ABSTRACT
Diabetes mellitus is a serious pathologic condition that is responsible for major health care problems worldwide and costing billions of dollars annually. Diabetes mellitus is a group of metabolic disorders with a number of etiologies characterized by hyperglycemia along with impairment of carbohydrate, fat and proteins metabolism. It can occur due to an imbalance of insulin secretion, insulin action or both. Diabetes mellitus management is associated with the episodes of hypoglycemia. The hypoglycemia complications are mainly associated in elderly and also in some cases of type I diabetes subjects.

Furthermore, prolonged insulin deficiency and longer disease duration increase the risk of hypoglycemia in type II diabetes mellitus. Diabetes and its associated complications are the possible cause of morbidity and mortality worldwide. This calls for a firm action in part of its therapeutic potential. Insulin replacement therapy has been used in the clinical management of diabetes mellitus for more than 84 years. The present mode of insulin administration is by subcutaneous route through which insulin is presented to the body in a non-physiological manner having many challenges. Challenges of oral route of administration are: rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal lumen and poor permeability across intestinal epithelium because of its molecular weight and lack of lipophilicity. Liposomes, microemulsions, nanocubicles, and forth have been prepared for the oral delivery of insulin. Chitosan-coated microparticles protected insulin from gastric environment of the body and released intestinal PH. Limitations to the delivery of insulin have not been resulted in fruitful results to date and there is still need to prepare newer delivery systems, which can produce dose-dependent and reproducible effects, in addition to increased bioavailability. We haven’t developed a type of oral insulin that can make it through the digestive system unharmed. The acids in our stomach breakdown oral insulin before it can get into the liver. That means it’s not effective...
by the time it reaches our liver. Further, our body has trouble absorbing insulin from our intestines. The mucus layer in our intestines is thick and studies have shown that only low levels of insulin pass through this lining and into your bloodstream. As a result, some researchers believe that high doses of insulin would be needed to be effective in managing diabetes.

**KEYWORDS:** Liposomes, microemulsions, nanocubicles.

**INTRODUCTION**

Diabetes mellitus is a common disease and its complications are responsible for excess morbidity and loss of independence and reduced quality of life.[2] Diabetes mellitus is a group of metabolic disorders of multiple etiologies characterized by chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism resulting from a defect in insulin secretion or action or both. Diabetes mellitus is the full medical name for diabetes, a condition where the body has a problem making insulin or using it effectively to process glucose (sugar) from food. Diabetes mellitus is a life-long condition and includes type 1 and type 2 diabetes.

**Type 1 diabetes:** Type 1 diabetes is an autoimmune condition. It used to be called insulin-dependent diabetes and is caused by the body attacking its own pancreas with antibodies. In people with type 1 diabetes, the damaged pancreas doesn't make insulin.

This type of diabetes may be caused by a genetic predisposition. It could also be the result of faulty beta cells in the pancreas that normally produce insulin.

A number of medical risks are associated with type 1 diabetes. Many of them stem from damage to the tiny blood vessels in your eyes (called diabetic retinopathy), nerves (diabetic neuropathy) and kidneys (diabetic nephropathy). In addition, there is the increased risk of heart disease and stroke.

Treatment for type 1 diabetes involves taking insulin, which needs to be injected through the skin into the fatty tissue below. The methods of injecting insulin include[3]:

- Syringes
- Insulin pens that use prefilled cartridges and a fine needle
- Jet injectors that use high pressure air to send a spray of insulin through the skin
Having type 1 diabetes does require significant lifestyle changes that include:

- Frequent testing of your blood sugar levels
- Careful meal planning
- Daily exercise
- Taking insulin and other medication as needed

People with type 1 diabetes can lead long, active lives if they carefully monitor their glucose, make the needed lifestyle changes and adhere to the treatment plan.

**Type 2 diabetes:** In type 2 diabetes mellitus, a person’s pancreas doesn’t produce enough insulin or their body doesn’t react to insulin called insulin resistance.

For some people, type 2 diabetes may be managed through diet and exercise. Other people may also need medication, and sometimes insulin, to manage blood sugar.

