

Breaking Barriers: The Development of Oral Insulin Therapy

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Abstract: Diabetes mellitus (DM) is a prevalent metabolic disorder with significant mortality rates, prompting the need for effective management strategies. Current insulin therapies primarily rely on parenteral administration, which poses challenges such as patient discomfort and local tissue complications. This review explores the development of oral insulin therapy as a promising alternative, aimed at enhancing patient compliance and mimicking physiological insulin release. We discuss the mechanisms of diabetes, the hurdles faced in oral insulin delivery, and recent advancements in formulation technologies. Key innovations include nanoparticle delivery systems, enteric coatings, and peptide conjugates, which aim to improve insulin stability and absorption in the gastrointestinal tract. The potential of polymeric nanoparticles, particularly, offers significant benefits in oral insulin administration, paving the way for more effective diabetes management solutions.

Keywords:- Diabetes Mellitus (DM), Therapy, Insulin, Polymeric Nanoparticles, Bioavailability, Controlled Release, Patient Compliance, Solid Lipid Nanoparticles, Resistance.

INTRODUCTION

Diabetes mellitus (DM) is one of the most widespread fatal diseases, responsible for more than 4 million deaths each year worldwide.

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by high levels of blood glucose (hyperglycemia) due to either insufficient insulin production, ineffective insulin action, or both.

Insulin, a hormone produced by the pancreas, regulates glucose metabolism by facilitating the uptake of glucose into cells for energy production or storage as glycogen. When this mechanism fails, it leads to persistently elevated glucose levels in the blood, resulting in various acute and chronic complications.

There are three main types of diabetes:

- Type 1 Diabetes Mellitus (T1DM): An autoimmune condition where the immune system mistakenly attacks and destroys the insulin-

producing beta cells of the pancreas. As a result, the body produces little to no insulin.

- Type 2 Diabetes Mellitus (T2DM): A more common form of diabetes, often associated with obesity and insulin resistance. In this case, the pancreas may still produce insulin, but the body's cells do not respond effectively to it, leading to hyperglycemia. Over time, insulin production may decrease.
- Gestational Diabetes: Occurs during pregnancy when the body cannot produce enough insulin to meet the increased demands, leading to elevated blood glucose levels. This form of diabetes usually resolves after childbirth but increases the risk of developing type 2 diabetes later in life.

Mechanism of Diabetes Mellitus

Type 1 Diabetes: Autoimmune destruction of pancreatic beta cells → Lack of insulin → Hyperglycemia.

Type 2 Diabetes: Insulin resistance + Impaired insulin secretion → Insufficient insulin action → Hyperglycemia.

Gestational Diabetes: Pregnancy-induced insulin resistance → Inadequate insulin production → Temporary hyperglycemia.

- Mechanism of Secretion of Insulin :-

Insulin is a vital hormone that plays a crucial role in regulating blood glucose levels and maintaining metabolic homeostasis. It is produced and secreted by the beta cells of the islets of Langerhans in the pancreas. Insulin allows cells to absorb glucose from the bloodstream and either utilize it for energy or store it as glycogen for future use. This hormone also influences lipid and protein metabolism, making it essential for overall metabolic regulation.

The most common route of administration remains parenteral delivery of insulin, which causes local fatty deposits and hypertrophy at injection sites, and this

pathway cannot replicate insulin's natural hypoglycemic action.

This is why there is interest in and work being done on other administration routes, such as oral, nasal, and pulmonary. Specifically, oral insulin treatment is thought to shield pancreatic cells from autoimmune damage by simulating the physiology of endogenous insulin produced in the liver following gastrointestinal (GI) absorption.

Although insulin must keep its structure through the gastrointestinal tract (GIT), oral insulin delivery also lessens patient discomfort and improves drug

administration convenience. The underlying intestinal epithelial membrane barrier in the GIT, the existence of a mucus layer, and enzyme breakdown are the main obstacles to effective oral insulin delivery.

Oral insulin therapy is a method of delivering insulin via the oral route rather than through traditional injection. While it offers the potential for improved patient compliance and convenience, its development has faced significant challenges.

Research into oral insulin formulations, such as oral insulin capsules and coated tablets, has seen progress, but many products remain in the experimental stage.

