IASR J. Med. Pharm. Sci.
ISSN: 2582-9343
Website: https://ijmps.com/
Open Access Journal
Country: India

IASR Journal of
Medical and Pharmaceutical
Science

ORIGINAL ARTICLE OPEN ACCESS

A review of Novel drug delivery systems for oral insulin

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Received: 15-09-2024
Accepted: 24-10-2024
Available online: 25-11-2024

ABSTRACT

The beta cell of the pancreas (in the Langerhans islets) integrates and secretes insulin, a peptide hormone. The body builds glucose in the blood, supplying it to fat, liver, and skeletal muscle cells for carbohydrate, fat, and protein metabolism. More than millions of people die from diabetes mellitus (DM) each year worldwide. It is a leading effect of cognitive state and destruction. Drugs among increasing numbers on the market fail to provide a complete and effective treatment for DM due to their side effects, such as nausea, vomiting, and gastrointestinal irritation. A novel drug delivery system (NDDS) can be defined as a new technique for developing inventive formulations, procedures, and techniques to safely deliver pharmaceutical compounds in the body and achieve their desired pharmacological effects. New pharmaceutical forms are formulated to have smaller particle sizes, higher permeability parameters, and selective site targeting. NDDSs (Nasal Delivery Systems) serve as carriers, maintaining the drug concentration within the therapeutic window for extended periods to ensure controlled and sustained release. The aim is to minimize undesired effect and improve the therapeutic effect. In this paper, we aimed to assess how well people with diabetes who visit our clinic understand various topics related to preventing and treating diabetes-related issues.

Key Words: *Insulin, Diabetes, Drug delivery system, Oral delivery*

Introduction:

Novel Drug Delivery System

Various carriers offer advantages over traditional drug delivery systems (NDDS) in terms of performance, protection, patient compliance, and product shelf life. Traditional dosage forms, on the other hand, have disadvantages such as medicines experience instability, low availability, and fast release despite being administered in high doses. The first pass effect, plasma drug level fluctuations, and instability all contribute to the unpredictability of their actions. [1]

Nanoparticles are mitigated to address problems. The increasing awareness of their potential impacts on human health and environmental sustainability, as well as the growing environmental practice of human-made nanoparticles, has made them a topic of current interest. In numerous applications, they are utilized and produced through various processes. Nanoparticles are described as having theoretical problems that involve their calculation and characterization. Particles with a diameter ranging from 1 to 100 nm are referred to as nanoparticles. The small and large molecules are effectively distributed through altered pharmacodynamics and pharmacokinetic properties of the targeted source mechanism. The target tissue can be described as being affected by a system of nanoparticles encapsulated in a matrix substance. This system improves the retention stability of the medication in the tissue through enzyme interaction and intravascular solubilization. In the design process of nanoparticles, certain controls must be exercised. These controls involve the release pattern, dimensions, and surface characteristics, which determine the optimal site action and effective dosage scheme. A non-biodegradable polymeric framework (polyacrylamide, polymethyl-methacrylate, polystyrene) was used to develop the first nanoparticles. Pharmaceuticals or proteins can be held by the nanoparticles, such as in the case of (s). Bioactives are trapped within the polymer matrix as particulates or solid solutions, or they can be adsorbed physically or chemically to the particle surface. Nanoparticles can incorporate the medicine(s) during their preparation. In the realm of nano medicine, the connection to the system is not necessarily morphological or structural. This term is used in nanomedicine, an innovative branch of medicine.[2]

Need of Novel Drug Delivery System:-

Drug delivery systems can be based on physical and biochemical mechanisms. In physical mechanisms, or controlled drug delivery systems, osmosis, diffusion, erosion, dissolution, and electron transport are utilized. In biochemical mechanisms,

monoclonal antibodies (immunoglobulin), gene therapy, vector systems, polymer-drug adducts, and liposomes are used. The site of interest can be reached by the drug-loaded system through the aptitude known as targeting. Two primary mechanisms for achieving this contact and the desired drug release sites can be distinguished: (i) passive targeting and (ii) active targeting.

