Review Article

From Injection to Ingestion: Future of Oral Insulin Diabetic Formulation

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ABSTRACT

Insulin, discovered in 1922. It is recognized as the safest and most effective medication for lowering glucose levels. Despite its efficacy, a significant challenge associated with insulin therapy has been the high prevalence of hypoglycaemia, often leading to patients being prescribed sub-optimal dosages.

Keywords: Insulin, diabetes, oral dosage form, liposomes.

INTRODUCTION

Insulin is a protein hormone with a molecular weight of 5800 Da composed of two chains, alpha and beta linked by two disulfide bonds. It is classified as a Class III according to the Biopharmaceutics Classification System. The favourable administration of insulin is subcutaneous injection. Local administration is investigated in oral, transdermal, inhalation, ocular and vaginal routes with their unique obstruction.

The first oral insulin preparations were tried, with poor results, by Joslin, in 1922 and 1923. Since then, many researchers have worked on this concept, with no success.[5]

Oral insulin has several merits over the conventional method, including patient compliance, enhanced quality of life, flexible dosing, reduced risk of injection related issues, and reduced cost, and it also mimics endogenous insulin and hence reaches the liver by the portal vein at a higher concentration, thereby showing improved efficiency However, oral insulin must pass through several barriers in the gastrointestinal tract. Some strategies that could be utilised to bypass these barriers include the use of permeation enhancers, absorption enhancers, use of suitable polymers, use of suitable carriers, and other agents. Several formulation types have been explored for the oral delivery of insulin like hydrogels, capsules, tablets, and patches, which have been described briefly by the article. A lot of attempts have been made to develop oral insulin delivery; however, none of them have been commercialised due to numerous shortcomings. Currently, there are several formulations from the companies that are still in the clinical phase; the success or failure of some is yet to be seen in the future.

The excerpt discusses the extensive, yet largely unsuccessful, efforts over the past century to develop an effective oral insulin formulation, highlighting the persistent challenges despite numerous clinical trials and technological advancements.[1]

History of Oral Insulin: Research into oral insulin began shortly after its discovery in 1921. The first attempt at oral administration in 1922 showed no metabolic improvement in patients. A subsequent attempt in 1923 to enhance absorption by adding alcohol also failed to yield positive results.[1]

Continued Efforts (2001-2019): Despite early setbacks, various companies, including Emisphere, Diabetology, and Oramed, continued to pursue oral insulin development and conducted several clinical trials between 2001 and 2019.[4]

Emisphere's Trials: Emisphere received FDA approval for a Phase I clinical trial of its oral insulin formulation in 2001, with a Phase II trial following five years later. However, the Phase II results were disappointing, showing no significant differences between treatment and control groups, largely due to a small sample size of only eight subjects.[4]

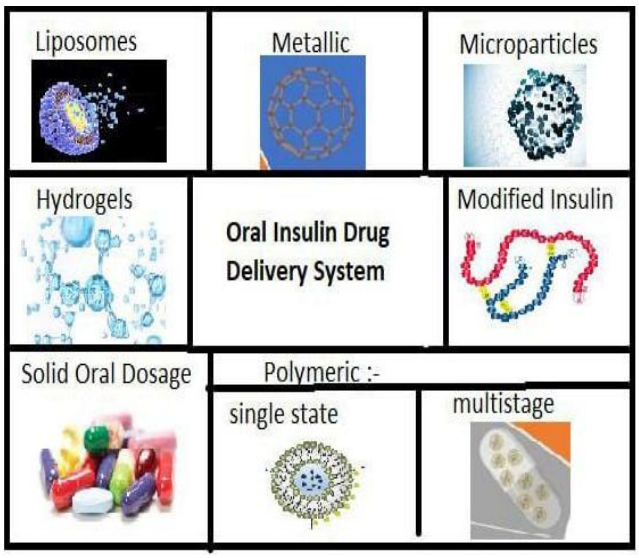
Oramed's ORMD-0801: In 2014, Oramed's ORMD-0801 received FDA approval to proceed to Phase III clinical trials. Despite involving a larger sample size of 710 diabetic patients, the results were still disappointing, as no superior glycaemic control was observed in patients treated with oral insulin compared to placebo after 26 weeks of treatment.[5]

