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Current Progress in Various Drug Delivery Strategies for Diabetes Management using Oral Insulin.

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Abstract:

Oral administration of insulin can significantly improve the quality of life of diabetic patients who routinely receive subcutaneous insulin. Indeed, oral administration of insulin offers several advantages compared to this route of administration: improved patient compliance, rapid hepatic insulinization, and reduced peripheral hyperinsulinemia, hypoglycemia, and body weight. Avoidance of other side effects such as increased likelihood. However, oral administration of insulin remains a challenge because of limited oral absorption of insulin. The major barriers faced by insulin in the gastrointestinal tract are proteolytic enzymatic degradation and lack of transport across the intestinal epithelium. Several strategies have been proposed for the oral administration of insulin, but with limited clinical or commercial success. Protein encapsulation into nanoparticles is considered a promising alternative for oral insulin delivery due to its ability to facilitate the paracellular or transcellular transport of insulin across the intestinal mucosa. This review provides an overview of strategies for oral delivery of insulin, from insulin conjugation to encapsulation into nanoparticles. These strategies are still evolving to achieve potency and efficacy soon.

Keywords: Insulin, Diabetes, Nanoparticles , Enzymatic degradation , encapsulation

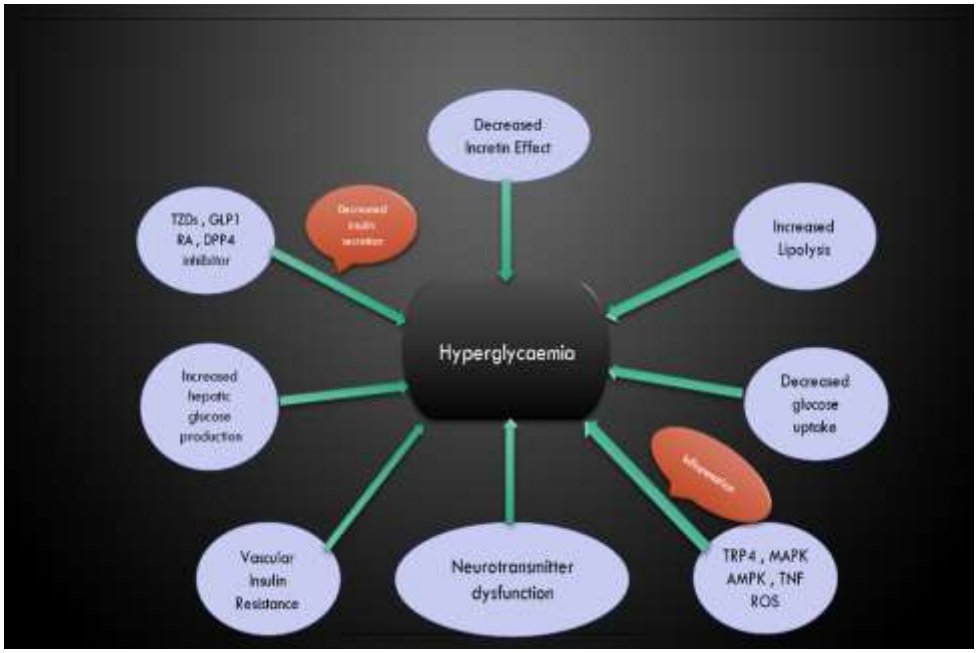
Introduction

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it does produce. Insulin is a hormone that regulates blood glucose levels. Hyperglycaemia, also called high blood glucose or high blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many body systems, especially nerves and blood vessels. [1].