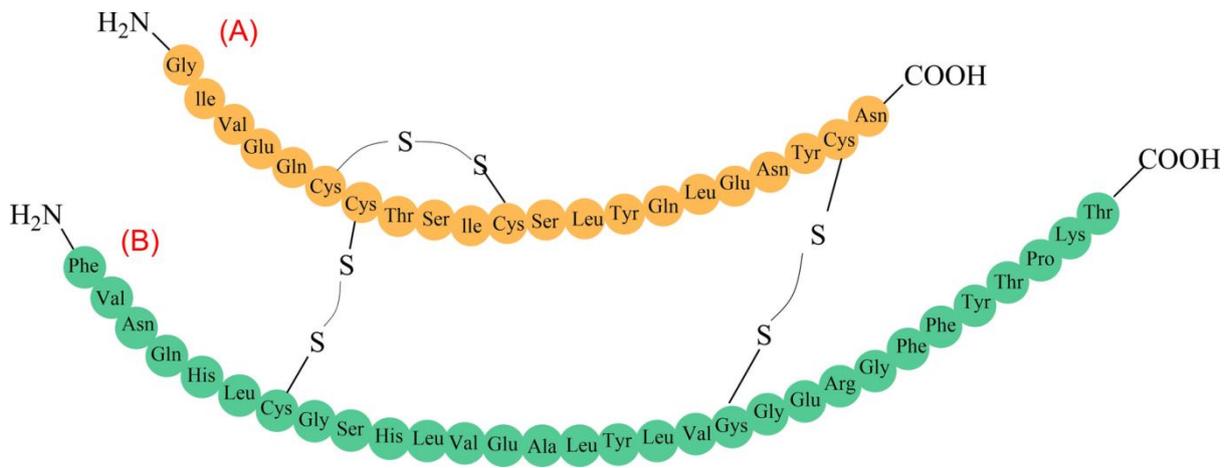


Fig no.1:- Schematic representation of human insulin. Insulin is a 51 amino acid peptide.

OVERVIEW

Recent developments in oral insulin formulations have focused on improving absorption and stability.

Here are some notable advancements:

1. **Nanoparticle Delivery Systems:** Researchers are exploring the use of nanoparticles to enhance the stability and absorption of insulin in the gastrointestinal tract.
2. **Enteric Coatings:** New enteric-coated formulations protect insulin from stomach acid and release it in the intestine, where absorption is more effective.
3. **Peptide Conjugates:** Some studies are investigating the use of peptide conjugates that can facilitate insulin transport across the intestinal wall.
4. **Combination Therapies:** Combining oral insulin with other oral antidiabetic agents is being researched to improve overall glycemic control.

One of this i.e Nanoparticle Delivery Systems Future developments may focus on tailoring nanoparticle systems to individual patient needs,

optimizing dosing and release profiles based on specific conditions.

Nanoparticle delivery systems for oral insulin formulations represent an innovative approach to enhance the stability and absorption of insulin in the gastrointestinal tract.

Nanoparticle delivery systems aim to protect insulin from degradation, facilitate its absorption, and control its release profile. These systems can be designed to enhance bioavailability and ensure targeted delivery to the site of action.

Factors Influencing Nanoparticle Design :-

- **Particle Size:** Ideally, nanoparticles should range from 10 to 1000 nanometers. Smaller particles generally improve absorption due to a higher surface area-to-volume ratio.
- **Surface Charge:** The zeta potential influences the stability of nanoparticles in suspension and their interactions with biological membranes. A positive or neutral charge can enhance absorption through cellular membranes.
- **Biocompatibility:** Materials used to fabricate nanoparticles should be non-toxic and

biocompatible to avoid adverse reactions in the body.

- **Degradation Rate:** The rate at which nanoparticles degrade should be controlled to ensure that insulin is released at the desired rate and time.
- **Insulin Stability:** Formulations should maintain insulin's structural integrity and activity during storage and after oral administration.