![Fig. 1: Effect of Type 2 Diabetes in the body.](image)

When glucose builds up in the blood instead of going into cells, the cells are not able to function properly. Other problems associated with the build-up of glucose in the blood include:

- **Dehydration:** The build-up of sugar in the blood leads to excess glucose in the urine because the kidneys can’t deal with the high sugar levels. The sugar in the urine draws
water with it, causing an increase in urination. When the kidneys lose the glucose through the urine, a large amount of water is also lost, causing dehydration.

- **Diabetic coma (hyperosmolar hyperglycaemic non-ketotic syndrome):** When a person with type 2 diabetes becomes severely dehydrated and is not able to drink enough fluids to make up for the fluid losses, they may develop this life-threatening complication.

- **Damage to the body:** Over time, the high glucose levels in the blood may damage the nerves and predispose a person to atherosclerosis (narrowing) of the arteries that can cause heart attack and stroke, and damage the eyes and kidneys.

**Symptoms of type 2 diabetes**
The symptoms of type 2 diabetes due to high blood sugar may include:

- Increased thirst
- Increased hunger (especially after eating)
- Dry mouth
- Frequent urination
- Unexplained weight loss (even though you are eating and feel hungry)
- Fatigue (weak, tired feeling)
- Blurred vision
- Headaches
- Loss of consciousness (rare)
- Recurrent infections, including thrush infections

**Current Routes for Insulin Delivery and Their Problems**
The present mode of insulin administration is by subcutaneous route by which insulin is presented to the body in a non-physiological manner. The subcutaneous administration has many challenges. Insulin injected subcutaneously at least twice a day is having many inherent disadvantages include local pain, inconvenience of multiple injections and occasional hypoglycemia as a result of overdose, Itching, allergy, hyperinsulinemia and insulin lipodystrophy around the injection site. Because of this problem, novel approaches for insulin delivery are being explored, including oral, transdermal, nasal, rectal, pulmonary, uterine and ocular delivery as well as s.c implants.
Why oral delivery of insulin?
Making needles needless is gaining widespread prominence, to offset the aforementioned disadvantages by oral delivery of insulin. The oral route is considered to be the most acceptable and convenient route of drug administration for chronic therapy. Insulin if administered via oral route will help eliminate the pain caused by injection, psychological barriers associated with multiple daily injections such as needle anxiety and possible infections.[5] In addition, oral insulin is advantageous because it is delivered directly to the liver, its primary site of action, via the portal circulation, a mechanism very similar to endogenous insulin; subcutaneous insulin treatment however does not replicate the normal dynamics of endogenous insulin release, resulting in a failure to achieve a lasting glycemic control in patients.[6]

To keep our blood sugar levels in safe range, it is important to follow diabetes treatment plan which includes injections. These injections can be inconvenient, they require training to self-administer and they may need to be given several times per day. For these reasons, many people don’t follow their diabetes treatment plan, which can lead to severe complications.

So the idea of swallowing a pill appeals to many people. Doctors believe that the ease of using a pill could make more people willing to start and maintain a successful insulin therapy routine.[7] That could lead to better control of their diabetes.

How Oral Insulin Would Work
With injectable insulin, we use a needle to inject the insulin into the fatty tissue beneath the skin. From there, the insulin travels to our bloodstream. It goes into general circulation throughout our body and then travels to our liver.[8]

Oral insulin, on the other hand, would move through the digestive system. It would be absorbed into our bloodstream through the intestines. From the intestines, it would move into your portal vein, a blood vessel that connects to the liver. Then the insulin would move directly into the liver where glucose (blood sugar) is stored. Moving insulin more quickly into the liver could help our body absorb and use glucose better. This could mean insulin works faster. It could also mean a reduced risk of excess insulin in our blood, which could lead to a decreased risk of hypoglycemia (low blood sugar).
Challenges in Oral Delivery of Insulin
Generally peptides and proteins such as insulin cannot be administered via the oral route due to rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal lumen and poor permeability across the intestinal epithelium because of its high molecular weight and lack of lipophilicity. The oral bioavailability of most peptides and proteins therefore is less than 1%. The challenge here is to improve the bioavailability to anywhere between 30-50%.