Diabetes is one of the biggest global health challenges of this century. The number of people living with both type 1 and type 2 diabetes is increasing every day, causing a serious economic burden on patients and society. Between the two types, type 2 diabetes, which is common and more common, is a major contributor to the rising trend. The International Diabetes Federation estimated that there were 415 million people with diabetes worldwide in 2015, and this number is expected to increase to 642 million by 2040.1 It is alarming that more than 47% of the world's population is still undiagnosed diabetes, the prevalence of which is still bound to increase further. Furthermore, it is estimated that 318 million people have impaired glucose tolerance, and 20.9 million live births are affected by some form of hyperglycaemia in pregnancy, of which 85.1% are due to gestational diabetes. People with type 2 diabetes are increasing in every country, but more than 80% live in low- and middle-income countries such as India, Bangladesh, Bhutan, Pakistan, Sri Lanka, the Philippines, and Indonesia. Among the world's top 10 countries is India, with 69.2 million people with diabetes and another 36.5 million with prediabetes, a high-risk condition for diabetes and cardiovascular disease. This rising incidence is mainly attributed to lifestyle changes, eating junk food and being physically inactive.

Diabetes affects children and adolescents. Type 1 diabetes, although uncommon, is increasing by 3% each year, especially in children. In 2015, the number of children worldwide with type 1 diabetes exceeded half a million for the first time. There are more than 70,000 children with the condition in India alone, the second highest number in the world after the US. Diabetes during pregnancy (gestational diabetes) poses a higher risk of diabetes in women and long-term consequences for the offspring. Long-term diabetes causes an increased risk of complications and damage to the heart, eyes, kidneys, and nerves. Cardiovascular disease is one of the leading causes of death in people with diabetes.

In India, 85-95% of all healthcare costs are met by individuals and their families from household income. Direct expenditure consumes 27–34% of the household income of the rural and urban poor, while the middle to high income groups in rural and urban areas spend 5.0–12.6% and 4.8–16.9% of income on care about diabetes.



Types of Diabetes

- ***Type 1 diabetes***

Type 1 diabetes (formerly known as insulin-dependent, juvenile, or childhood-onset diabetes) is characterized by insufficient insulin production and requires daily insulin administration. In 2017, there were 9 million people with type 1 diabetes; most of them live in high-income countries. Neither its cause nor the way to prevent it is known.

In this condition, the immune system attacks and destroys the insulin-producing beta cells of the pancreas. There is a lack of beta cells leading to a complete lack of insulin. That is why it is called an autoimmune disease, when antibodies against insulin or against islet cells are present in the blood. These cause lymphocytic infiltration and destruction of pancreatic islets. Destruction may take time, but disease onset is rapid and may occur within days to weeks.

Symptoms include excessive urination (polyuria), thirst (polydipsia), constant hunger, weight loss, vision changes, and fatigue. These symptoms may appear suddenly.

- ***Type 2 diabetes***

Type 2 diabetes (formerly called non-insulin-dependent or adult-onset) is the result of the body's ineffective use of insulin. More than 95% of people with diabetes have type 2 diabetes. This type of diabetes is largely the result of excess body weight and physical inactivity.

This condition is caused by a relative lack of insulin, not an absolute lack. This means that the body is unable to produce adequate insulin to meet the needs. There is beta cell deficiency associated with peripheral insulin resistance.

Peripheral insulin resistance means that even when insulin levels in the blood are high, hypoglycemia or low blood sugar does not occur. This may be due to changes in the insulin receptors that cause insulin to act.

Symptoms can be like those of type 1 diabetes but are often less severe. As a result, the disease can be diagnosed several years after the onset, after complications have already occurred.

- ***Gestational diabetes***

Gestational diabetes is hyperglycaemia with blood glucose levels above normal but below diagnostic values for diabetes. Gestational diabetes occurs during pregnancy.

Pathophysiology behind symptoms and complications of diabetes:

Polydipsia, or increased thirst, is caused by high blood glucose, which increases the osmolarity of the blood and makes it more concentrated.

Polyuria, or increased frequency of urination, is caused by excessive fluid intake and glucose-induced urination.

Weight loss occurs due to the loss of calories in the urine.

Polyphagia, or increased hunger due to a loss or excess of glucose in the urine, leading the body to crave more glucose.

Poor healing of wounds, gums, and other infections due to increased blood glucose, which provides a good source of nutrition for microbes, and due to reduced immunity.

