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Review Paper

A Review on Oral Drug Delivery of Insulin

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ABSTRACT

The use of orally administered insulin delivery system represents an interesting alternative to the currently used subcutaneous delivery of insulin in the treatment of diabetes mellitus. Oral insulin provides better patient compliance, convenience, and a more physiological route of insulin absorption via the portal vein. Nevertheless, oral insulin delivery faces numerous difficulties, which are mainly related to the gastrointestinal tract (enzymatic degradation, acidic environment of stomach, low permeability of intestine walls, and low bioavailability). Different drug delivery systems like liposomes, hydrogels, nanoparticles, encapsulation, and mucoadhesive carriers have been designed to address the mentioned difficulties. The developments of nanotechnology, bioadhesive systems, and absorption enhancers allow achieving increased stability and increased intestinal uptake of insulin. A number of oral insulin formulations have been already developed and tested clinically and have shown satisfactory results. Although significant efforts have been made, the problem of stability, manufacturing and bioavailability still exist

INTRODUCTION

The Diabetes Mellitus (DM) is a metabolic condition that involves high levels of glucose concentration in blood due to inadequate secretion of the hormone insulin. The Type 1 Diabetes Mellitus (T1DM) is caused mainly due to autoimmune reactions that attack and destroy β-cells in the pancreas. On the other hand, the Type 2 Diabetes Mellitus (T2DM) is the most prevalent kind, being caused by insulin resistance and failure of insulin secretion. The complications of uncontrolled diabetes may include heart disease, nerve and kidney complications, blindness, amputation of limbs, disabilities, low quality of life. Since the discovery of insulin in 1922, the insulin replacement therapy has been indispensable especially for patients of T1DM and advanced T2DM.

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Nevertheless, insulin therapy relies on the use of subcutaneous injections or insulin pumps. The repeated administration of these drugs is accompanied by pain and discomfort and can lead to skin irritation, infections and non-compliance. Traditional insulin treatment may be connected with hypoglycemia, hyperinsulinemia, and weight gain as well. That is why a more convenient and physiological way of insulin delivery is needed. Oral insulin delivery has received much attention since it allows to copy a physiological insulin delivery route from the gastrointestinal tract into portal circulation [16,20,27,30].

Nevertheless, the process of making oral insulin is complex due to the fact that it is a protein with the molecular mass of 5.7 kDa and high degradation potential. The oral cavity has a number of obstacles to be dealt with such as the presence of acids in the stomach, proteases, mucus barrier, and intestinal epithelium leading to the extremely poor absorption and bioavailability of insulin in the oral form. In order to overcome all these barriers, a number of advanced technologies have been considered including permeation enhancers, protease inhibitors, enteric coating, mucoadhesion, smart polymers, nanoparticles and many others. Recent advances in nanotechnology, polymer technology, and bioresponsive materials have opened new avenues for the protection of insulin from degradation, increased permeability of the intestines, and improved efficiency. However, this problem still remains open and challenging [1,9,12,15,17,21,25].

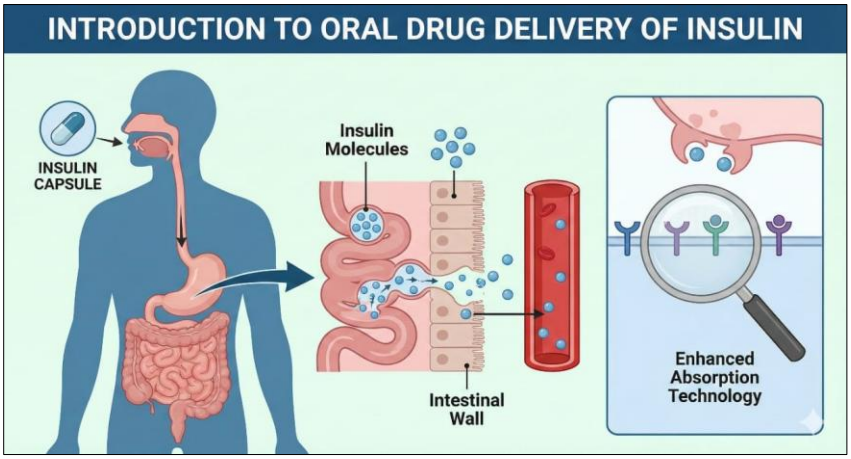

Fig. 1 Introduction to Oral Drug Delivery of Insulin

1. IMPORTANCE OF ORAL INSULIN

Insulin by mouth appears to be an attractive and patient-friendly treatment modality for diabetes mellitus patients. The most important role played by this drug is the similarity to the physiological process of insulin production in the body. Insulin that is administered orally and absorbed from the gastrointestinal tract travels through the portal vein directly to the liver, just like in the case of naturally produced insulin. This makes it possible to manage hepatic glucose production efficiently. As opposed to subcutaneous injection where the insulin goes directly into the systemic circulation, oral insulin restores the physiological portal to peripheral insulin ratio, minimizing the possibility of developing peripheral hyperinsulinemia complications. Also, the oral administration of insulin gets rid of discomfort, pain, and stress caused by needle pricks. Besides increasing the patient's adherence to the therapy, it minimizes weight gain, hypoglycemic events, and other