Despite a century of dedicated research and numerous clinical trials, oral insulin formulations have consistently faced significant challenges, with most attempts failing to demonstrate superior glycaemic control or sufficient efficacy compared to existing treatments. The needs of ingestible insulin are resistance to injectable insulin, lack of achievement of target glycaemic goals, need of needle pricks, and chances of weight gains.[1]

Formulation of Oral Insulin:

Polymeric nanoparticles, made from biocompatible and biodegradable polymers such as chitosan, alginate, and gelatin, can encapsulate or adsorb insulin for oral delivery. Chitosan-based nanoparticles are widely studied due to their ability to transiently open tight junctions in intestinal cells and enhance absorption. For example, pH-responsive chitosan/poly(γ-glutamic acid) nanoparticles loaded with insulin aspart showed a slower but sustained hypoglycemic

effect after oral administration in diabetic rats, with a relative bioavailability of 15%, resembling the profile of subcutaneous NPH insulin and potentially reducing the risk of hyperinsulinemia. Similarly, thiolated chitosan nanoparticles (TCNPs) demonstrated prolonged insulin release, with oral Ins-TCNPs lowering blood glucose more gradually and maintaining insulin levels longer than subcutaneous injections, likely due to interactions between thiol groups and intestinal mucus glycoproteins. Importantly, TCNPs showed good safety, maintaining cell viability at high concentrations. These findings suggest that polymeric nanoparticles, particularly chitosan-based systems, hold strong potential for sustained and controlled oral insulin delivery.



Liposomal Nanoparticles:

Liposomal nanoparticles, made of phospholipid bilayers, are promising nanodrug delivery systems for oral insulin, as they enhance absorption while protecting the drug from enzymatic degradation and immune responses. Two main formulations have been studied: hepatic-directed vesicle insulin (HDV-I) and DSPE-PEG3400-FA liposomes. HDV-I encapsulates insulin with a hepatocyte-targeting molecule, ensuring protection in the gastrointestinal tract and directing delivery to hepatocytes to mimic natural insulin action; it has been formulated into small (<150 nm), stable oral capsules, though animal studies remain limited. In contrast, DSPE-PEG3400-FA liposomes incorporate polyethylene glycol and folic acid ligands to improve stability, resist mucus penetration, and reduce nonspecific absorption, with hydrogenated soy phosphatidylcholine added for thermal resistance. Studies indicate these liposomes exhibit antidiabetic effects, highlighting the potential of liposomal nanoparticles in the development of effective oral insulin therapies.[3,6]

Metallic Nanoparticles:

Metallic nanoparticles, composed of a metal core with an organic, inorganic, or oxide shell, have been explored for oral insulin delivery, particularly gold and selenium nanoparticles. Gold nanoparticles are biocompatible and bind well to insulin, with studies showing that insulin-loaded gold nanoparticles (Au-Ins and Au-Asp-Ins) reduced blood glucose in diabetic rats by 19% and 31%, respectively, though less effectively than subcutaneous insulin (53%). Selenium nanoparticles (INS-SeNPs), prepared using ionic cross-linking and in situ reduction, demonstrated strong hypoglycemic effects in both normal and diabetic rats, with the 50 IU/kg oral dose comparable to 1 IU/kg subcutaneous insulin. These nanoparticles resisted enzymatic degradation, enhanced insulin absorption, and exhibited dose-dependent effects, though higher doses showed lower bioavailability. Moreover, selenium itself contributed antidiabetic activity, with blank SeNPs reducing glucose by 21%. Importantly, selenium intake at the estimated human equivalent dose (2 mg/day) is considered safe, with no reported genetic or immunological toxic ity.[3,7]

Polymeric nanoparticles:

Polymeric nanoparticles are made from biocompatible and biodegradable polymers such as chitosan, alginate, and gelatin, and can encapsulate or adsorb insulin for oral delivery. Chitosan-based nanoparticles are widely studied due to their ability to transiently open tight junctions in intestinal cells, enhancing absorption. For example, pH-responsive chitosan/poly(γ-glutamic acid) nanoparticles loaded with insulin aspart showed a slower but sustained hypoglycemic effect after oral administration in diabetic rats, with a relative bioavailability of 15%, resembling the profile of subcutaneous NPH insulin and potentially reducing the risk of hyperinsulinemia. Similarly, thiolated chitosan nanoparticles (TCNPs) demonstrated prolonged insulin release, with oral Ins-TCNPs lowering blood glucose more gradually and maintaining insulin levels longer than subcutaneous injections, likely due to interactions between thiol groups and intestinal mucus glycoproteins. Importantly, TCNPs showed good safety, maintaining cell viability at high concentrations. These findings suggest that polymeric nanoparticles, particularly chitosan-based systems, hold strong potential for sustained and controlled oral insulin delivery.[3,8]

Hydrogels :

Hydrogels are hydrophilic, crosslinked polymer networks that can retain water and are explored for insulin delivery. Polymethacrylic acid (PMAA)-based hydrogels improve epithelial permeability and inhibit protease activity by binding calcium. A PMAA-chitosan-PEG (PCP) hydrogel was developed, with thiolation enhancing mucoadhesion. Non-thiolized PCP requires insulin complexation with methyl-β-cyclodextrin to improve absorption and prevent self-association. The system showed pH-sensitive release (minimal at pH 1.2, rapid at pH 7.4) and reduced blood glucose in diabetic rats by 30% within 2 h, with sustained effects up to 10 h and a pharmacological bioavailability of 1.95. Methyl-β-cyclodextrin was safe below 10 mM but cytotoxic at higher concentrations.[3,9]

Solid Oral Insulin:

Enteric-coated oral insulin capsules (ORMD-0801) have been developed for the treatment of both type 1 and type 2 diabetes. The formulation includes a soybean trypsin inhibitor and disodium EDTA to enhance intestinal absorption, along with Aerosil 200 as a stabilizer and Tween 80 as a surfactant. Preclinical studies demonstrated that in pig models with intestinal access bypassing gastric digestion, ORMD-0801 reduced blood glucose AUC by 7.0–7.5% and suppressed postprandial glucose when administered directly into the duodenum, compared to placebo. In beagle dogs, oral administration resulted in the highest exogenous insulin concentration, with a Tmax of 0.75 hours, relative bioavailability of 5.41%, and onset of action at 15 minutes. The pharmacokinetic profile of oral ORMD-0801 was comparable to duodenal administration and superior to subcutaneous insulin in terms of AUC. To further overcome gastrointestinal permeability barriers, Eligen® technology has been introduced, where insulin is non-covalently complexed with the permeation enhancer 4-CNAB, enabling epithelial transport without tissue damage. Another approach, Capsulin, combines enteric coating, aromatic alcohols, and a dissolution aid to allow rapid dissolution at the intestinal lining, thereby enhancing insulin permeation.

Modified Insulin:

Two oral insulin analogs were developed by modifying the unbound Lys-β29 residue of human insulin. IN-105 was created by attaching a methoxy triethylene glycol propionyl group via a stable amide bond, improving water solubility through PEGylation. Alternatively, hexyl insulin monoconjugate 2 (HIM-2), developed by Nobex and Biocon, linked an amphiphilic oligomer to Lys-29, enhancing stability against enzymatic degradation and promoting intestinal absorption when delivered in gelatin capsules.