1. **Enzymatic barrier**: The harsh environment of gastrointestinal tract causes insulin to undergo degradation. This is because digestive process are designed to breakdown proteins and peptides without any discrimination.\(^9\) Insulin therefore undergo enzymatic degradation by pepsin and pancreatic proteolytic enzymes such as trypsin and alpha-chymotrypsin.\(^10\)

2. **Intestinal transport of insulin**: Another major barrier to the absorption of hydrophilic macromolecules of insulin is that they cannot diffuse across epithelial cells through lipid bilayer cell membranes to the blood stream.\(^11\) Insulin has low permeability through intestinal mucosa.

3. **Dosage form stability**: The activity of proteins depends upon three-dimensional molecular structure.\(^12\) During dosage form development, proteins might be subject to physical and chemical degradation. Physical degradation involves modification of the native structure to higher order structure while chemical degradation involves bond cleavage that results in the formation of new product.\(^13\)

Approaches Used for Oral Insulin Delivery
In developing oral protein delivery systems with high bioavailability, three practical approaches might be most helpful.\(^14\):

1. Modification of physiochemical properties such as lipophilicity and enzyme susceptibility.
2. Addition of novel function to macromolecules.
3. Use of improved carrier systems.\(^15\)
The various oral delivery systems attempted to deliver insulin orally either singly or in synergistic approach can be categorized as follows:

1. **Enzyme inhibitors**: Insulin is degraded in the GIT by pepsin and other proteolytic enzymes. Enzyme inhibitors slow the rate of degradation of insulin which increases the amount of insulin available for absorption.\(^{[16]}\)

   For example: sodium cholate along with aprotinin.

2. **Penetration enhancers**: Hydrophilic molecules like insulin are adsorbed to the apical membrane and are internalized by endocytosis.\(^{[17]}\) Absorption may be enhanced when the product is formulated with acceptable safe excipients. These include substances like bile salts, surfactants, trisodium citrates, chelating agents like EDTA, labrasol.\(^{[18]}\) The drawback with penetration enhancers involves lack of specificity.

3. **Chemical modifications**: Modifying the chemical structure of a peptide or protein is another approach to enhance the bioavailability by increasing its stability against possible enzymatic degradation, or its membrane permeation.\(^{[19]}\) For example, substitution of D-amino acids for L-amino acids in the primary structure can improve the enzyme stability of peptides.

**Carrier Systems for Insulin Delivery**

1. **Hydrogels**: These are cross-linked networks of hydrophilic polymers, which are able to absorb large amounts of water and swell, while maintaining their three dimensional structure.\(^{[20]}\)

2. **Liposomes**: Insulin-entrapped liposomes cause dose-dependent hypoglycemia.

3. **Erythrocytes**: Human red cells have been developed as oral carrier systems for human insulin.

4. **Nanospheres**: Using 14C-labeled nanospheres with insulin, it was found that nanospheres increased the uptake of insulin or its metabolite in the gastrointestinal tract, blood and liver while the excretion was delayed when compared to insulin non-associated to nanospheres.\(^{[21]}\)

5. **Nanocubicles**: A liquid formula that can be easily dispersed in water to produce particles named “Nanocubicles” was developed by Chung et al.\(^{[22]}\) These nanocubicles containing insulin were administered to fastened streptozotocin-induced diabetic rats. For
comparsion, an aqueous solution was also administered.[23] A nanocubicle without insulin and insulin in phosphate buffer saline (PBS) was administered as controls.

6. **Thiolated chitosan insulin tablets:** The efficiency of orally administered insulin has also been improved using Thiolated chitosan.

7. **Microemulsions:** Cho and Flynn developed water-in-oil microemulsions[^24] in which the aqueous phase is insulin and oil phase is lecithin, non-esterified fatty acids and cholesterol in critical proportions. In vivo studies showed substantial reduction in blood glucose.

8. **Oral insulin pills:** Insulin administration in the form of a pill, have always been an attractive concept in research. Due to numerous limitations of this mode of insulin administration, efficacy has been hard to demonstrate.

9. **Oral Spray:** An alternative for injected insulin that is currently explored by researchers is a mouth spray containing insulin that would be absorbed through the lining of the mouth and throat.[^25] The liquid formulation allows the insulin to be absorbed by the mucus membranes in the cheeks, tongue, and throat. The benefit from oral spray is identical to an insulin injection in its ability to lower blood glucose levels.