injection-related problems. Due to its convenience, increased patient acceptability, and the possibility of mimicking physiological insulin production, insulin by mouth can be classified as an attractive and innovative approach to treating diabetes mellitus [10,12,13].

2. GASTROINTESTINAL TRACT AS THE CENTRAL BARRIER

The GIT is a two-way system; it is highly efficient at absorbing essential nutrients while at the same time offering a powerful means of protection against any harmful materials including foreign proteins and peptides . This dual nature makes it extremely hard to deliver therapeutic drugs orally, particularly insulin. For orally delivered insulin to enter the bloodstream, there are several hurdles that it must cross such as crossing the mucus layer, dealing with the corrosive environment of the GIT, avoiding enzymatic degradation, and finally crossing the intestinal epithelium [21,22,23,24,29].

Table 1: Comprehensive Table: Barriers to Oral Insulin Delivery

Subtype	Barrier/Location	Nature of Barrier	Biochemical/Physical Features	Impact on Insulin
Physical	Mucous Layer	Viscous protective layer	Mucin, negative charge, continuous turnover	Traps insulin and limits diffusion.
Physical	Intestinal Epithelium	Selective permeability barrier	Tight junctions and lipid-rich membranes	Restricts insulin transport due to its size and hydrophilicity.
Biochemical	Luminal Enzymes – Stomach	Proteolytic degradation	Pepsin and acidic environment	Denatures and degrades insulin.
Biochemical	Luminal Enzymes – Intestine	Proteolytic degradation	Trypsin, chymotrypsin and other proteases	Rapidly breaks down insulin.
Biochemical	Brush Border Enzymes	Enzymatic degradation	Peptidases and aminopeptidases	Degrades insulin before absorption.
Biochemical	Hepatic First-Pass Metabolism	Presystemic metabolism	Liver enzymes	Reduces active insulin reaching circulation.
Chemical	Gastric Acid	Acidic instability	pH 1.2–3.0	Causes protein denaturation and loss of activity.
Chemical	Intestinal pH	pH-related instability	pH 6.5–8.0	May affect insulin stability and bioactivity.
Formulation	Insulin Structural Stability	Physical/chemical instability	Aggregation, denaturation and oxidation	Reduces insulin activity and bioavailability.

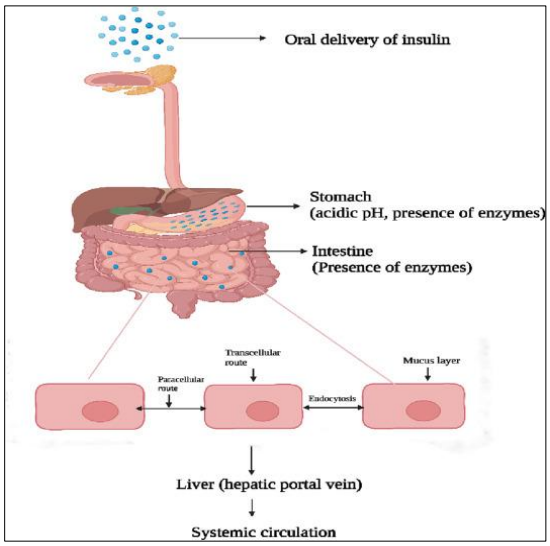

Fig.2 Barriers to Oral Insulin Delivery

3. CHALLENGES OF ORAL INSULIN DELIVERY

Table 2. Major Challenges Associated with Oral Insulin Delivery

S. No.	Challenges	Key Points
1	Absorption through GIT	Insulin is poorly absorbed from the gastrointestinal tract because it is a large, hydrophilic peptide that cannot easily cross the intestinal epithelial barrier.
2	Presystemic Degradation	Gastric acidity and digestive enzymes such as pepsin, trypsin, and chymotrypsin degrade insulin before it can reach systemic circulation, resulting in very low bioavailability.
3	Poor Intestinal Transport	Insulin has difficulty crossing the lipid-rich intestinal membrane. Its large molecular size and hydrophilic nature make passive diffusion across the intestinal wall extremely limited.
4	Dosage Form Stability	Insulin may lose its biological activity during formulation and storage due to unfolding, aggregation, oxidation, and other structural changes[15,16,17,21].

