetes management and enhance the quality of life for individuals living with this chronic condition.

2.0 Literature review

2.1 Insulin injection vs oral challenges and benefits

The most common treatments for diabetes mellitus are conventional insulins, such as insulin analogues and glucagon-like peptide-1 analogues, that need to be injected (12). Patients with diabetes mellitus frequently fail to adhere to their injectable insulin therapy regimens due to impracticality, injection issues, lifestyle constraints, and strict regimens, which may lead to many patients' conditions not being managed as effectively as possible (13). In addition, it also showed that the adherence rate for the insulin injection and the oral antidiabetic is low; the self-reported medication non-adherence rate was 25% in 2017, 21% in 2018, and 27% in 2019 in the United States of America (14).

Diabetes patients often lack knowledge about proper injection techniques, which can lead to insufficient glycaemic control (15). De Coninck et al., 2010, conducted a survey of 4352 type 1 or type 2 diabetic patients in 16 countries between 2008 and 2009, and they found patients reported receiving vastly differing levels of education on 14 injection-related topics, including the site of injection, the depth of the injection, the duration of the injection, rotating the injection site, and using a needle only once. 80% or more of patients across all nations claimed to have received instruction on only one of these areas, which was the injection site. Fewer patients reported having received training for all other issues (16).

About 53 cases of local complications, including skin hyperpigmentation and lipohypertrophy, were found in 100 individuals with type 1 or type 2 diabetes who frequently insulin (17). These adverse events were linked to improper injection technique. Such side effects from inappropriate insulin administration may hinder patient adherence to therapy and obstruct insulin absorption.

The likelihood of developing either hyperglycaemia or nocturnal hypoglycaemia might be increased by selecting the wrong injection site and using poor technique. Pain from poor technique may also make patients forego injections. The most effective insulin injection is dependent on choosing the right needle, the right injection location, which is determined by the type of insulin being used, and the appropriate injection method (18).

All these challenges of injectable insulin, in theory, can be avoided completely by using oral insulin. When compared to the other modalities, administering insulin orally provides a number of benefits over those methods of systemic delivery. For instance, there isn't any injection-related local pain, discomfort, irritation, or risk of infections of the skin like Staphylococcus aureus and Mycobacterium chelonae (19). The pancreas detects a rise in blood glucose after a meal in accordance with normal human physiology and then secretes insulin to keep blood sugar levels within a normal range. The most prominent advantage of oral insulin is that it may be administered more comfortably than the conventional method of injecting insulin, where the injection site might eventually become painful and inflamed. Oral insulin administration enhances portal levels of medication and minimizes peripheral hyperinsulinemia, which is linked with neuropathy and retinopathy in other routes of administration (20). Insulin benefits from hepatic first-pass metabolism. Despite the fact that oral insulin is more vulnerable to liver metabolism, limiting its total bioavailability, it can reduce the risk of hypoglycaemia and immunological responses in peripheral tissues that occur with parenteral delivery. Other benefits include lowering insulin exposure in the peripheral system, which reduces the likelihood of weight gain (21).

Improvements in cell function were seen after starting a 6-month course of insulin therapy, particularly in T2DM patients with significant hyperglycaemia at an early stage. The oral route of insulin therapy has the potential to promote early introduction and compliance with insulin therapy and reduce the progression of diabetes owing to its ease and fewer adverse effects, such as weight gain and hypoglycaemia (21).

There are a few challenges to overcome, even if oral insulin delivery is the optimal alternate delivery method for diabetic patients. In order to maintain its complete structure, integrity, and conformation via the stomach and intestine, insulin must first enter the systemic circulation. Since intact insulin is a protein drug, its limited oral bioavailability can be related to its vulnerability to digestive enzymes, large molecular weight, and slow diffusion rate through the mucin barrier (22, 23).

2.2 Pharmacokinetics and pharmacodynamics of oral insulin

A study to determine the pharmacokinetics and pharmacodynamic properties of oral insulin combined with 4-CNAB compared with subcutaneous regular human insulin in type 2 diabetes patients (24).Gastrointestinal absorption of oral insulin alone is hindered by enzymatic degradation and lack of permeation through epithelial cells; thus, it was combined with N-(4-chlorosalicyloyl)-4-aminobutyrate (4-CNAB), which is a novel drug carrier used to create more favourable physicochemical properties for gastrointestinal insulin absorption (24).