Techniques for Nanoparticle Preparation

Several techniques can be employed to create nanoparticles for oral insulin delivery:

- **Solvent Evaporation:** Involves dissolving the polymer in a volatile organic solvent, followed by evaporation to form nanoparticles. This technique can encapsulate insulin effectively.
- **Emulsion Solvent Diffusion:** In this method, an oil-in-water emulsion is formed, allowing the solvent to diffuse out and resulting in the formation of nanoparticles.
- **Electrospinning:** A high-voltage process that produces nanofibers or nanoparticles by drawing a polymer solution into fine fibers, which can encapsulate insulin.
- **Coacervation:** This technique involves the separation of a liquid phase from a polymer solution to form nanoparticles. It can be useful for creating core-shell structures.
- **Nanoprecipitation:** A method that involves mixing a polymer solution with a non-solvent to induce the formation of nanoparticles through precipitation.

Types of Nanoparticles Used

- **Liposomes:** Spherical vesicles that can encapsulate insulin and protect it from degradation. They can also enhance absorption through their lipid bilayers.
- **Polymeric Nanoparticles:** Made from biodegradable polymers such as PLGA (poly(lactic-co-glycolic acid)), these can encapsulate insulin and allow for controlled release.
- **Solid Lipid Nanoparticles (SLNs):** These combine the benefits of lipid-based and polymeric nanoparticles, providing a controlled release of insulin while improving stability.
- **Chitosan Nanoparticles:** Derived from chitosan, a biopolymer, these nanoparticles can enhance insulin absorption due to their mucoadhesive

properties and ability to open tight junctions in the intestinal epithelium.

- **Gold Nanoparticles:** Although primarily used for imaging and diagnostics, gold nanoparticles can also be utilized for drug delivery, including insulin.

While having look to this all we Polymeric nanoparticles represent a significant advancement in the development of oral insulin formulations, addressing some of the key challenges associated with insulin therapy. Continued research and development in this area hold promise for more effective and patient-friendly diabetes management options.

Composition and Structure

Polymeric nanoparticles are typically made from biodegradable polymers, such as:

- **Poly(lactic-co-glycolic acid) (PLGA):** Known for its biocompatibility and controlled degradation, PLGA is widely used for drug encapsulation and release.
- **Chitosan:** This natural polymer offers mucoadhesive properties, which can enhance insulin absorption in the gut.
- **Polyethylene glycol (PEG):** Often used to modify the surface of nanoparticles, PEG can improve stability and reduce immunogenicity.

Mechanism of Action :-

Polymeric nanoparticles protect insulin from the harsh acidic environment of the stomach and enzymatic degradation. They facilitate the following processes:

- **Encapsulation:** Insulin is encapsulated within the polymer matrix, preventing premature release and degradation.
- **Controlled Release:** The degradation of the polymer matrix allows for a sustained release of insulin over time, which can help in maintaining stable blood glucose levels.
- **Enhanced Absorption:** Certain polymers can promote transport across intestinal barriers, improving bioavailability.

Preparation Techniques

Several methods can be used to fabricate polymeric nanoparticles:

- **Solvent Evaporation:** In this technique, a polymer is dissolved in an organic solvent along with

insulin, and then the solvent is evaporated to form nanoparticles.

- Nanoprecipitation: This involves mixing the polymer solution with a non-solvent, causing the polymer to precipitate and form nanoparticles that encapsulate insulin.
- Emulsion Techniques: These methods involve forming an emulsion of oil and water to encapsulate insulin within the polymer.

Benefits of Polymeric Nanoparticles for Oral Insulin

- Stability: They protect insulin from degradation in the GI tract, enhancing its stability and efficacy.
- Bioavailability: Improved absorption rates can lead to better therapeutic outcomes.
- Controlled Release: They provide a sustained release profile, minimizing peaks and troughs in insulin levels.
- Reduced Side Effects: Targeted delivery can potentially reduce systemic side effects associated with insulin therapy.

Challenges and Considerations

- Scale-up: Developing methods for large-scale production of polymeric nanoparticles while maintaining quality and uniformity can be challenging.
- Regulatory Hurdles: Ensuring safety and efficacy through regulatory pathways can be complex and time-consuming.
- Patient Acceptance: As with any new delivery system, patient acceptance and compliance will play a significant role in the success of oral insulin formulations.

Recent Advances

Research continues to explore innovative polymeric materials and combinations that enhance the performance of insulin-loaded nanoparticles. Some trends include:

- Smart Polymers: Polymers that respond to environmental stimuli (like pH or temperature) for targeted release.
- Combination Therapies: Using polymeric nanoparticles to co-deliver insulin with other agents, such as peptides or oral hypoglycemics, for synergistic effects.