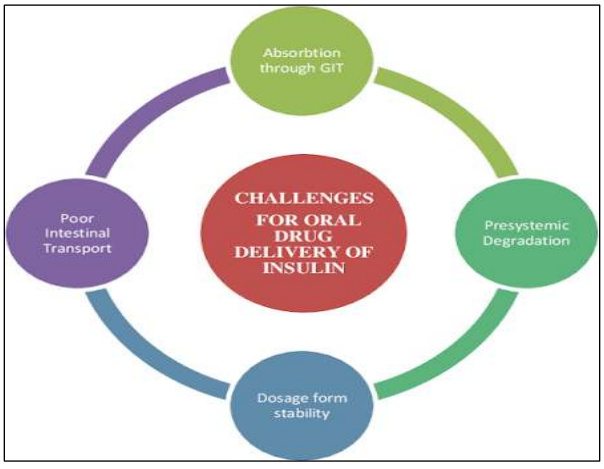

Fig 3. Challenges for Oral Insulin Delivery System

4. NOVEL APPROACHES FOR ORAL INSULIN DELIVERY

The use of oral delivery system in insulin has become a highly popular field of research as a way of delivering insulin that has been used traditionally through subcutaneous injection. The problems facing the delivery of insulin through the oral route include the fact that the insulin gets degraded in the digestive system, poor permeation, and poor bioavailability. In order to address this problem, novel drug delivery systems have been developed that would enable the protection of insulin from enzymatic breakdown, increase intestinal permeation, and sustain the release of insulin [14,15,18,19].

Table 3. Novel Approaches of Oral Insulin Delivery

S. No.	Approach	Mechanism/Working	Advantages	Major Limitations
1	Liposomes	Entrap insulin within phospholipid bilayers to protect it from GI enzymes and enhance intestinal transport.	Biocompatible; protects insulin; bile salts can improve absorption.	Low gastric stability and limited controlled release.
2	Hydrogels	pH-sensitive polymers protect insulin in the stomach and release it upon reaching intestinal pH.	Enzymatic protection; controlled release; mucoadhesion may improve absorption.	Burst release and variable swelling may affect dosing.
3	Nanospheres	Encapsulate insulin in polymeric nanoparticles to protect it from degradation and improve intestinal uptake.	Enhanced protection and potential improvement in systemic absorption.	Complex formulation and difficulty in controlling release.
4	Encapsulation	Encloses insulin in carriers such as alginate, PLGA nanoparticles, liposomes, or metal-organic frameworks.	Improves stability, protection, controlled release, and absorption.	Costly and technically complex; carrier stability may vary[14,15,18].

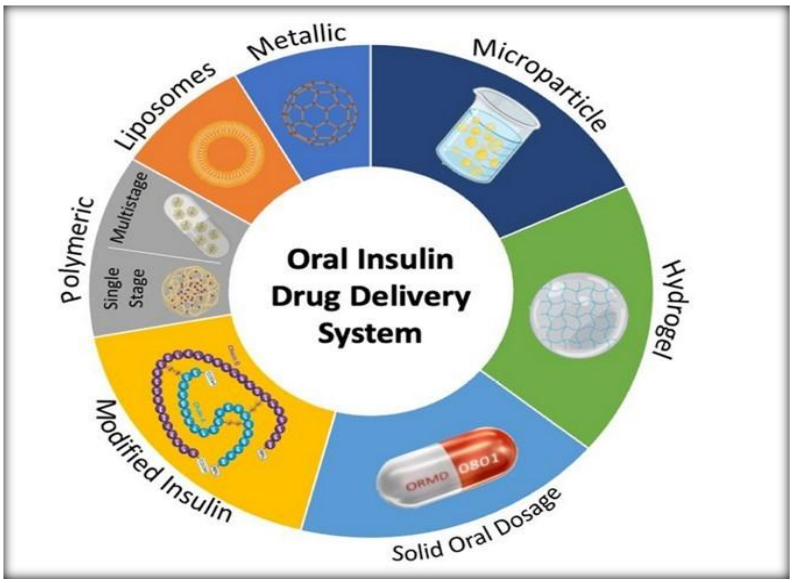

Fig. 4 Oral Insulin Drug Delivery System

6. NON-INVASIVE APPROCHES FOR INSULIN DELIVERY

Insulin injection into the subcutaneous region has been the traditional method for insulin administration for over five decades now. Despite being efficient, it is normally quite painful for the patient undergoing it since they require it lifelong. This is why researchers around the globe have been working hard in order to discover new means of delivering insulin which are relatively safe and comfortable. Some of these methods include thiolated chitosan-based tablets, microemulsion systems, oral insulin tablets, oral sprays, and inhalational insulin [2,10,12].

