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# A REVIEW ON: DEVELOPMENT OF A NOVEL APPROACHES FOR THE FORMULATION OF INSULIN DELIVERY

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## ABSTRACT

Diabetes mellitus (DM), one of the most prevalent and fatal diseases, is responsible for over 4 million deaths worldwide. Parenteral delivery is still the most common way to administer insulin, but it can't replicate the natural hypoglycemic action of insulin and causes fatty deposits and localized hypertrophy at injection sites. As a result, there is interest in and effort being made toward alternative administration routes, such as oral, nasal, and pulmonary. Insulin must maintain its form while it travels through the gastrointestinal tract (GIT), however oral insulin administration reduces patient pain and facilitates medicine administration. The GIT's underlying intestinal epithelial membrane barrier, the presence of a mucus layer, and enzyme degradation are the three primary barriers to efficient oral insulin delivery. The A- chain, which has 21 amino acids, and the B-chain, which has 30 amino acids, make up its two chains, which add up to 51 amino acids. Two covalent disulfide bonds, CysA7 to CysB7 and CysA20 to CysB19, bind these two chains together.

## INTRODUCTION

Over 4 million fatalities globally are attributed to diabetes mellitus (DM), one of the most common and deadly diseases. The most popular method of administering insulin is still parenteral delivery, which results in fatty deposits and localized hypertrophy at injection sites and cannot replicate the normal hypoglycemic action of insulin This has led to interest in and effort towards other administration routes, such as oral, nasal, and pulmonary. Specifically, oral insulin therapy is intended to prevent autoimmune death of pancreatic cells by imitating the physiology of endogenous insulin produced in the liver

following gastrointestinal (GI) absorption.

Moreover, oral insulin administration lessens pain for patients and makes medication administration more convenient; yet, insulin needs to keep its shape as it passes through the gastrointestinal tract (GIT). Enzyme breakdown, the existence of a mucus layer, and the underlying intestinal epithelial membrane barrier in the GIT are the three main obstacles to effective oral insulin administration. The pancreatic β cells are the main source of insulin, a dipeptide hormone that controls blood glucose levels. It is composed of two chains, the A-chain (consisting of 21 amino acids) and the B-chain (30 amino acids), totaling 51 amino acids.

These two chains are joined by two covalent disulfide linkages, CysA7 to CysB7 and CysA20 to CysB19. Moreover, CysA6 and CysA11 in the A-chain have an intra-chain disulfide bond. The development of innovative oral insulin formulations that can get past these obstacles and increase oral insulin bioavailability has been the main focus of efforts. Certain strategies entail co-administration with established enhancers of absorption, such as fatty acids and protease inhibitors (PI); alternative strategies make use of carrier systems or smart polymers that can shield insulin from proteolytic processing and facilitate its absorption via the GIT epithelium. One intriguing way to get over the aforementioned obstacles has also been proposed: the use of submicron colloidal carriers.

It has also been investigated to alter the structure of insulin in order to make it more resistant to GI acids and enzymes and/or to increase its permeability through the intestinal wall by changing it into enteric-coated carriers or other unique forms. Since its discovery by Frederick Banting and Charles Best in 1921 that insulin can lower blood glucose levels, the drug has been widely used due to its remarkable life-extending properties.

It is an endogenous protein hormone that is generated by the pancreatic endocrine β-cells. The 51 amino acids that make up human insulin are arranged into two distinct chains, the A chain and the B chain, which are joined by sulfide bonds. There are 21 amino acids in the insulin A chain and 30 in the insulin B chain.

**Objective**

Achieving plasma insulin levels that most nearly resemble the natural production of insulin in people without diabetes mellitus is the objective of insulin therapy for patients with

insulin- dependent diabetes.

This entails accounting for both the release of insulin produced in response to meals, which normally results in peak serum insulin levels of 60–80 U/ml 17, 33, and the release of basal or baseline insulin, which is normally in the range of 5–15 U/ml. Since the hormone's initial discovery, the primary insulin.

**Classification of diabetes**

An indication of diabetes, a chronic endocrine illness, is an increase in blood glucose levels brought on by an insulin shortage in the body. The two primary hormones that control the body's glucose homeostasis are insulin and glucagon. Blood glucose levels were lowered as a result of pancreatic β-cells secreting insulin in response to rising blood glucose levels. Pancreatic α-cell glucagon release and the rise in blood glucose levels are influenced by low glucose levels.