The authors found that oral insulin exhibits early augmented pharmacokinetic and pharmacodynamic responses (24). When compared to subcutaneous regular human insulin, oral insulin has a much shorter duration of action and returns to its baseline effect within two to three hours (24). By restoring normal first-phase insulin secretion in patients with type 2 diabetes and possibly

improving glycaemic control, the quick pharmacokinetic and metabolic time profiles of oral insulin seen in this study may be beneficial (Bruce, 1988). Oral insulin's onset of action appears to be comparable to (or faster than) those of subcutaneous fast-acting analogues that have been reported (24), but a direct comparison has not yet been made (24).

In comparison to subcutaneous insulin preparations, oral insulin has the advantage of reaching the liver in high concentration via the portal vein after gastrointestinal absorption (24). This results in a more physiological and powerful effect on hepatic glucose production and a weaker effect on the peripheral tissues (possibly avoiding hypoglycaemia) (24). Only 7% of the oral insulin-CNAB was absorbed after 2 hours of administration under fasting conditions with high variability (coefficient of variation 60–70%), similar to subcutaneous insulin, and may further increase under a prandial state (24).

A study by Cernea et al. (2004) using oral insulin spray on healthy subjects also found similar results. It was associated with a higher Cmax, a shorter Tmax, and a faster time to peak glucose uptake compared with SC insulin (25). It was also rapidly absorbed (25). Table 1 summarizes the pharmacokinetic and pharmacodynamic properties of oral insulin.

2.3 Formulation strategies for oral insulin delivery

The specific requirements of the intended application should ultimately guide the choice of formulation strategy for oral insulin delivery. Researchers should carefully consider factors such as stability, release kinetics, dosing frequency, patient compliance, and cost-effectiveness when selecting the most appropriate approach for their needs. Additionally, conducting thorough preclinical and clinical studies is essential to validating the effectiveness and safety of the chosen strategy. A number of strategies have already been developed to overcome the barriers to oral insulin. In this part, the most common strategies for addressing the barriers are summarized.

2.3.1 PEGylation of Insulin

The covalent attachment of PEG to insulin influences insulin's molecular size, charge, and capacity to bind to receptors (23, 26, 27). This conjugation inhibits insulin from being eliminated from the body through the reticuloendothelial system (RES) and liver factors. Insulin is protected from degradation by PEG peptidases (27). By inhibiting the development of these aggregates, the conjugated product serves to increase the stability of insulin. Additionally, it lowers the immunogenicity and allergenicity of insulin aggregates. IN-105, a second-generation oral tablet created by Biocon (23), is an example of PEGylated insulin. This substance was resistant to protease activity and had pharmacological action similar to insulin (28, 29). The medication also exhibited an enhanced half-life in the GI tract, enhanced absorption, lower immunogenicity, decreased mitotic induction, and a favourable safety profile (29).

2.3.2 Targeting Moieties-mediated Transport Strategy

The immune system uses antibodies, also known as immunoglobulins (Ig), to destroy pathogens. Using the variable fragment antigen-binding region, the antibody identifies the antigen. Stimulated by physiological and immune factors such as cytokines and antigens, the intestinal mucosal barrier self-regulates with expanded tight junctions (TJs) and enhanced endocytosis of epithelial cells; therefore, targeting antibodies in the intestinal

epithelium could be a novel therapeutic direction.

Neonatal Fc receptor (FcRn) binds immunoglobulin G (IgG) in an acidic pH-dependent manner, mediated by an electrostatic contact between the histidine residues of IgG and the acidic residues of FcRn. Consequently, it facilitates the transport of IgG over the intestinal mucosal barrier. In light of this knowledge, our team designed Fc-modified poly (lactic acid)-b-poly (ethylene glycol) polymeric nanoparticles (NP-Fc) with enhanced biocompatibility and biodegradability to target FcRn (30). In the acidic gut, these NPs identify and bind the FcRn on the apical side of epithelial cells prior to absorption. The NPs move through endosomes and then leave the cell through exocytosis on the bottom side of the epithelial layer. This lets them get into the neutral lamina propria and spread throughout the body (31).