Heart disease - arises as a result of changes in large vessels leading to coronary, cerebral and peripheral artery diseases, atherosclerosis, dyslipidaemia, etc.

Eye damage – this is called diabetic retinopathy and occurs due to damage to the delicate blood vessels of the retina in the eye due to long-term exposure to high blood sugar.

Kidney damage - similar damage to the small and large vessels of the kidney. Proteinuria or increased protein efflux occurs initially and can lead to end-stage renal disease (ESRD).

Nerve damage – can affect the arms and legs and is called numbness/tingling in stockings. It can also affect autonomic functions leading to impotence, erectile dysfunction, indigestion, or gastroparesis, etc.

Diabetic foot - occurs because of peripheral nerve damage, as well as vascular damage due to long-term diabetes. Small trauma, ulcers, and blisters go unnoticed due to lack of sensitivity, and peripheral vascular disease impairs healing and allows infection.

Diabetic ketoacidosis is caused by type 1 diabetes where there is a complete lack of insulin and a reliance on fatty acids for energy. This uncontrolled breakdown of lipids leads to the formation of ketones and causes acidosis and ketonemia. This is a medical emergency.

Non-ketotic hyperosmolarity – is caused by an extreme increase in blood sugar. This is seen in type 2 diabetics. There is just enough insulin to suppress the synthesis of ketones. High blood sugar leads to excessive blood concentration or osmolarity, which in turn leads to dieresis and collapse of blood vessels and cardiovascular shock.

Women with gestational diabetes are at increased risk of complications during pregnancy and childbirth. These women, and possibly their children, are also at increased risk of developing type 2 diabetes in the future. Gestational diabetes is diagnosed through prenatal screening rather than reported symptoms [2].

Causes

The cause of diabetes, regardless of the type, is having too much glucose circulating in your bloodstream. However, the reason why your blood glucose levels are high differs depending on the type of diabetes.

- **Causes of Type 1 diabetes:** This is an immune system disease. Your body attacks and destroys insulin-producing cells in your pancreas. Without insulin to allow glucose to enter your cells, glucose builds up in your bloodstream. Genes may also play a role in some patients. Also, a virus may trigger the immune system attack.
- **Cause of Type 2 diabetes and prediabetes:** Your body's cells don't allow insulin to work as it should to let glucose into its cells. Your body's cells have become resistant to insulin. Your pancreas can't keep up and make enough insulin to overcome this resistance. Glucose levels rise in your bloodstream.
- **Gestational diabetes:** Hormones produced by the placenta during your pregnancy make your body's cells more resistant to insulin. Your pancreas can't make enough insulin to overcome this resistance. Too much glucose remains in your bloodstream [3].

Symptoms

- Increased thirst.
- Weak, tired feeling.
- Blurred vision.
- Numbness or tingling in the hands or feet.
- Slow-healing sores or cuts.
- Unplanned weight loss.
- Frequent urination.
- Frequent unexplained infections.
- Dry mouth[4].

Complications

- Cardiovascular issues including coronary artery disease, chest pain, heart attack, stroke, high blood pressure, high cholesterol, atherosclerosis (narrowing of the arteries).
- Nerve damage (neuropathy) that causes numbing and tingling that starts at toes or fingers then spreads.
- Kidney damage (nephropathy) that can lead to kidney failure or the need for dialysis or transplant.
- Eye damage (retinopathy) that can lead to blindness; cataracts, glaucoma.
- Foot damage including nerve damage, poor blood flow and poor healing of cuts and sores.
- Skin infections.
- Erectile dysfunction.
- Hearing loss.
- Depression.
- Dementia.
- Dental problems[5].