Microparticles:

A microparticle is the solid-in-oil-in-water emulsion, which uses hydroxypropyl methylcellulose phthalate as the enteric polymer in the aqueous phase. These particles showed a pH-dependent release, with more insulin released at higher pH levels, and the release was further enhanced in the presence of lipase.[3]

The Need for Ingestible Insulin:

Resistance to injectable insulin has been identified as a major reason for clinical inertia and lack of achievement of target glycaemic goals. Physicians as well as patients fear the complexity of insulin regimes, the risk of hypoglycaemia, and the chances of weight gain, as well as the necessity of a needle prick with insulin therapy. Insulin is perceived to have a high index of intrusion, as the conventional insulins need to be given prior to meals. Patients anticipate the early development of an oral insulin, as it will be easy to administer, have a lower index of intrusion, be more convenient, have more compliance or adherence from the patient, and finally lead to better glycaemic control, and thus, prevention of complications of diabetes. Oral insulin may improve β-cell function by providing β-cell rest and may help in preventing diabetes via induction of 'oral tolerance' or immune modulation. Oral insulin is able to achieve a high portosystemic gradient, as it is delivered to the liver from the gastrointestinal tract. This reduces systemic insulin exposure and may obviate the excessive weight gain sometimes seen with subcutaneous insulin. Oral insulin may also be able to correct the blunting of first-phase release of insulin, which is difficult with conventional subcutaneous insulins.[1],[5]

Point to Ensure in Ingestible insulin administration:

Physiological Barriers

GIT environment:

Ingestibles drug absorbs mostly at the small intestine, however GI have diverse pH levels, multiple enzymes, mucus. pH levels of GI are 2.5 of gastric acid and at the end rising to 6 due to bile, in jejunum rises to >7.5 and in colon lowers to 6.5

Proteinase:

Proteinase like pepsin in stomach and trypsin, chymotrypsin cleave insulin into many peptides and turn it inactive

Mucus:

The composition of mucus is mainly water (≥90%), mucin (5%), lipids, and electrolytes. The presence of mucus leads to decreased permeation of drug into epithelial cells via encapsulating drug.[1]

Approaches to increase Ingestible Insulin Efficiency:

Encapsulation:

To protect the insulin from gastric pH and enzymatic condition. The most effective way to insure this issue doesn't occur is to have enteric coated tablets or capsules.

Nanocarries:

This is very effective to increase stability and enhance its permeability across the intestinal barrier.

Proteinase Inhabitors:

The easiest way to fix the proteinase enzymatic barrier is to formulate insulin with proteinase inhibits which shows good results of insulin, however they lower the proteinase enzymes and other side effects.[1]

Oral Drug Delivery System:

The most preferred way to increase efficiency of ingestible insulin in oral administration is nanocarries. Drugs can be encapsulated in matrix or core forming particles with size lower than 1000 nm. (In 2021 article) Nanocarries are the most effective way of oral administration of insulin depending upon their carrier materials. They are categorised into lipid NPs, Polymeric NPs and Inorganic NPs.

Surface Coating:

Functional coatings are done to increase stability and penetrability of drugs. In case of Insulin coating used are hydrogel, pollen, gelatin.

Hydrogel coating prevents instant release of insulin in Gastric acid (acidic pH).

Arginine-insulin-loaded liposomes have been incorporated into cysteine modified Alg Hydrogels. At pH 1. This coating have researched to release insulin about 10% in 1 hour Gelatin is similar to Hydrogel however they are more biocompatible and cost effective.[1]

Surface Charge:

Mucus is a negatively charged substance which entraps the positively charged materials, by improving negative charges on nanocarriers the drug stability increases and permeation improves and absorption increases. In contrast the positively charged nanocarriers decrease the absorption. The nanocarriers are prepared with negatively charged NPs with Alginates (Alg) and positively charged NPs with Chitosan (CS). Their zeta potentials were −20.6 and +27.6 mV respectively and show 80% and 30% increase in absorption respectively.[1]

Electro Neutral nanocarrier:

Zwitterions are compounds carrying both positive and nega-tive charges. The most common examples of zwitterions are hosphatidyl-choline and carboxybetaine. Shan et al. developed insulin NPs based on PLA and the zwitterion dimyristoyl phosphatidylcholine (DLPC) with mol size 107.5nm and electrostatically -6mV. This results in a 1.7% increase in absorption of insulin ingestibles. The electroneutral nanocarriers mimic the properties of viral capsids and act as highly negative in epithelial cells which quickly absorbs the nanocarriers into the the cells.[1]

Protein Protection nanocarriers:

The protein helps prevent the degradation of insulin by proteinase which improves the stability of drugs. The Albumin (ALB) modification resulted in large NPs with a size of 300.8 nm and a zeta potential of +28.9 mV. The Alb modification is reported to be attracted by the negatively charged glycocalyx of epithelial cells, increasing the absorption of the insulin. However, the *in-vivo* studies are not performed hence the efficacy of this formulation is uncertain.[1]

Casein and dextran complexes (CN-DEX) have also been utilized to enhance the stability of NPs. They are shown to increase the resistance of drugs against proteinase such as pepsin and trypsin and are stable at the pH level 2. This complex has shown to have bioavailability of 12.5% to 20.2% in T1DM.[1]

Targeted Modification:

Oligopeptides modification:

Oligopeptides, consisting of 2 to 20 amino acids, enhance the stability and absorption of nanoparticles (NPs) by protecting against enzymatic degradation and facilitating drug uptake. A study by Bai et al. demonstrated that oligopeptide-modified PLGA scaffolds resulted in smaller NPs (152.83 nm) with a cellular uptake 7.8 times higher than PEG NPs, although the encapsulation efficiency (EE) was low at 23.86%, leading to potential drug wastage. Long-term safety studies showed no toxicity in mice, and other modifications, such as L-valine, improved insulin uptake and pharmacological availability, although overall insulin bioavailability typically remains below 10%.[1]

Vitamin-Modified Nanoparticles:

Vitamins in Nanoparticle Modification: B vitamins, especially folic acid (FA), biotin, and vitamin B12 (VB12), are used to modify nanoparticles (NPs) to enhance drug absorption by targeting specific receptors in the small intestine.

Folic Acid (FA) NPs: Surface-modified chitosan (CS) NPs using FA showed a size of approximately 288 nm and reduced blood glucose levels by about 50% in diabetic rats, with an oral insulin bioavailability of 17%.

Biotin and VB12 NPs: Biotin-modified carriers improved insulin bioavailability to 4.6% and 8.23%, while VB12-modified NPs, sized around 52 nm, achieved a 54% reduction in blood glucose levels, outperforming unmodified NPs. FA modification is highlighted as particularly effective for enhancing oral insulin bioavailability.

Thiolated Nanoparticles:

Thiol-modified nanoparticles (NPs) enhance insulin absorption by forming disulfide bonds with mucin, leading to prolonged retention in the intestine. Formulations showed improved bioavailability (11.3%) and greater hypoglycemic effects compared to free insulin, but exhibited burst release under gastric conditions, necessitating enteric capsules for stability.

Cholic Acid-Modified Nanoparticles:

Cholic acid-modified NPs improve drug absorption via endocytosis mediated by the apical sodium-dependent bile acid transporter (ASBT), achieving high oral bioavailability (26.7% in diabetic mice). Other formulations, including deoxycholic acid-modified liposomes, also demonstrated enhanced bioavailability, suggesting ASBT targeting as a promising strategy for oral insulin delivery.

Specific Cell-Targeted Nanoparticles:

Targeting specific intestinal epithelial cells, such as M cells and goblet cells, has shown to increase insulin bioavailability. For instance, wheat germ agglutinin (WGA) modified NPs improved bioavailability from 4.99% to 7.11%, while CSK peptide-modified NPs enhanced absorption,

indicating that targeted delivery can improve oral insulin uptake despite the limited number of target cells compared to enterocytes.[1]

CONCLUSION

The working of ingestible insulin is yet uncertain compared to injection insulin. However, the new ingestible insulin is showing prominent growth due to the new approaches provided by research and shows positive growth in ingestible insulin formulation.

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