Fig. 5 Insulin Pills

Table 4. Non-Invasive Approaches for Insulin Delivery

S. No.	Approach	Mechanism/Working	Major Advantages	Key Limitations
1	Thiolated Chitosan Tablets	Thiolated chitosan enhances mucoadhesion, while protease inhibitors protect insulin from enzymatic degradation.	Prolonged GI residence; controlled release; improved insulin stability.	Complex formulation and limited clinical evidence.
2	Oral Insulin Pills	Insulin is protected using stabilizers, protease inhibitors, absorption enhancers, coatings, or nanoparticles.	Convenient, painless, and patient-friendly.	Low bioavailability due to degradation and poor intestinal absorption.
3	Oral Insulin Sprays	Insulin is absorbed through oral mucosal tissues, partially bypassing GI degradation and first-pass metabolism.	Non-invasive; rapid onset; convenient administration.	Variable absorption and stability challenges.
4	Pulmonary (Inhaled) Insulin	Inhaled insulin reaches the alveoli and rapidly enters systemic circulation, bypassing the GI tract.	Needle-free; rapid onset; large absorptive surface area.	Dose variability and respiratory considerations; requires specialized devices [2,3,4,7,8,10,12].

7. OVERVIEW OF CLINICAL STUDIES FOR ORAL INSULIN

Several oral insulin candidates have progressed through clinical trials using approaches such as liposomal nanoparticles, absorption-enhancing solid oral formulations, and modified insulin delivery systems. These studies mainly evaluated postprandial glucose control, HbA1c reduction, pharmacokinetics, and safety, particularly the risk of hypoglycemia in patients with diabetes [3,4,5,6].

- **Liposomal Nanoparticle-Based Insulin – HDV-I**

The HDV-I product developed by Diasome Pharmaceuticals is an orally administered insulin via liposomal nanoparticles. Studies for the drug have been done using doses between 0.05-0.4 U/kg of oral doses in randomised and placebo-controlled experiments. There was significant reduction in glucose exposure after breakfast and the lowest dose also worked effectively without any noted side effects. Further study on HbA1c and fasting glucose is needed [5] .

- **Absorption-Enhancer-Based Oral Insulin – NN1952**

NN1952 is an oral insulin that has been formulated by Novo Nordisk, which uses an absorption enhancer for increasing insulin stability and gastrointestinal absorption. According to the results of a randomized Phase I study, at the maximum dose, the drug demonstrated the same hypoglycemic activity compared to insulin aspart administered parenterally in a fasting state. Postprandial response was inconsistent [6].

- **Solid Oral Insulin Formulation – I-338**

I-338 is an oral form of solid insulin being developed by Novo Nordisk, which has undergone trials in phases I and II. Through randomized double-blind trials, the effect of I-338 on glucose lowering was compared with insulin glargine. I-338 had a comparable effect to glargine with regard to reduction of HbA1c and fasting glucose, with no significant difference in overall glycemic control [6].

8. RECENT ADVANCES IN ORAL ADMINISTRATION OF INSULIN

The progress in oral insulin has been one of the most quickly evolving fields of diabetes research. Since insulin is a peptide drug, it is confronted by two key challenges when administered orally: rapid degradation from stomach acid and enzymes, as well as extremely poor absorption by the intestinal lining. Over the past decade, scientists have been working on innovative delivery platforms that can protect insulin during digestion, enhance its absorption, and ensure it works effectively without harmful side effects. Recent progress has been remarkable, particularly through the use of bioadhesive systems, nanotechnology, permeation enhancers, and biomimetic carriers [10,12,18,28].

Table 5. Recent Advances in Oral Insulin Delivery Systems

Recent Advances / Approaches	Technology / Examples	Key Features & Findings
Gut-targeted bioadhesive & patch-based systems	Bioadhesive grooves and cone-shaped patches	Adhere to the intestinal wall and provide controlled insulin release. Micro-grooved devices enable directional release, while cone-shaped patches use enteric coatings and absorption enhancers to improve intestinal uptake.
Nanoparticles & microspheres	Polyglutamic acid microspheres and ionic nanocomposites	Protect insulin from degradation and enhance absorption. Chitosan-based microspheres produced significant glucose reduction in diabetic rats, while peptide-targeted ionic nanocomposites achieved up to 7% absorption in rats.
Microemulsions & hydrophobic ion-pairing (HIP)	HIP–microemulsion systems	Insulin is combined with an amphiphilic counterion to form a lipid-soluble complex, which is incorporated into microemulsions to protect insulin and improve membrane penetration[11,15,18,26].