Drug delivery systems can optimize the duration of action, reduce the need for frequent dosages, control the site of release, and maintain consistent levels of drugs for patients. [3-5]

There are advantage of novel drug delivery system:

1. Offers protection from physical and chemical degradation.
2. Provides sustained delivery.
3. Improves tissue macrophages distribution.
4. enhances stability,
5. enhances pharmacological activity,
6. protects from toxicity.
7. increases bioavailability.
8. enhances solubility.[6]

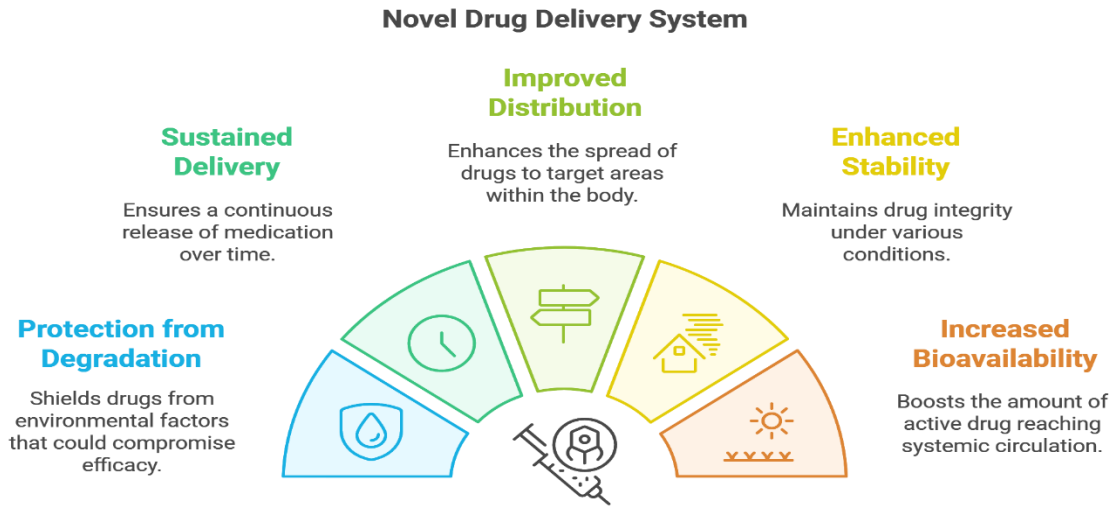


Figure:1

Diabetes mellitus

More than countless deaths occur each year worldwide due to Diabetes Mellitus (DM) being one of the major fatal (mortal) diseases.[7]

Insulin is most commonly delivered parenterally today, resulting in local hypertrophy and fatty deposits at injection sites. However, this method does not replicate the physiological hypoglycemic mechanism of insulin. [8,9]

Due to this, there is a improving interest in substitute ways to administer insulin, such as by the lungs, nose, or mouth. Specifically, holding insulin orally is thought to closely replicate how the body naturally releases insulin to the liver after it's absorbed from the digestive system, and the insulin-producing cells in the pancreas may be protected from attack by the immune system through this process. Insulin can alleviate patient suffering and improve drug effectiveness through oral delivery, maintaining its conformation throughout the gastrointestinal tract. [10]

The β cells are served as the main producer of the dipeptide hormone insulin, which regulates blood sugar levels. The A-chain and B-chain of insulin each consist of 21 and 30 amino acids, respectively. A disulfide bond forms between CysA7 and CysB7, and another between CysA20 and CysB19. The A-chain also forms an intra-chain disulfide bond between CysA6 and CysA11. [11]

Types of diabetes mellitus:

Type 1 and Type 2 diabetes mellitus are the two types of the condition.

1. In Type 1 diabetes mellitus (IDDM), insulin dependence is present.
2. In Type 2 diabetes mellitus (NIDDM), insulin independence characterizes.

1. **In Type 1 diabetes mellitus (IDDM), insulin dependence is present :**
   The β cells in pancreatic islets are cracked up, resulting in low or very low insulin levels in all type 1 diabetes cases. Most instances are caused by autoimmune antibodies that destroy β cells, which can be detected in blood. However, some cases are idiopathic, with no β cell antibodies present. Type 1 diabetes is less common and has a low degree of genetic susceptibility.
2. **In Type 2 diabetes mellitus (NIDDM), insulin independence characterizes:**

The onset of Type 2 DM is typically late, and there is a high genetic susceptibility. B cell number is not significantly reduced or damaged. Insulin levels in the blood may be low, normal, or high. Anti-β-cell antibodies are not detected. Approximately, over 90% cases exhibit this condition. causation may be :

- The abnormality in the gluco-receptors of β cells results in their excessive response at normal.