Fig no.2:- Schematic diagrams showing the unique features of PNPs

PNPs have significant potential for oral insulin administration. In recent years, many nanoparticle systems for oral insulin administration have been developed, including natural polymer nanocarriers and synthetic porous polymer nanocarriers. While some are promising, but their long-term efficacy in larger animals and humans must be proven. The majority of the better nanocarrier systems are made from natural small-molecular polymers, but their pore size cannot be controlled.

Some merits of oral insulin therapy from a future perspective:

1. Improved Patient Compliance: Oral administration is generally more acceptable to patients than injections, potentially increasing adherence to insulin therapy.
2. Mimics Physiological Insulin Release: Oral insulin can more closely replicate the natural secretion of insulin by the pancreas, enhancing glycemic control.
3. Reduced Injection-Related Complications: Minimizing the need for injections can decrease the risk of injection-site complications, such as lipodystrophy and discomfort.

4. Convenience: Oral therapy simplifies the insulin administration process, making it easier for patients to integrate into their daily routines.
 5. Potential for Combination Therapies: Oral insulin can be developed in conjunction with other oral antidiabetic agents, offering a comprehensive approach to managing diabetes.
 6. Enhanced Stability and Bioavailability: Innovations in formulation technologies, such as nanoparticle systems, can improve insulin stability in the gastrointestinal tract and enhance absorption.
 7. Customizable Delivery Systems: Future developments may allow for personalized insulin delivery systems that can be tailored to individual patient needs, optimizing dosing and release profiles.
 8. Minimized Stigma: Oral therapy may reduce the stigma associated with diabetes management, making it less conspicuous and more socially acceptable.
 9. Broader Application: The potential to use oral insulin in various patient populations, including those with type 1, type 2, and gestational diabetes, could lead to more inclusive treatment options.
 10. Research and Innovation Opportunities: Continued advancements in drug delivery technologies and materials science will foster ongoing research and innovation in oral insulin formulations, driving improvements in efficacy and safety.
6. Regulatory Challenges: Gaining regulatory approval for new oral insulin formulations can be lengthy and complex, delaying availability for patients.
 7. Patient Education: Patients may require extensive education on the use of oral insulin, including understanding its differences from injectable forms, which could impact compliance.
 8. Manufacturing Limitations: Producing oral insulin formulations that maintain stability and efficacy during storage and transit can pose significant manufacturing challenges.
 9. Cost Considerations: The development and production of innovative oral formulations may lead to higher costs, potentially making them less accessible to patients.
 10. Cultural Acceptance: Some patients may still prefer traditional injection methods due to familiarity or a lack of trust in newer delivery systems.

Some demerits of oral insulin therapy to consider:

1. Gastrointestinal Degradation: Insulin is sensitive to the acidic environment of the stomach and digestive enzymes, which can lead to significant degradation before it reaches systemic circulation.
2. Variable Absorption: Oral insulin may exhibit inconsistent absorption rates due to differences in gastrointestinal motility and other physiological factors, complicating blood glucose control.
3. Limited Formulation Availability: Many oral insulin formulations are still in experimental stages, with few approved options available on the market.
4. Dosing Complexity: Determining the appropriate dosage for oral insulin can be challenging, particularly when accounting for varying absorption rates.
5. Potential for Increased Hypoglycemia Risk: If absorption is unpredictable, patients may

experience fluctuations in insulin levels, increasing the risk of hypoglycemia.

CONCLUSION

The advancement of oral insulin therapy holds great promise in transforming diabetes management by improving patient compliance and mitigating the drawbacks of traditional parenteral delivery methods. Nanoparticle delivery systems, particularly polymeric nanoparticles, represent a significant leap forward in addressing the challenges of insulin stability and absorption in the gastrointestinal tract. While substantial progress has been made in the development of innovative formulations, further research is essential to validate their long-term efficacy and safety in clinical settings. Overcoming regulatory hurdles and ensuring patient acceptance will be crucial for the successful implementation of oral insulin therapies, ultimately enhancing the quality of life for individuals living with diabetes.

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