9. MARKET STATUS OF ORAL INSULIN PRODUCT

Table 6. Market Status of Oral Insulin Products

Oral Insulin Product	Developers	Clinical / Market Status	Key Features
IN-105 (Insulin Tregopil)	Biocon, India	Phase III completed; primary HbA1c endpoint not achieved, although postprandial glucose reduction was observed.	PEG-modified oral insulin analog; rapidly absorbed; intended for mealtime use; generally weight-neutral.
Oral-Lyn	Generex Biotechnology, Canada	Available in India since 2007; investigated in Phase III trials in several countries.	Buccal insulin spray that bypasses the gastrointestinal tract; rapid absorption and potential to improve patient convenience and adherence[3,6,8].

Overall, oral insulin products remain at different stages of clinical development and market introduction. While products such as Oral-Lyn have achieved limited market availability, candidates such as IN-105 continue to face challenges in demonstrating consistent clinical efficacy [3,8].

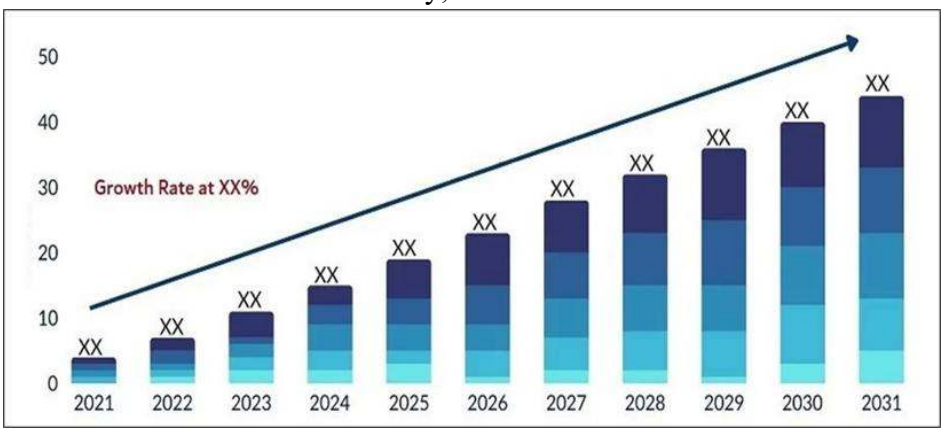

Fig 6. Growth Rate of Oral Insulin Product

FUTURE SCOPE

Oral insulin in the future must take into account the following aspects: increased clinical efficiency, enhanced safety, improved bioavailability, scalability, and cost-effectiveness. Novel encapsulation techniques, nanoparticles, liposomes, and chitosan nanocarrier can be useful for improving gastrointestinal stability and absorption of insulin from the gut; however, the problem of increased manufacturing costs and industrialization is still present. Targeted delivery systems using safe permeation enhancers, bile salts, and surfactants as well as controlled release systems will increase efficiency of the drug absorption. Last but not least, it is essential to conduct more precise preclinical studies, using the animal models that reflect the reality of human physiology better than rats, for example. Novel formulations should provide rapid, consistent and dosable absorption, especially in case of mealtime insulin, taking into account the large dose and

manufacturing complexity, thus impacting on cost-effectiveness of the drug.

CONCLUSION

In summary, despite the effectiveness of SC administered insulin, diabetes mellitus continues to be one of the world's leading diseases. However, due to its invasiveness, repetitive nature, pain, and possible side effects associated with injection sites, there might be a lack of patient compliance with such treatment. That is why oral insulin has become an appealing alternative to injectable insulin. Nanoparticles, microspheres, hydrogels, liposomes, mucoadhesive delivery systems, and ionic liquids have proven themselves capable of providing protection to insulin from destruction by the digestive tract and ensuring its absorption. Nevertheless, the clinical effect was not better with injectable insulin due to low bioavailability of insulin in such systems, large doses, variable absorption, and expenses associated with production. I-338 had insufficient bioavailability and required higher doses compared to injected insulin. ORMD-0801 was unable to demonstrate any superiority over placebo during Phase 3 trials. Moreover, the safety of permeability enhancers, which temporarily alter the permeability of the intestinal mucosa, is still questionable. Thus, future research should aim at developing oral insulin systems, which have sufficient and reproducible bioavailability, predictable pharmacodynamics, long-term safety scalability, and reasonable price, which would make it an appealing alternative to injectable therapy.

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