- Insulin receptors decrease in mass, leading to a decline in peripheral tissues' sensitivity to insulin. Separate individuals present insulin intransigence, being hypertensive and hyperinsulinemic yet normoglycaemic. An excess of hyperglycemic hormones, such as glucagon, results in a relative insulin deficiency. [12]

The incidence and prevalence of diabetes in India have alarmingly increased, leading the Globe Health Organization (WHO) to label it the Diabetic Capital of the world. Studies indicate that an enhanced awareness among patients regarding the condition and its complications significantly improves treatment compliance and reduces diabetes-related issues. People with diabetes who visit our clinic were aimed to be assessed in terms of their understanding of various topics related to preventing and treating diabetes-related issues.[13]

Drugs for diabetes mellitus (DM) multiply on the market, but none provide a complete and effective treatment due to their side effects, such as nausea, vomiting, and gastrointestinal irritation. These drugs ultimately lead patients to become non-compliant, necessitating highly skilled medical knowledge. [14,15]

Stable and non-invasive medication delivery methods with controlled release could be more advantageous for Pharmaceutical Investigators. They have primarily focused on overcoming the physical and biological barriers that hinder drugs from reaching their therapeutic targets, the specific site must be reached exactly and safely with the drug for the scheduled duration of time to ensure controlled and sustained release, novel drug delivery systems (NDDSs) have become more popular recently because they offer clear benefits, such as less frequent dosing, better absorption, protection from stomach acids, targeted delivery to specific areas, and fewer side effects. Numerous experiments, conducted in vitro, ex vivo, and in vivo around the world, strongly recommend that NDDSs are a new and promising focus for treating serious conditions and diseases.[16]

Insulins:

Insulin, a peptide hormone, is produced by the beta cells in the Langerhans islets of the pancreas. This hormone regulates carbohydrate, fat, and protein intake by allowing glucose access to fat, liver, and skeletal muscle cells in the circulation. Insulin activity in the body becomes unacceptable when the beta cells, which produce insulin, are damaged, resulting in Diabetes. The invention of insulin has been a ground-breaking development in treating and appreciating diabetes. [17,18]

History of insulin : In 1923, just two years after Banting and Best found out insulin, Eli Lilly, working with the university of Toronto, superveneed in producing insulin on a large scale. This achievement led to substantial profits for the company. [19,20]

The world's first recombinant DNA drug, Humulin (human insulin), was approved by the UK, US, West Germany, and the Netherlands in 1982, for insulin to be isolated from animal sources, primarily bovine and porcine pancreata, for the first 60 years after its discovery. The formulation and amino acid structure of the drug were modified, resulting in an improvement in its effectiveness rather than just focusing on its purification. [21]

The amino acids at positions 28 and 29 of the B-chain in human insulin, originally B1996 and B29), were changed to Lys and Pro, respectively, resulting in the creation of insulin lispro (Humalog) by Eli Lilly and company in 1996. [21,22]

Different types of insulin are used in medical practice in the 21st century, each having a unique amino acid sequence. Insulin produced from human, bovine, porcine sources, and synthetic analogues of human insulin differ in composition. Bovine insulin is rarely used in production nowadays, as most insulin is produced using recombinant DNA technology in bacteria or yeast. [23]

Insulin formulations that do not require invasive methods, such as non-invasive insulins and colon-transformed insulin, are being developed following the FDA's approval of Pfizer's inhaled insulin product Exubera in 2006, despite its failure.[24]

The FDA and European Medicines Agency (EMA) have approved two new developments in the area, which have been improved by Novo Nordisk Limited. Tresiba, the longer-acting insulin, has been approved by both the FDA and EMA for injections. Fiasp, the ultra-fast acting insulin, has been approved by the EMA for part injections.[25-27]

Fiasp works more quickly and consistently than traditional insulin as part (like Novorapid or NovoLog) because it contains two additional ingredients, nicotinamide and arginine. These extra components help Fiasp mimic the natural release of insulin in the body more closely. [28]

Year	Event
1923	Eli Lilly, in collaboration with the University of Toronto, begins large-scale insulin production.
1982	Humulin, the first recombinant DNA drug, is approved for use.
1996	Insulin lispro (Humalog) is introduced, with modified amino acid sequences for improved effectiveness.
21st Century	Various insulin types, including human, bovine, porcine, and synthetic analogues, are used in medical practice.
2006	FDA approves Pfizer's inhaled insulin product Exubera, though it later fails in the market.
Recent Years	Novo Nordisk develops and receives FDA and EMA approval for Tresiba (longer-acting insulin) and Fiasp (ultra-fast-acting insulin).

Mode of action of insulin :

Figure 2 depicts the effects of insulin: It inhibits glycogenolysis, ketogenesis, gluconeogenesis, proteolysis, and lipolysis. The hormone also facilitates the uptake of glucose by muscles and tissues, the process of glycolysis, glycogen synthesis, and protein synthesis. The tyrosine kinase activity of insulin's receptor is activated, resulting in regulation of glucose in

the blood. This activation leads to the receptor phosphorylating itself (autophosphorylation) and attracting signaling proteins like insulin receptor substrates (IRS). The PI-3-kinase pathway is stimulated, resulting in the phosphorylation and dephosphorylation reactions triggered by proteins, which in turn cause various metabolic and growth effects of insulin, which in turn moves glucose transporters like GLUT4 to the cell surface. This process is crucial for allowing glucose to enter cells, particularly in muscles and fat tissue. [29]