Another important factor determining the frequency and susceptibility to diabetes is ethnicity. Numerous research works have emphasized how ethnicity affects diabetes risk, with some ethnic groups exhibiting a greater inclination than others. Compared to people of European heritage, those of South Asian, African, Hispanic, and Native American descent have an increased chance of developing diabetes. The risk of developing diabetes is influenced by ethnic disparities, which can be attributed to a variety of factors including lifestyle choices, socio-cultural influences, genetic variants, and challenges in accessing appropriate healthcare systems.

**Type I diabetes, type II diabetes, latent autoimmune diabetes in adults (Lada) and Gestational diabetes are the four forms of the disease**

**Type I Diabetes**

Approximately 5–10% of all people with diabetes have type-I diabetes. The destruction of β- cells by the immune systems, both innate and adaptive, is part of the pathogenesis of this disease. This type of diabetes is called "juvenile diabetes" due to its early onset and insulin dependence. The only treatment for it is insulin. Here, the main factor contributing to the development of this illness is hereditary predispositions. Patients with type I diabetes are susceptible to vitiligo, pernicious anemia, Hashimoto's thyroiditis, Addison's disease, myasthenia gravis, Graves' disease, and autoimmune hepatitis.

**Type-II diabetes**

One of the most common types of metabolic disorders worldwide is type-II diabetes mellitus (T2DM), which is primarily brought on by a combination of two factors: the pancreatic β-cells' abnormally high secretion of insulin and the tissues' poor response to insulin. T2DM accounts for about 90% of diabetes mellitus cases globally. The main causes of T2DM epidemics include obesity, sedentary lifestyles, high-calorie meals, and population aging. Additionally, individuals who have a history of hypertension, dyslipidemia, or gestational diabetes mellitus of any kind are more susceptible to this illness.

**Latent autoimmune diabetes in adults (Lada)**

Patients with islet antigen-reactive autoantibodies are known to have this form of diabetes. Approximately 10% of individuals with type II diabetes have at least one of these autoantibodies. Because of the autoimmune nature of the illness, the patient exhibits immunological and genetic similarities to type I diabetes; nevertheless, hereditary susceptibility, T cell reactivity, and autoantibody clustering serve as unique identifying features. Adults develop diabetes fairly early on because of the loss of β-cells and increased resistance to insulin. The one method with some promise to treat this illness is immunomodulator therapy.

**Gestational diabetes mellitus (GDM)**

Pregnant women with previously undetected diabetes who have chronic hyperglycemia during their gestational period may develop gestational diabetes mellitus. This kind of hyperglycemia is typically brought on by pancreatic β-cell malfunction, which weakens insulin resistance and glucose tolerance. The primary causes include obesity and overweight brought on by pregnancy, older gestational ages, and a personal or family history of diabetes in any form. There are several long-term risk factors linked to gestational diabetes mellitus (GDM), including abnormal glucose metabolism, delivery difficulties, and cardiovascular illnesses in both the mother and the child. Dietary adjustments and increased physical exercise are part of the standard treatment for GDM. Metformin, glibenclamide, and insulin are also used to control hyperglycemia.

**Pre development procedures**

Before clinical trials (Human testing) can start, preclinical drug development is a stage of research conducted on suitable animal models. In order to bring the right molecules to

human trials, preclinical investigations are done to assess a new compound's safety. In addition to having treatment regimens (Dosage, dosage form and frequency of administration) that are consistent with the target patient group and disease, compounds must be effective in treating diseases and comparatively devoid of undesirable side effects. Preclinical drug development is a risk-based process that extrapolates safety and efficacy data from nonhuman (Animal model) studies to possible human outcomes.

Actually, when there is little evidence to support the use of the animal model being studied, the preclinical research agenda for many novel treatments is considerably riskier in forecasting clinical outcomes. Clinical investigations (Human studies) are ultimately used to validate the findings of preclinical research (Nonhuman models). Scientists can start and sustain human trials in a reasonable and moral manner if they have a solid grasp of the pharmacological and toxicological preclinical drug response with regard to dose, frequency, and route of administration.

To obtain high-quality data from the preclinical agenda, it is essential to comprehend the parallels and discrepancies between the physiological systems of humans and nonhuman animals. The presumption that preclinical models predict human exposure will be the basis for almost all research and decisions about the development of a medication candidate. The information basis for a drug candidate to go into and thorough clinical evaluation is ultimately completed by an understanding of cell or tissue specific activity/toxicity in conjunction with an understanding of preclinical drug disposition (distribution, metabolism, and excretion).