Neonatal Fc receptor (FcRn) binds immunoglobulin G (IgG) in a way that depends on the acidity of the environment. This happens because the histidine residues of IgG make electrostatic contact with the acidic residues of FcRn. It thereby facilitates IgG trafficking over the intestinal mucosal barrier. Our group created Fc-modified poly (lactic acid)-b-poly (ethylene glycol) polymeric nanoparticles (NP-Fc) with enhanced biocompatibility and biodegradability to target FcRn based on this insight. Gu et al. developed insulin-encapsulated Fc-Rn-targeted liposomes for postprandial glucose control. A hyaluronic acid (HA) shell was utilised to shield Fc from the harsh conditions of the stomach. Additionally, phenylboronic acid was coupled with HA to confer glucose-responsive detachment behaviour on the shell. The liposomes were subsequently transported across the intestinal epithelium via an FcRn-mediated route. Furthermore, in vivo treatment of diabetic mice revealed that the Fc-targeting liposome regulated BGLs with a low risk of hypoglycaemia, even after oral glucose solution administration.

Table 1: Pharmacokinetic and pharmacodynamic properties of oral insulin

Pharmacokinetics and Pharmacodynamics Properties	Oral Insulin	References
Maximum plasma insulin concentration (Cmax)	Higher than subcutaneous insulin Similar with subcutaneous insulin	(24, 25, 31)
Time to Cmax (Tmax)	Shorter than subcutaneous insulin	(24, 25)
Duration of action	Shorter than subcutaneous regular human insulin (return to the baseline effect within 2 to 3 hours)	(24, 25)
Onset	Faster than subcutaneous insulin Increase absorption and onset	(24, 32)
Absorption	Small amount absorbed under fasting condition. Highly variable especially with prandial administration. Rapidly absorbed. Low bioavailability Reduces the gastrointestinal barrier function	(24, 25, 30, 33 - 36)

FcRn binds and transports albumin across the intestinal epithelium in addition to IgG. Santos et al. created new porous silicon nanoparticles that are conjugated to albumin and loaded with insulin. They then wrapped them in a pH-sensitive polymeric particle that the FDA has approved. Transferrin (Tf), another targeting protein that binds to Tf receptors on epithelial cells and traverses the transcytosis pathway, is also frequently used in oral delivery. Xi et al. (2022) stated that even with a high oral insulin bioavailability of 14.3%, it can provide a prolonged hypoglycemic effect. It is because the target functional nanoparticle (PG-FAPEP) with dual modification was constructed to sequentially address these important absorption obstacles for improved oral insulin delivery.

2.3.3 Cell Penetrating Peptides (CPPs)-assisted permeation strategy

Cell-penetrating peptides (CPPs) are a particular class of short peptides that facilitate the transport and penetration of macromolecules. Because CPPs carry a large number of positive charges and their capacity to penetrate membranes does not rely on endocytosis, they are now being employed to enhance the transepithelial transport efficiency of oral medication administration (8). In 2005, a study showed that conjugating Tat to the B29 Lys residue of insulin facilitated its penetration across Caco-2 cells, demonstrating the potential of CPPs for oral insulin delivery. CPPs are short peptides that facilitate the transport and absorption of substances through three mechanisms: (a) direct penetration into cell membranes by disrupting the structure of the lipid bilayer; (b) endocytosis, by which external molecules enter cells via cell membranes; and (c) translocation of molecules through the formation of inverted micelles. This indicates that CPPs do not rely solely on endocytosis (27).

Li et al. created insulin-loaded chitosan (CS) nanoparticles that were functionalized with the CPP SAR6EW. These nanoparticles had a mean diameter of 150 2.0 nm, 75.4 2.1% entrapment efficiency, and 7.58 0.2% loading efficiency. Because clathrin and caveolae help with endocytosis, cells were able to take in more insulin (27, 37). In the other study, insulin was conjugated with CPP, a low-molecular-weight protamine (LMWP), resulting in increased intestinal permeability. These conjugates were then encapsulated within PLGA nanoparticles coated with mucoadhesive N-trimethyl chitosan chloride. Insulin was discovered to be protected against enzymatic breakdown, resulting in enhanced retention inside the gut mucosal layer (27, 38).