The administration of insulin through a SC route is conventionally chosen, with insulin units marked on the route. Insulin injections can be rapid, short, intermediate, or long-acting and may be given individually or mixed in the same syringe. Syringes, available in sizes of 0.NUM and 2 ml, come with varying needle lengths. Insulin units should not be used more than once to prevent infection from blood-borne viruses. Humilin is offered in concentrations of 100 units per milliliter (U-100) and 500 units per milliliter (U-500), with one unit approximating 36 micrograms of insulin. [30]

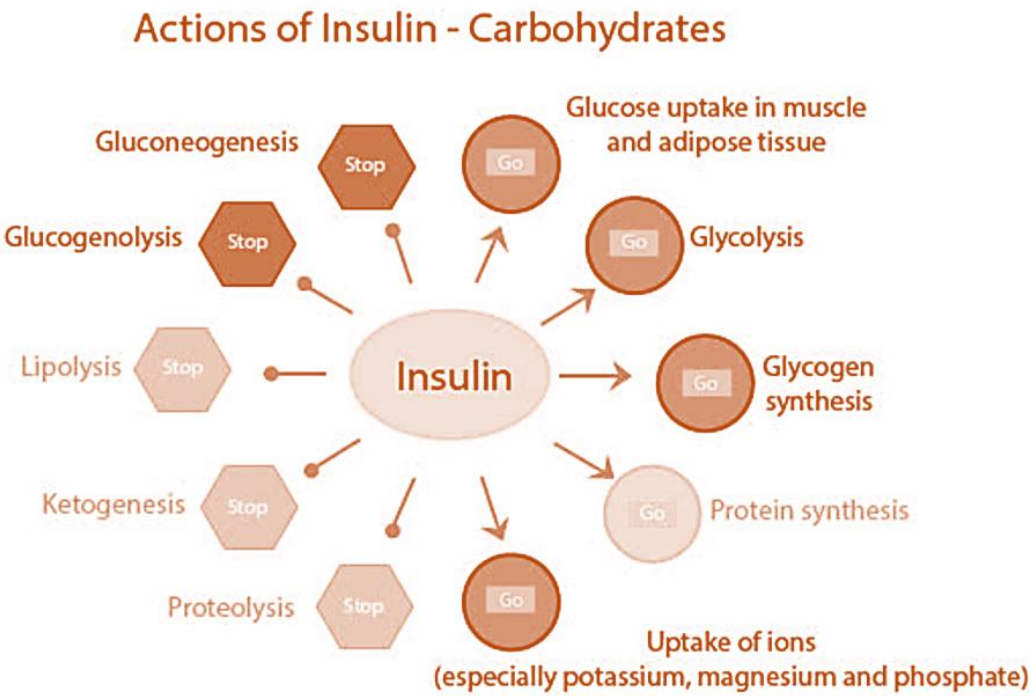


Figure: 2

Structure of insulin :

Pro-insulin is initially produced as a molecule and later transformed into insulin. The A-chain and B-chain of insulin are each composed of 21 and 30 amino acids, respectively, making up the total hormone with a molecular weight of approximately 6000. These two chains are connected by two disulphide bonds. Before its release by the pancreas, insulin exists as pro-insulin. The C-peptide links the insulin A and B chains in pro-insulin, The molecular weight is 9000 for a molecule consisting of 31 amino acids. Most insulin supplies are sourced from the pancreas of cattle, despite insulin now being synthesizable in laboratories. [31]

