REVIEW ARTICLE

Oral Insulin: Challenges and Potential Solutions with a Case Study of Pharmaceutical Company Ventures

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ABSTRACT

Oral insulin, in pill form, presents a non-injectable alternative. It is a transformative approach to diabetes management, potentially enhancing patient compliance. This paper examines challenges and potential solutions in oral insulin development, which are further bolstered by a case study on pharmaceutical ventures, namely, oramed, diasome, diabetology, biocon and emisphere.

Keywords: Oral insulin, Pharmaceutical, Diabetes, Medicine, Clinical Trials.

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INTRODUCTION

Diabetes, marked by chronic high blood sugar levels, affects 10.5% of the global adult population, projected to surpass 12% by 2045. China leads with 141 million cases, while French Polynesia, Mauritius, and Kuwait exhibit high prevalence rates. Obesity and lifestyle changes contribute to rising diabetes rates.[1]

Insulin is vital for managing diabetes, with injections being the primary delivery method. The insulin market, valued at USD 19.94 billion in 2022, is forecasted to reach USD 22.20 billion by 2031, emphasizing indirectly the reliance on injections and hence, the need for innovative and patient friendly delivery systems. Continuous subcutaneous insulin infusion (CSII) and insulin pens offer alternatives, but cost and needle deterrents persist.[2-5]

Oral insulin, as pills or capsules, represents a needlefree breakthrough, potentially enhancing compliance and quality of life. Its development, however, faces intricate challenges discussed in this paper, along with potential solutions. The paper concludes with a case study on pharmaceutical ventures, including Oramed, Diasome, Diabetology, Biocon, and Emisphere, which have either failed or are working on developing oral insulin.[6-8]

Challenges

Oral insulin development faces the below listed challenges.

Gastric Acid as a Barrier

Gastric acid, composed of hydrochloric acid, secreted by the parietal cells within the gastric glands of the stomach establish an extremely acidic environment with a pH ranging from 1 to 2. This results in insulin denaturation.

Proteases as a Barrier

Insulin is subjected to protein degradation in the stomach and small intestine by proteolytic enzymes such as pepsin, trypsin, chymotrypsin, pancreas derived carboxypeptidases.

Physical Barrier

The intestinal mucosal lining, a barrier between luminal contents and the epithelium, is actively maintained by goblet cells, renewing the mucus layer every 4-5 hours. This gel-like network of glycosylated mucin molecules selectively permits small molecules but hinders large particles and pathogens, presenting a challenge for oral insulin delivery platforms.

Beneath the mucus layer, oral insulin faces the challenge of traversing the intestinal epithelium through either a transcellular or paracellular pathway before being released into the bloodstream. The paracellular pathway, regulated by tight junctions (TJs) between adjacent epithelial cells, serves as the preferred route for the translocation of hydrophilic molecules. However, the paracellular pathway imposes exclusivity, with a sealing space of about 8-13 Å created by junctional complexes, allowing only hydrophilic molecules with a molecular weight below 200 Da for transport, while nanoparticles and protein drugs are typically excluded. Hence, oral insulin is absorbed through the transcellular pathway, involving intermembrane transport, adsorption, fusion, and endocytosis. Achieving efficient transcellular transport remains as significant challenge[9]

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Manufacturing Stability of Insulin

The formulating methods pose a number of factors like temperature, pH, solvent, solutes, and crystallinity which impact the stability of insulin. They must be optimized keeping in mind the stability to ensure a successful oral insulin formulation.[10,11]

Potential Solutions

Enteric coatings

pH-sensitive enteric coatings, such as Eudragit polymers, protect oral insulin from stomach acidity, enabling release in the intestine for enhanced bioavailability and studies have shown glucose reductions in rats when administered with enterically coated insulin.

Protease inhibitors

Protease inhibitors like sodium glycocholate, camostat mesilate, bacitracin, soybean trypsin inhibitor and aprotinin were effective in enhancing insulin availability in the large intestine.

Permeation enhancers

Bile salts and fatty acids enhance lipid bilayer permeability and have been studied for hypoglycemic effects in rabbits.