10. **Pulmonary or inhaled insulin:** The inhaled insulin systems delivers a dose of insulin, either in liquid or dry powder form, through the mouth, directly into the lungs, where it enters to the blood circulation as rapid-acting insulin. With inhaled insulin, the highly permeable alveolar epithelium and large surface area of the lungs provide an effective, efficient portal for macromolecular delivery.[^26]

---

**Advantages of Oral Insulin**

1. Most acceptable and convenient route of drug administration.
2. Orally administered insulin would eliminate complications associated with insulin injection therapy such as pain caused by injection, physiological barriers associated with multiple daily injections such as needle anxiety and possible infections.
3. Hepatic insulinization
4. Avoidance of peripheral hyperinsulinemia
5. Avoidance of possible hypoglycemia and weight gain.

**Limitations of Oral Insulin**

1. They carries a high risk of low blood sugar reactions if too much is used
2. Many people gain weight when treated with insulin.
Future Trends for Insulin Delivery Systems

While researchers continue to strive for a pill form of insulin, another form is now available. AFREZZA inhalation powder was approved by Food and Drug Administration in 2014. Using an inhaler, you breathe in this drug at the start of a meal to help control spikes in blood sugar after your meal. The drug is absorbed into your bloodstream through the walls of our lungs. This method is not quite as desirable as a pill form, as it doesn’t go into our liver as quickly.

We can use AFREZZA if we have type 1t or type 2 diabetes. However with type 1, we must use injectable insulin as well.

Some insulin delivery systems are:

1. Islet Cell Transplantation

It is the transplantation of isolated islets from a donar pancreas into another person. It is an experimental treatment for Type 1 diabetes mellitus. Once transplanted, the islets begin to produce insulin, actively regulating the level of glucose in the blood. Islets are usually infused into the patient’s liver.[27] If the cells are not from a genetically identical donar the patient’s body will recognize them as foreign and the immune system will begin to attack them as with any transplant rejection. To prevent this, immunosuppressant drugs are used.

![Image](image_url)

**Fig. 2: Islet cell Transplantation.**

2. Insulin Nanopump

They were developed to avoid repetitive subcutaneous injections. The pump itself is essentially a device that holds a syringe tilled with insulin. Insulin delivery is exquisitely controlled by a mechanism that pushes the plunger of a syringe down to infuse insulin into the subject via an infusion set.[28] This is an open-loop system that has two concurrent modes
of insulin delivery: continuously through basal infusion and intermittently through bolus
insulin delivery.

**Advantages of insulin pump**
1. More physiologic
2. Less variable insulin absorption
3. Better match between insulin and food
4. Greater lifestyle flexibility
5. Easier to travel – improved portability

**3. Gene Therapy**
Gene therapy is an experimental technique that uses genes to treat or prevent disease. In the
future, this technique may allow doctors to treat a disorder by inserting a gene into a patient’s
cells instead of using drugs or surgery. Researchers are testing several approaches to gene
therapy, including:
- Replacing a mutated gene that causes disease with a healthy copy of the gene.
- Inactivating, or “knocking out,” a mutated gene that is functioning improperly.

Gene therapy is currently being tested only for diseases that have no other cures.

Gene therapy is under study to determine whether it could be used to treat disease. Current
research is evaluating the safety of gene therapy; future studies will test whether it is an
effective treatment option. Several studies have already shown that this approach can have
very serious health risks, such as toxicity, inflammation and cancer. Because the techniques
are relatively new, some of the risks\[29\] may be unpredictable; however, medical researchers,
institutions and regulatory agencies are working to ensure that gene therapy research is as
safe as possible.