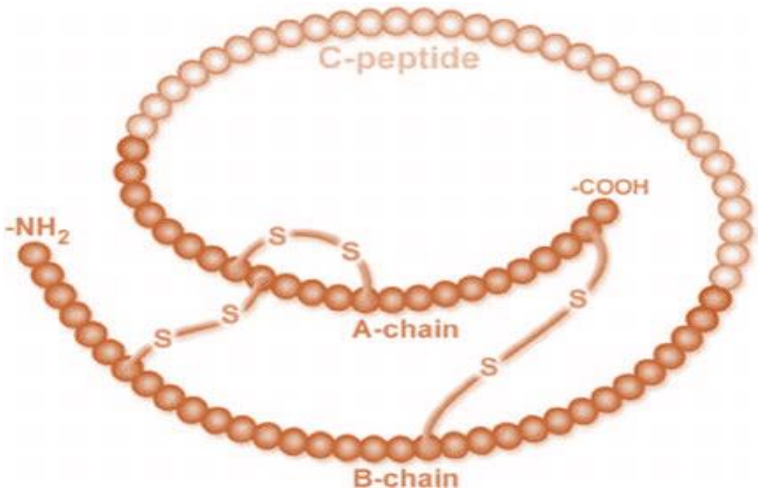
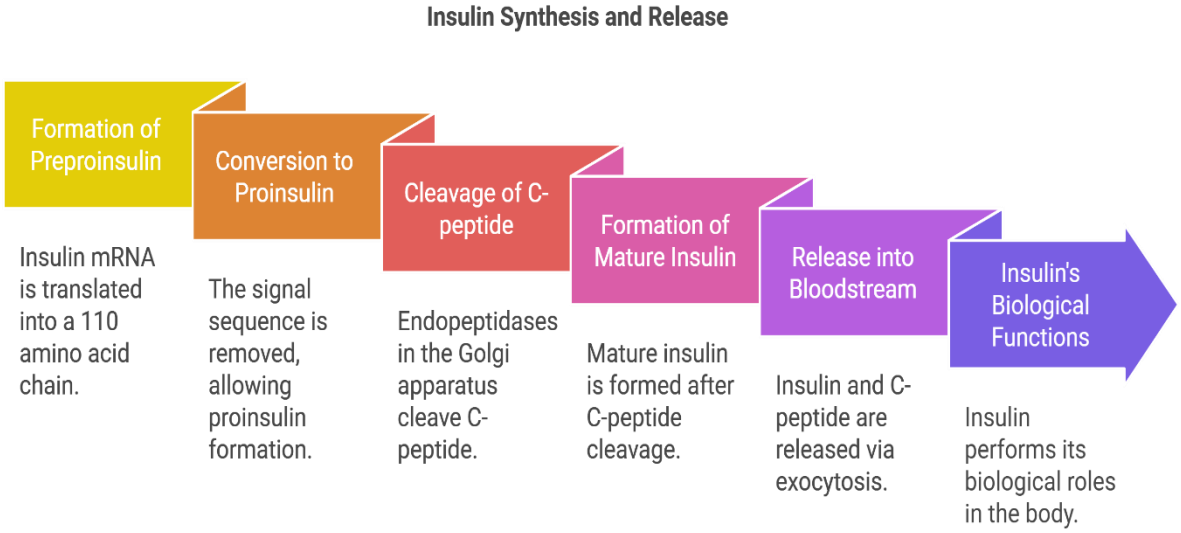


Figure 3: Structure of insulin

Synthesis of insulin :

The single molecule of preproinsulin, which is a biosynthetic product, is formed when insulin mRNA is converted into a chain of 110 amino acids. This precursor undergoes proteolytic processes between cellular compartments, resulting in the formation of insulin. The signal sequence of 24 amino acids is removed from a structure within the endoplasmic reticulum, allowing it to fold and bind together, forming the proinsulin structure. The specific endopeptidases in the golgi apparatus expose proinsulin, allowing the C peptide (consisting of 33 amino acids) to be cleaved and inducing the formation of mature insulin. C-peptide and insulin are released from the pancreatic cells into the bloodstream during the process of exocytosis. Insulin performs its biological functions in the body, but C-peptide does not. However, it is useful as an indicator for measuring insulin secretion. [32-34]



(Figure 4: Insulin synthesis & release)

Insulin receptor:-

The alpha-beta subunits of the insulin receptor, synthesized as a single polypeptide, are the ones that form part of the transmembrane signal proteins of the tyrosine kinase family. After glycosylation and splitting, one chain is developed and held together by disulfide bonds. The hydrophobic portions of each subunit are located within the plasma membrane. The alpha subunit of the humilin receiver has a binding site for humilin. When insulin attaches to this site, the beta subunit's cytoplasmic domain becomes active as a tyrosine kinase. Insulin secure to the alpha portions provokes the tyrosine kinase venture of the beta portion. (Figure: 5) [35]

The tyrosine unit in these structures induces auto phosphorylation, leading to the communication of changes to beta subunits. Humilin-site substratum (IRS-1 and IRS-2)) become activated, in turn activating phosphorylated phosphatidylinositol-3 kinase (PI3K) and mitogen-inspirited protein kinase (MAPK) passageway. Eventually, insulin influences the Target tissues through these activated signaling cascades. [36-38]