Treatment

Diabetes medication drug classes include:

- **Sulfonylureas:** These drugs lower blood glucose by causing the pancreas to release more insulin.
- **Glinides (also called meglitinides):** These drugs lower blood glucose by getting the pancreas to release more insulin.
- **Biguanides:** These drugs reduce how much glucose the liver produces. It also improves how insulin works in the body and slows down the conversion of carbohydrates into sugar.
- **DPP-4 inhibitors (also called dipeptidyl peptidase-4 inhibitors):** These drugs help your pancreas release more insulin after meals. They also lower the amount of glucose released by the liver.
- **SGLT2 inhibitors (also called sodium-glucose cotransporter 2 inhibitors):** These drugs work on your kidneys to remove glucose in your body through your urine.
- **Bile acid sequestrants:** These drugs lower cholesterol and blood sugar levels.
- **Dopamine agonist:** This medication lowers the amount of glucose released by the liver[6].

Insulin

Insulin is a peptide hormone produced by beta cells of the pancreatic islets encoded in humans by the INS gene. It is considered to be the main anabolic hormone of the body. It regulates the metabolism of carbohydrates, fats and protein by promoting the absorption of glucose from the blood into liver, fat and skeletal muscle cells[7].

Insulin is the primary treatment in all patients with type 1 diabetes. It is necessary for life which therefore, type 1 diabetes was once called insulin-dependent diabetes mellitus, or IDDM. In 1997, Published by the American Diabetes Association (ADA). New recommendations for classification and Diagnosis of diabetes requiring the use of type 1 and enter 2 with Arabic numerals only (not Roman digits) rather than IDDM/Type I and NIDDM/ Type II. Although IDDM is still used describe type 1 diabetes, it is no longer the preferred abbreviation. People with type 2 diabetes may also require insulin to achieve glucose control due to high levels of insulin resistance and/or decreasing ability of the pancreas to fill physical requirements. Treatment of people with type 2 diabetes (formerly known as NIDDM or type II diabetes) will always include diet and exercise therapy and usually metformin as first-line drug.

With the insulin preparations available today, patients have more flexibility in timing their meals, but adjust to the effect of the insulin it can be more complex for individual needs. Initiation of insulin Patients with type 1 diabetes usually require starting with multiple daily injections (ie, mealtimes or bolus doses with fast-acting agents and once daily dose of long-acting or basal insulin) at time of diagnosis. This is known as basal/bolus therapy. The preferred method of insulin initiation in type 2 diabetes is to start with addition of long-acting (basal) insulin to oral preparations. If glucose targets are desired unmet, rapid-acting (bolus or prandial) insulin can be added at mealtime to control the expected amount postprandial glucose increase.

Types of Insulin

- **Rapid-acting insulins:** These insulins are taken 15 minutes before meals, they peak (when it best lowers blood glucose) at one hour and work for another two to four hours.
- **Short-acting insulins:** These insulins take about 30 minutes to reach your bloodstream, reach their peak effects in two to three hours and last for three to six hours.
- **Intermediate-acting insulins:** These insulins reach your bloodstream in two to four hours, peak in four to 12 hours and work for up to 18 hours.
- **Long-acting insulins:** These insulins work to keep your blood sugar stable all day. Usually, these insulins last for about 18 hours.[8].

Half Life

Systemic insulin disposition (apparent terminal half-life) following oral inhalation of 4 to 48 units of human insulin was 120-206 minutes[9].

➢ ***Current Routes of Administration Of Insulin***

- Inject subcutaneously via syringe, pre-filled pen device or insulin pen
- Insulin infusion via a wearable personal insulin pump
- Administer through an intravenous insulin infusion[10].

➢ ***Current Challenges in Insulin Therapy***

- Patient perception that insulin therapy is too complicated and time consuming, can interfere with its timely initiation.
- Educating patients regarding their condition
- Slow absorption rate and onset of action
- Use of Needles and frequent penetrations in the skin for Insulin administration
- Less convenient to patients
- Frequent skin punctures can be dangerous for old age people and children[11].

➢ ***Oral Administration of Insulin***

Oral administration of Insulin can be very much convenient for the patient as the patient does not have to administer insulin through needles and insulin pen which can be irritable to the patient. Moreover, oral administration is more convenient for old age people and children.