Vibrio cholera's Zonula occludens toxin (ZOT) selectively increases tight junction permeability, promising controlled enhancement for safe insulin absorption in the jejunum and ileum, demonstrating up to 8–16% bioavailability compared to parenteral insulin.[12]

Combination strategies

Combining Eudragit-coated insulin with sodium salicylate achieved notable 13–14% bioavailability compared to intraperitoneal delivery. The formulation, released at controlled pH levels, demonstrated significant blood glucose reductions in surgically delivered capsules to diabetic rats. While sodium salicylate shows promise as an enhancer, further investigations without surgical intervention are needed. Another effective approach involves combining the permeation enhancer sodium cholate with the proteinase inhibitor aprotinin. Co-administration of these agents with insulin resulted in a substantial 70% reduction in fasting blood glucose, showcasing a synergistic effect. This strategy holds promise in overcoming both enzymatic and physical barriers to oral insulin absorption, suggesting a fruitful path for future research.

Microsphere encapsulations

Polymer microspheres safeguard insulin against enzymatic degradation, help cross the intestinal mucosa and alter protein distribution.

Isobutyl 2-cyanoacrylate microspheres show promise in reducing blood glucose but faces inconsistent response.

A biodegradable alternative, using poly(fumaric anhydride) and poly(lactide-co-glycolide) microspheres with phase-inversion nanoencapsulation, presents potential for maintaining normoglycemia, addressing physical barriers in oral insulin delivery.[13,14]

Case Study

Oramed, an Israeli company, developed ORMD-0801, a formulation comprising 8 mg of insulin powder with various excipients to enhance GI absorbance properties. This formulation underwent Phase I trials for safety and dosage, followed by Phase II for safety and efficacy. The Phase III placebo test however, did not meet the criteria, prompting reassessment of ORMD-0801's development strategy. Phase III studies with type 2 diabetes failed to show a reduction in the baseline A1C levels when compared to a placebo patient after 26 weeks of the treatment.[15]

Diasome, a US based company developed HDV TM. HDV (Hepatic-directed Vesicles) are liposomes that are loaded with insulin HDV-I.

HDV TM passed Phase I clinical trials. The study conducted was a single-blind, placebo-controlled, dose-ranging trial of oral HDV-I. This was administered to the patients before meals in a 3-test meal per day model. The patients were assigned sequentially in order of the treatment as follows - On day 1 they were given oral placebo capsules, on day 2 they were given the HDV-I capsule containing 0.05U/kg of dosage, and on each day the dosage was doubled until day 5. The results showed that all the 4 dosages of oral HDV-I showed a reduction in the mean incremental glucose area under the curve. The company is yet to complete Phase II b trials, which are double-blind randomized controlled trials conducted over a period of six months.[15]

Diabetology, a UK-based pharmaceutical company, has developed CapsulinTM, an insulin delivery system involving enteric-coated capsules containing stabilizers and solubilizers. This method ensures safe passage through the stomach, enhancing absorption in the intestine. The carefully encapsulated insulin maintains stability, protecting it from gastrointestinal degradation. Phase I trials confirmed safety, and ongoing Phase II b trials are evaluating efficacy and safety in a larger patient group through randomized controlled trials. Capsulin TM shows promise as a convenient and effective advancement in insulin delivery for individuals with diabetes. Capsulin can be administred twice a day in dosages of 150 iu per capsule. It results in a significant decrease from baseline HbA1c, FPG and triglycerides in the body.[15]

Biocon, an Indian based company, developed Tregopil. For the formulation, recombinant insulin was combined with sodium caprate, serving as an excipient to enhance certain characteristics of the insulin formulation. Tregopil has successfully undergone Phase I trials and is set to undergo Phase II trials. The formulation showed a post-prandial glucose control that is more effective than the placebo throughout the meal period.[15]

Emisphere, an American based company, developed an oral capsule by combining human insulin with the carrier molecule monosodium N-(4-chloro salicyloyl)4-aminobutyrate. Phase 1a and Phase 2a experiments were conducted from 2001-2004. In 2010, Emisphere signed a development agreement with Novo