A gene that is inserted directly into a cell usually does not function. Instead, a carrier called a
vector is genetically engineered to deliver the gene. Certain viruses are often used as vectors
because they can deliver the new gene by infecting the cell. The viruses are modified so they
can’t cause disease when used in people. Some types of virus, such as retroviruses, integrate
their genetic material (including the new gene) into a chromosome in the human cell. Other
viruses, such as adenoviruses, introduce their DNA into the nucleus of the cell, but the DNA
is not integrated into a chromosome.
The vector can be injected or given intravenously (by IV) directly into a specific tissue in the body, where it is taken up by individual cells. Alternately, a sample of the patient's cells can be removed and exposed to the vector in a laboratory setting. The cells containing the vector are then returned to the patient. If the treatment is successful, the new gene delivered by the vector will make a functioning protein.

Researchers must overcome many technical challenges before gene therapy will be a practical approach to treating disease. For example, scientists must find better ways to deliver genes and target them to particular cells. They must also ensure that new genes are precisely controlled by the body.

A new gene is injected into an adenovirus vector, which is used to introduce the modified DNA into a human cell. If the treatment is successful, the new gene will make a functional protein.

Fig. 3: Gene therapy using a vector.

Artificial Pancreas: Future of Diabetes Mellitus

The artificial pancreas is a technology in development to help people with diabetes automatically control their blood glucose level by providing the substitute endocrine functionality of a healthy pancreas.
The goal of the artificial pancreas is two-fold:

1. To improve insulin replacement therapy until glycemic control is practically normal as evident by the avoidance of the complications of hyperglycemia, and
2. To ease the burden of therapy for the insulin-dependent.

![Bioartificial pancreas](image)

**Fig. 4: Bioartificial pancreas.**

There are three main artificial pancreas systems being worked on by researchers:

- Closed-loop artificial pancreas
- Bionic pancreas
- Implanted artificial pancreas

**CONCLUSION**

Attempts have been made to achieve oral insulin delivery using various systems. It has been proved that insulin is subjected to acid catalyzed degradation in stomach, luminal degradation in intestine, and intracellular degradation. Scientists have been able to protect the insulin delivery systems from acidic environment of the stomach and target it to the intestine. The maximum bioavailability of insulin has been reported to be very low because of the poor absorption of insulin from the intestine. Attempts have been made to increase the absorption of insulin from intestine using absorption enhancers such as aprotinin, tween, oligoarginine, sodium glycol-cholate, deoxycholic acid and taurodeoxycholate. Liposomes, microemulsions, nanocubicles, etc have been prepared for the oral delivery of insulin. Chitosan-coated microparticles protected insulin from the gastric environment of the body and released it in the intestinal PH. Limitations to the delivery of insulin have not resulted in fruitful results to
date and there is still a need to prepare newer delivery systems, which can produce dose-dependent and reproducible effects in addition to increased bioavailability.

REFERENCES
16. Eaimtrakarn S, Ramprasad YV, Ohno T, Konishi T, Yoshikawa y, Shibata N. Absorption-
    enhancing effect of labrasol on the intestinal absorption of insulin in rats. J. Drug Target.,
    chymotrypsin inhibitor flk-448 on the intestinal absorption of insulin in rats and dogs. J.
19. Gowthamarajan K, Kulharni GT. Oral insulin- Fact or Fiction? Possibilities of achieving
21. Jain D, Panda AK, Majumdar DK. Eudragit S100 entrapped insulin microspheres for oral
22. Kim BY, Jeong JH, Park K, Kim JD. Bioadhesive Interaction and hypoglycemic effect of
    insulin-Loaded-Lectin-Microparticle conjugates in Oral Insulin Delivery System. J.
    Academy of sciences, 1999; 12: 1.5-11.
24. Korytkowski M. When oral agents fail: Practical barriers to starting insulin. Int. J. obesity,
25. Krauland AH. Gugi D. Bernkop-Schnurch A. Oral Insulin Delivery: The Potential of
    Thiolated Chitosan-insulin tablets on Nanodiabetic Rats. J Control release, 2004; 95(3):
    547-55.
27. Lee VH. Oral route of peptide and protein drug delivery in peptide and protein drug
28. Li CL, Deng YJ. Oil based formulations for oral delivery of insulin. J. Pharm.
    Pharmacol., 2004; 56(9): 1101-1107.
29. Lin YH, Chen CT, Liang HF, kulkarni AR, Lee PW, Chen CH. for oral insulin delivery
    via the paracellular pathway.., 2007; 18: 105102, 1-10.