Although oral administration seems a much better option in insulin therapy but there are certain problems such as

- Lesser absorption and bioavailability of insulin through oral route
- Degradation of insulin by gastrointestinal juices
- Less penetration through epithelial barriers on sites of absorption

➢ ***Current Ongoing Researches For Oral delivery of Insulin***

Several strategies for oral insulin delivery have been proposed, but without much clinical or commercial success. Encapsulation of proteins into nanoparticles is considered a promising alternative to oral insulin administration because of their ability to promote paracellular or transcellular transport of insulin across the intestinal mucosa. In this review, various delivery systems designed to increase the oral bioavailability of insulin will be discussed, with a special focus on nanoparticulate carrier systems, as well as the efforts made by pharmaceutical companies to bring the first oral insulin delivery system to market.

- Insulin delivery via covalent organic frameworking : The development of imine-linked-covalent organic framework nanoparticles for oral delivery of insulin via layered nanosheets to overcome delivery barriers. A gastro-resistant nCOF was prepared from layered nanosheets with insulin loaded between the nanosheet layers . The insulin loaded nCOF exhibited insulin protection in digestive fluids *in vitro* as well as glucose responsive release[12] .
- Labrasol as absorption enhancer: The co-administration of Labrasol-related formulations with insulin reduced the blood glucose levels[13] .

- Chitosan nanoparticles and mucoadhesive films: Chitosan nanoparticles loaded with insulin using ionic gelation method using sodium tripolyphosphate as a crosslinker. Later the nanoparticles were dispersed in buccal films[14]. Mucoadhesive chitosan based films, incorporated with insulin loaded nanoparticles made of poly(ethylene glycol)methyl ether-block-polylactide (PEG-b-PLA). Blank-nanoparticles were prepared by double emulsion solvent evaporation technique with varying concentrations of the copolymer[15].
- Insulin entrapping Niosomes : Nonionic surfactants are used for the preparation of insulin entrapping niosomes. Niosomes effectively prolong the release of insulin in both SGF and SIF and protect this protein against different proteolytic enzymes including pepsin, trypsin and the α-chymotrypsin[16].
- Bioadhesive buccal tablets : Insulin is formulated into bioadhesive buccal tablets using Carbopol 934, Hydroxypropyl cellulose (HPC) or Hydroxypropyl methyl cellulose (HPMC) and different absorption promoters. Tablets made using polymer mixture of HPMC: Carbopol 934 in a ratio of 1:1 and containing 1% POELE resulted in 26% reduction in plasma glucose levels and producing 9.42% RH[17].
- Another strategy is to graft a ligand onto the surface of nanoparticles for specific targeting of nanoparticles to receptors on enterocytes or M cells.86 For example, lectins are involved in many cell recognition and adhesion processes that significantly enhance the transport of nanoparticles through the intestine.92 Both SLN and WGA–N-glutaryl modified lectins -phosphatidylethanolamine-modified SLN containing insulin, when administered orally to rats, were able to improve insulin bioavailability and protect insulin from degrading enzymes in vitro.
- Eligen Insulin: Carrier agents appear to form conformational complexes with insulin, preventing hormone degradation and facilitating absorption across the intestinal wall. In animal studies and phase I clinical trials, administration of Eligen insulin resulted in a rapid increase in plasma insulin followed by a decrease in plasma glucose levels. Eligen insulin had a faster onset of action and higher insulin concentrations than injected insulin. Eligen insulin formulations were well tolerated in all clinical studies conducted to date. In a Phase II clinical trial in patients with type 2 diabetes, the combination of Eligen insulin and metformin failed to achieve significantly better glycemic control than treatment with metformin alone.

➢ ***Other Possible Approaches***

- Adding a structural component to the insulin molecule with the help of molecular docking that will not affect the efficacy of the active molecule but will prevent its degradation from the gastric enzymes.
- Preparing buccal mucoadhesive liqui-tablets of insulin with the selection of a mucoadhesive and penetrating polymer that will prevent it from degradation and will also help in a faster absorption of the insulin,
- Entrapping the insulin in a protein coat to ensure more absorption of the active ingredient. The selection of protein will depend on the condition that the coat material should not degrade in GI environment.

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