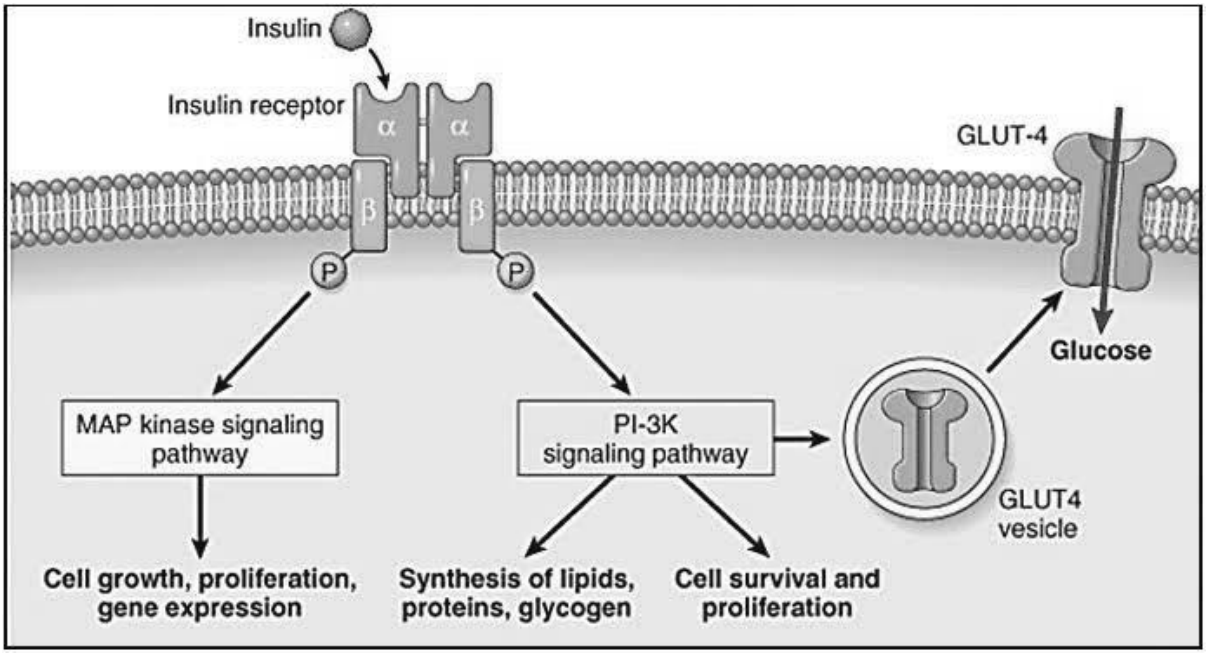


Figure 5: Receptor of insulin

Function of insulin:
Glucose homeostasis is maintained by insulin through keeping the plasma glucose value in a maximum range throughout the day. The major effects of insulin are:

i. Glucose is activated for oxidation and storage as glycogen in the liver. It is also converted into triglycerides and undergoes protein synthesis.
ii. The cells take in glucose and store it as glycogen in muscle tissue.
iii. Triglycerides are formed and stored in fat tissue through the process of glucose uptake and conversion. [39,40]

Stability of Insulin:
Insulin's structure is very sensitive, and components affect its stability through attachment to processing elements. Proteins can undergo various processes leading to their breakdown, including erosion, photolyzation, disulfide clambering, asparaginase, grouping, sleet, uncouple, and collapsed. Oxidation, for instance, happens when amino acids in proteins react with oxygen radicals, which can change how the protein folds, how its subunits associate, and lead to aggregation or fragmentation. These amino acids, including methionine, cysteine, histidine, tryptophan, and tyrosine, are prone to undergo deamidation, during which an amide group is removed.
Insulin is subjected to isomerization, racemization, and reduction in solution. In acidic conditions, extensive deamidation occurs at AsnA21. Conversely, in neutral solution, deamidation primarily affects AsnB3. Factors influencing insulin stability must be closely monitored to maintain the product's safety and efficacy. One such factor is light degradation. Exposure to light can cause oxidative damage to insulin proteins, altering their structure and potentially affecting their long-term stability, effectiveness, or causing unintended immune responses. The protein can be affected by light, initiating a series of molecular episode that carry on to act upon it, in spite of the luminous source has been displeased. This process depends on the degree of potency transferred to the protein and the residence of recyclable oxygen. The substances used in making and storing protein-based medicines can impact how the proteins degrade over time. Peroxide can be introduced into medicines through the use of excipients such as polysorbates and polyethylene glycols. These substances can cause oxidation. Likewise, containers and closures made of materials like plastics and rubber can also release peroxide. The importance lies in exercising care with the materials and methods used during the manufacturing and storage of medicines to prevent oxidation.
Mechanical stresses such as shaking, stirring, pipetting, and pumping by tubes during manufacture and storage can lead to the problem of protein aggregation. The aggregation process is initiated through these methods of agitation. Freezing and thawing processes also contribute to the improvement of protein aggregation. During manufacturing, Microaggregated particles are formed and can grow larger over time while being stored. Mechanical stress and ultrasound exposure can lead to protein breakdown. The increase in stress leads proteins to more readily adhere to interfaces between air and water or water and organic solvents, thereby enhancing hydrophobic interactions and promoting further aggregation. Equipment used in preparing water/oil emulsions influences protein stability. [70,71]