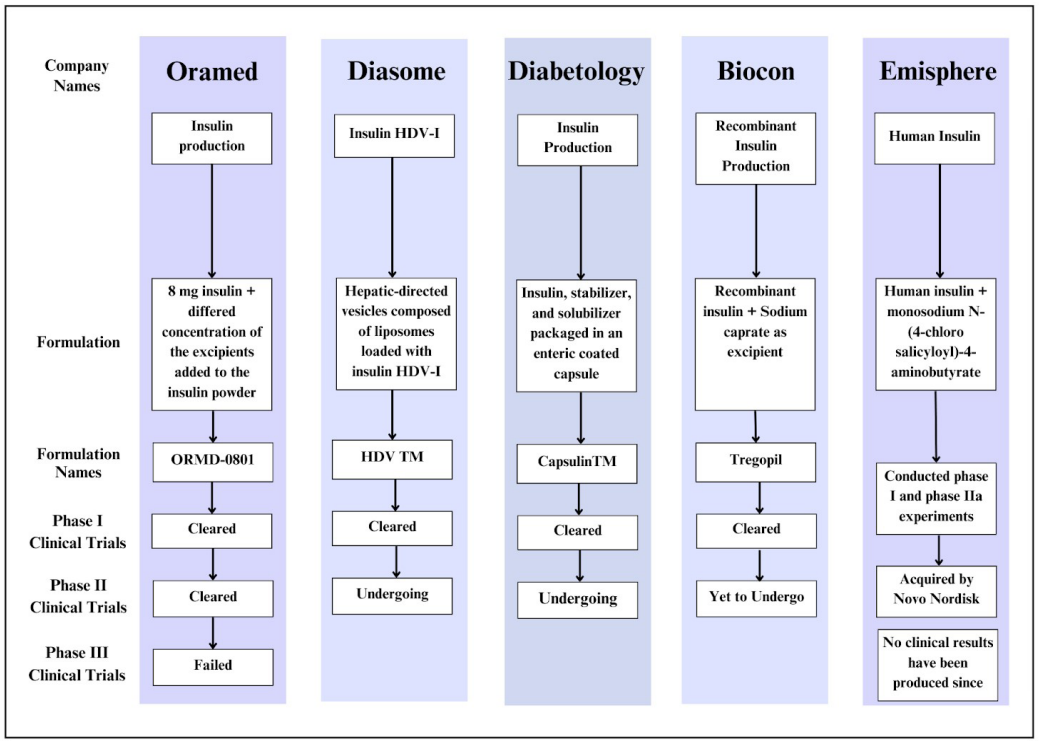

Figure 1: Flowcharts representing progress of oral insulin production by the companies

Table 1: Comparison of oral insulin production ventures

Comparison of Oral Insulin Companies that were presented in this review					
Oral insulin companies	*Dose (U)*	*Total daily dose*	*Functional bio-availability*	*Mechanism*	*Hepatic targeting*
Biocon	300-500	1200-2000	Low	Active Transport	No
Diabetology	150/300	600-1200	Low	Active Transport	No
Diasome	5	20	High	Tight Junction	Yes
Emisphere	300	1200	Low	Active transport	No
Oramed	236	944	Low	Active transport	Possible

Nordisk, and since then, no clinical results have been published. Novo Nordisk acquired Emisphere in 2020.[15]

Interpretations from Case Study

The major problem with oral insulin as identified from the case study is its low bioavailability which necessitates higher doses of insulin being administered (Table 1 and Figure 1). That poses a fundamental problem of being able to meet the production demand of insulin that would be created with the success of all phase trials of oral insulin in the future. The side effects of high doses of insulin being administered over a longer period also must be considered. Growth promoting factors like insulin might be linked to cancer or tumor activation which requires careful assessment of the same before launch. The excipients used in the formulation might also pose potential side effects to the human body over a longer exposure. Detailed long term pharmacodynamic studies of administering higher doses of insulin via oral insulin are yet to be addressed.

CONCLUSION

In conclusion, the pursuit of oral insulin delivery represents a promising avenue for transforming diabetes management, potentially enhancing patient compliance and overall treatment efficacy. Despite the considerable challenges discussed in the review paper, such as issues related to bioavailability and gastrointestinal conditions, the identified solutions offer hope for overcoming these obstacles. The case study on pharmaceutical ventures underscores the diversity of approaches and experiences in oral insulin development, emphasizing the need for ongoing innovation and collaboration. While some ventures faced setbacks, the collective insights gained contribute to the evolving landscape of oral insulin research. Moving forward, a commitment to continued research, technological advancements, and interdisciplinary collaboration will be essential to realize the full potential of oral insulin and address the complexities inherent in its

development, ultimately improving the lives of individuals with diabetes.

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