**Development procedures**

**1. Inhaled insulin**

The pulmonary alveoli are highly vascularized due to their major function in respiration. They provide the outside world access to a vast surface area. It may be anticipated that insulin delivered to the alveolar surface will enter the pulmonary capillaries swiftly and uniformly. Over the last ten years, it has been shown that this strategy is feasible. Initial research revealed that breathed insulin has a hypoglycemic impact. Before inhaled insulin can be regarded as a practical technique, the same practical challenges that were present with nasal insulin—namely, repeatability, dependability, and bioavailability—remain and need to be resolved. Regular inhaler use is infamously inaccurate and relies on the patient's timing of the dose with inspiration. Compared to bronchodilators, insulin

delivery requires a significantly higher level of precision.

Modern inhaler systems, such the AERx (Aradigm), release a precise dosage of medication only when the patient's inspiration airflow exceeds a predetermined rate. These devices have been demonstrated to significantly improve medicine dosage accuracy, and they may one day be used to deliver insulin.

**2. Oral insulin**

The necessity to frequently explain to patients the distinction between insulin and oral hypoglycemic medications demonstrates that oral administration of insulin has always been preferred from the standpoint of the patient. Despite attempts to administer insulin orally in the early 1980s, this method has not yet proven to be practical. The creation of insulin-absorbed microspheres that can pass through the intestinal mucosa has sparked renewed attention. By employing this method, researchers have shown that insulin appears to have an impact on reducing the rise in plasma glucose that occurs after oral glucose consumption in rats. To ascertain whether the carrier's safety, pharmacokinetics, and repeatability are consistent with routine clinical use, more investigation is required.

**3. Nanoparticle based insulin**

Drugs have been modified using nanocarriers with targeting ligands for their selective and targeted administration intended for oral and pulmonary delivery in response to the limitations of traditional injectable insulin. N-acetyl-d-glucosamine and β-(1-4)-linked d-glucosamine combine to form the linear polymer known as chitosan. Since the intestinal epithelium acts as a significant barrier to the absorption of hydrophilic medications, such as insulin, they are unable to diffuse across epithelial cells. As a result, they have trouble getting into the bloodstream. Thus, a great deal of research has been done on the transportation of hydrophilic medicines through paracellular routes. However, the transport of hydrophilic drugs via the paracellular pathway is limited by the existence of tight junctions at the luminal aspect of neighboring epithelial cells.

The tight connections between epithelial cells are momentarily opened by chitosan-insulin nanoparticles that penetrate the mucous layer. Consequently, because of their sensitivity to pH, these nanoparticles have degraded and released encapsulated insulin. The notable adsorption properties of chitosan-insulin nanoparticles by nasal delivery have also been investigated. Ionotropic gelation of chitosan was used to create these

nanoparticles, and an ionic interaction mechanism facilitated insulin loading. Insulin-loaded chitosan/alginate nanoparticles were also subjected to the polyelectrolyte complexation method, which demonstrated their intestinal mucosal internalization [Using Eudragit L100-55 and chitosan of different molecular weights, employed the complicated coacervation process to create nanoparticles with a diameter of 199 nm, achieving 3.38 percent entrapment and 30.56 percent insulin loading efficiency.

With a delayed release at pH 2.0 and a fast release at pH 6.8 and 7.4, these nanoparticles demonstrated pH sensitivity. In order to entrap insulin, Sarmento et al. synthesized dextran sulfate and chitosan nanoparticles in different ratios and demonstrated their effectiveness as an oral insulin delivery nanoparticulate system.

## CONCLUSION

Numerous techniques have been tried in an effort to give insulin orally. It has been demonstrated that insulin is susceptible to intracellular breakdown, luminal degradation in the intestine, and acid-catalyzed degradation in the stomach. Researchers have managed to direct insulin administration to the intestine while shielding it from the stomach's acidic environment. It has been noted that the limited intestinal absorption of insulin results in a very low maximal bioavailability of the hormone. Using absorption enhancers such aprotinin (Protease inhibitor), tween, oligoarginine, sodium glycol-cholate, deoxycholic acid, and taurodeoxycholate, attempts have been made to improve the intestinal absorption of insulin. For the oral administration of insulin, liposomes, microemulsions, nanocubicles, etc., have been created. Insulin was released in intestinal pH and shielded from the body's stomach environment by chitosan-coated microparticles. Insulin delivery limitations have not yet produced positive outcomes, and novel delivery strategies that can boost bioavailability while also producing dose-dependent and repeatable effects must be developed.

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