Insulin Delivery:
General to Novel Approaches: – In the early 19th century, a device for subcutaneous insulin delivery was developed. This innovation, known as the 'I-Port,' combined an injection port and an inserter into one complete set, eliminating the need for multiple skin punctures for each dose and the device helped insulin-requiring patients with needle phobia to gain effective glycemic control. [40]
The insulin pen, which is less painful and more convenient than previous methods, can be reused and easily integrated with vials and syringes. [41]
Insulin pump therapy was come across in 1976 and it was used as a substitute of long acting insulin; the device can be utilized to deliver variable amount of insulin to the patient even just after consumption of meals. [42, 43]
The Threshold Suspend (TS) system is an advanced feature added to insulin pumps. It includes a glucose sensor that monitors blood sugar levels and automatically stops insulin delivery if it detects a risk of hypoglycemia. The system prevents severe drops in blood sugar during the night, reducing the severity and shortening the duration of nocturnal hypoglycemia by up to 2 hours. If the patient does not take action with a low glucose alarm, the system postpones the delivery of insulin. [44,45]

Novel approaches in comparison to the common approaches of insulin delivery includes:

I. Inhaled insulin delivery.
II. Oral insulin delivery.
III. Colonic insulin delivery.
IV. Nasal insulin delivery.
V. Buccal insulin delivery.
VI. Transdermal insulin delivery.
VII. Intra-peritoneal insulin delivery.
VIII. Ocular insulin delivery.
IX. Rectal insulin delivery.
X. Vaginal insulin delivery. Etc.

Oral insulin:

In comparison to other routes, oral routes are the most selected, suitable and patient friendly and having some advantages like as maximum compliance, greater convenience, and decreased risk of cross infection and needle stick injuries. [46]

Three approaches can be taken to address the issues with oral insulin delivery: 1. By modifying the insulin's physicochemical properties, such as increasing its lipophilicity. 2. Through cross-linking with macromolecules. 3. By employing carrier systems. These methods for delivering oral insulin involve the use of liposomes, microsphere, nanoparticles, mouth dissolving strips, and sprays that exploit both the oral and pulmonary routes. [47]

Next generation efficient therapies may help enhance the status of life of diabetic patients, particularly those with humilin-dependent Diabetes Mellitus. [48]

Importance of oral insulin:

With the present understanding of diabetes, the importance of the hepatic route of delivery for physiological reasons has added to the stress of oral delivery, which earlier was mainly due to convenience and avoidance of needles. [49]

When insulin is injected directly into the bloodstream, it bypasses the normal route through the liver. Normally, insulin released by the pancreas first goes to the liver, where it helps regulate blood sugar before reaching the rest of the body. However, with injectable insulin, it travels directly to the peripheral tissues (like muscles) and doesn't pass through the liver first. As a result, the liver gets exposed to lower levels of insulin compared to what would occur naturally in people without diabetes. [50]

Significant reasons for clinical inertia and failure to reach target glycemic goals have long been resistance to injectable insulin. However, oral insulin, free from the fear and discomfort associated with insulin injections, could bring this drug back into prominence as first-line medical treatment. [51-55] However, Oral administration is considered a more effective method because it's cost-efficient, reliable, and avoids the need for injections. [56]

Oral delivery of insulin results in high concentrations in the portal vein, without sustained peripheral hyperinsulinemia, which is linked to neuropathy and retinopathy. [57] Oral insulin is beneficial in that it is delivered directly to the liver and functions similarly to insulin naturally produced in the body, distinguishing it from subcutaneous insulin injections. [58-60] The conventional dynamics of endogenous insulin release fail to result in long-lasting glycemic management for patients. [61]

Some barriers to oral insulin absorption include:

The oral medications undergo a sequence of hurdles in the gastrointestinal tract for insulin absorption, mainly enzymatic, manual, and synthetic in nature. The pharmaceuticals are processed by GIT, resulting in their adherence to the muculent layer, traversing the intestinal epithelium, and entering the circulation. The stomach undergoes a transition in pH value, ranging from (2.5) to (7.5), which creates a chemical barrier that reduces insulin bioavailability by more than 99 %. This instability of insulin in the GIT leads to significant changes in pH values during the epithelial penetration process. In the GIT, enzymes primarily break down proteins. The stomach houses pepsin, while the small intestine is where pancreatin with trypsin, chymotrypsin, and elastase reside. Aminopeptidases are located in the striated border membrane, and certain enzymes can be found in the cytosol. The mucus layer of the small intestine hinders the transport of insulin molecules due to its anionic charge. Insulin that manages to survive proteases is subsequently broken down by the liver's enzymes. [62,63]