2.3.4 Smart oral robotics associated traverse strategy

Physical strategies, such as nanorobots and micromotors that react with gastric acid to release gas, propelling them through the GI tract, and microneedles that can physically pierce tissue walls to escape the GI tract and sustainably release insulin, can be used in conjunction with chemical strategies to increase oral insulin bioavailability. Langer and Traverso created a number of innovative oral biologic delivery devices for this purpose. For instance, they created a self-locating millimeter applicator (SOMA) that implanted a milepost into the stomach tissue to release the payload. Due to its high-density stainless-steel core and polycaprolactone shell, which facilitate a shift in mass, the SOMA self-orients to an upright position when subjected to external forces, much like a tortoise that has been flipped over. Thus, when delivered orally, it adheres to the stomach wall and pierces the gastric mucosa

in order to inject insulin into the systemic circulation. In both rats and pigs, active quantities of medicinal components were detected without any visible stomach tissue injury or abnormalities. Langer and Traverso also created the luminal unfolding microneedle injector, an ingestible capsule. When administered orally, the capsule dissolves and disintegrates at an acidic pH. Then, the three degradable arms of the inside device stretch the tissue and propel a patch that dissolves microneedles into the tissue wall (30).

2.3.5 Hydrogels for Insulin: microenvironment-responsive hydrogels

Hydrogels are three-dimensional networks of hydrophilic polymer chains that are chemically or physically cross-linked. Due to the chemical or physical cross-linking of polymer chains, they can retain their original structure while absorbing a substantial amount of water. In addition, using pH-responsive hydrogel as an example, as it reaches the intestine, where the pH is greater than the hydrogel's pKa value, it ionises, absorbs water, and swells. This drastically enlarges its pores, allowing for the persistent and progressive release of insulin (30, 37).

Salecan-based hydrogels are one example of a hydrogel for oral insulin delivery. Salecan is a food gum with antioxidizing characteristics, and it’s a water-soluble polysaccharide derived from bacteria produced hydrogels from salecan and poly (acrylamide-co-acrylic acid) by polymerizing free radicals. Changing the amount of salecan in the hydrogels affected the rate of insulin release. Oral administration of these hydrogels to diabetic rats resulted in a 10-fold increase in insulin bioavailability compared to oral administration of free insulin. The other study (37) developed pH-sensitive hydrogels utilizing sodium carboxymethyl cellulose and poly (methacrylic acid) by free radical polymerization and the semi-interpenetrating polymer network technique (PMAA).

2.3.6 Zwitterionic micelles

In a recent investigation (Han et al., 2020), freeze-dried powder of zwitterionic insulin micelles was put into enteric-coated capsules. This innovative formulation had a zwitterionic surface like that of a virus, a betaine side chain, and an ultralow critical micelle concentration. This facilitated transporter-mediated insulin absorption via intestinal epithelial cells without the need to open tight junctions. The oral bioavailability of these carriers was greater than 40% (39, 40, 41).

3.0 Conclusion

One of the traditional management strategies for diabetes is daily injectable insulin. The primary issue, however, is that patient compliance is difficult since the injection sites ache and can get irritated. Comparing oral administration of insulin preparations to other systemic administration methods demonstrates possible advantages. It can prevent adverse implications, including weight gain and hypoglycaemia. However, there are several obstacles to be overcome, including the large molecular weight of insulin, vulnerability to enzymatic proteolysis, and the slow diffusion rate through the mucin barrier. Future oral insulin development will be resolved by non-erratic absorption and bioavailability. One method to deliver the therapeutic ingredient to the colon, improve insulin bioavailability, and eliminate small intestine absorption variation is to include compatible and appropriate excipients in an insulin tablet, such as an acid-resistant enteric coating, enzyme inhibitor, absorption enhancer, and muco-adhesive polymer.

Further research is needed to determine the bioavailability of insulin by combining the aforementioned ways to enhance it, the optimal insulin dosage, and the lack of side effects, including protein mal-absorption, local intestinal wall damage, and hypoglycaemia. Long-term safety and efficacy must be validated via significant research before oral insulin becomes a reality. Lastly, more thorough trials are needed to establish the viability of oral versus subcutaneous insulin injections in diabetic patients.

Conflict of Interest

No conflicts of interest to disclose.

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