Sr. No.	Physiological Barriers	Constitution	Mechanisms to Overcome
1	Digestive enzyme degradation	Chymotrypsin, carboxypeptidase, elastase, trypsin, and pepsin	Hydrophobic effect, shielding effect, and using a gastro-resistant framework
2	Degradation caused by stomach acid	pH 1-2 gastric acid	Coated by acid-resistant polymer, and pH responsiveness
3	Retention by the barriers of the mucus layer	Electrolytes, glycoproteins, lipids, proteins, and water	The mucus-inert electroneutral surface and charge-reversing
4	Intestinal epithelial cell barrier retardation	Apical endocytosis, basolateral to the circulation, degradation of lysosomes, and tight junction	Enhancer of permeation, raise the level of active transportation

Table 1 The mechanisms and barricades of oral insulin administration impose physiological challenges.

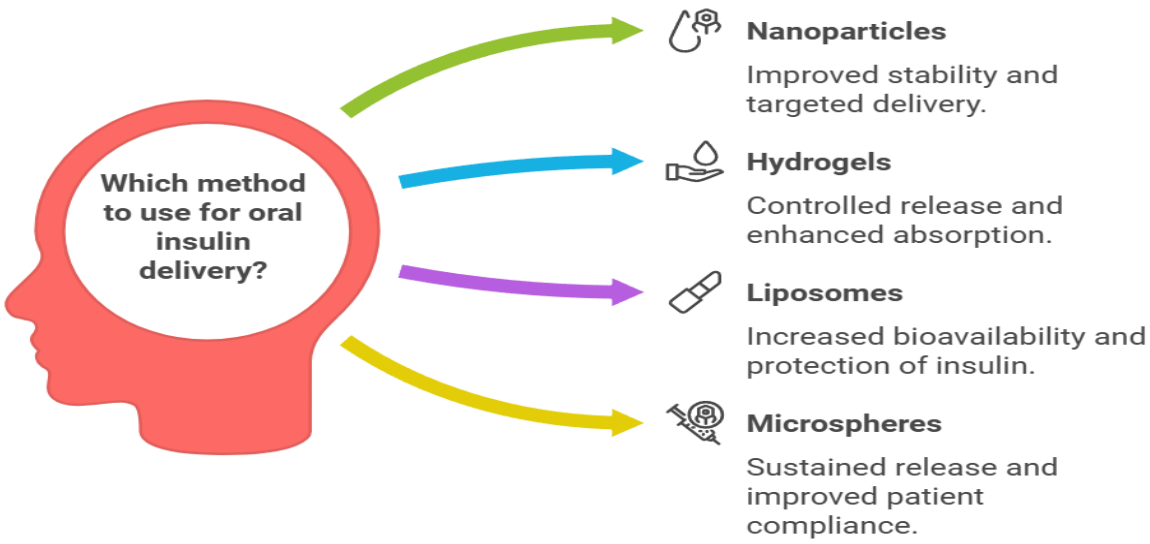
Approaches of Oral insulin delivery:

Oral ingestion insulin results in improved glucose homeostasis by closely mimicking the anatomic process of insulin in the body and having a huge plane area in the bowels. [64,65]

The oral route restricts the immersion of proteins like humilin by the epithelial cells in the GIT. [66]

Efforts to deliver insulin orally have faced challenges in achieving effective pharmacological action and maintaining stability. Oral insulin delivery has been explored through various methods by researchers, including nanoparticles, hydrogels, liposomes, and microspheres. [67]

Mucosal transport of insulin has been found to be potentially useful through the formation of chitosan (CS) micro- and nanospheres.[68] Various approaches of oral insulin delivery were summarized (outline) in Fig.6



(Fig. 6: Approaches Oral insulin delivery)

Benifits of oral insulin:

1. Compliance is ensured by the patient.
2. It is convenient for the patient.
3. The process is painless for the patient.
4. Self-medication is easier for the patient.
5. The patient can avoid weight gain.
6. The danger of hypoglycemic incidents, immune responses, and other issues associated with SC route is decreased.
7. The method is cost-effective for the patient. [69]

Conclusion:

Novel drug delivery systems have improved the efficacy, added safety layers, and enhanced patient compliance in diabetes management. These approaches to oral insulin delivery, which offer more physiological and patient-friendly methods compared to traditional subcutaneous injections, hinge on various forms of oral insulin delivery systems such as nanoparticles, hydrogels, liposomes, and microspheres. In diabetes patients, oral insulin delivery leads to improved glycemic control, fewer hypoglycemia episodes, and enhanced quality of life. Oral insulin's delivery challenges require further research and development for it to become a viable treatment option for diabetes.

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