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Ethosome loaded Repaglinide and Microneedling:- Novel approach for diabetes Mellitus Treatment

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Abstract:- Diabetes mellitus, a chronic metabolic disorder, poses significant health challenges worldwide, necessitating innovative treatment strategies. This study explores a novel approach combining ethosome-loaded repaglinide with microneedling to enhance the drug's transdermal delivery and therapeutic efficacy. Ethosomes, lipid-based carriers characterized by their enhanced permeability, are employed to encapsulate repaglinide, a widely used antidiabetic agent. The microneedling technique is introduced to create microchannels in the skin, facilitating deeper penetration of ethosomes and improving bioavailability. In vitro and in vivo evaluations demonstrate that this combination significantly enhances the drug's absorption and pharmacological effect compared to conventional delivery methods. This dual approach not only optimizes repaglinide delivery but also holds promise for improving patient compliance by minimizing systemic side effects and enabling localized treatment.

Key Words :-

- Ethosome
- Repaglinide
- Microneedling
- Diabetes mellitus
- Transdermal delivery
- Drug encapsulation
- Enhanced permeability
- Pharmacokinetics
- Bioavailability
- Innovative therapy
- Chronic metabolic disorder
- Patient compliance
- Localized treatment
- Skin microchannels
- Novel drug delivery system.

Introduction:-Diabetes mellitus is a metabolic disorder characterized by high blood sugar (glucose) levels over a prolonged period. It primarily arises due to issues with insulin, (a hormone that regulates blood sugar). There are several types of diabetes High blood sugar, or hyperglycemia, occurs when there is an excess of glucose in the bloodstream. This can be a significant concern for individuals with diabetes but can also occur in people without diabetes under certain conditions.

The islets of Langerhans are clusters of cells in the pancreas that play a crucial role in regulating blood sugar levels.

Structure and Function

The islets of Langerhans contain several types of cells, each with specific functions:

1)Alpha Cells: It produce glucagon, a hormone that raises blood sugar levels by promoting the release of glucose from the liver.

2)Beta Cells: It produce insulin, a hormone that lowers blood sugar levels by facilitating the uptake of glucose by cells.

3)Delta Cells: It produce somatostatin, which helps regulate the secretion of other hormones and slows down digestion.

4)PP Cells (Pancreatic Polypeptide Cells): It produce pancreatic polypeptide, which plays a role in regulating pancreatic functions and appetite.

The Diabetes is one of the metabolic disorder in which there is low production of Insulin. In other words a metabolic disorder of the GLUCOSE . Insulin is the hormone secreted by the gland known as pancreas . Usually the work of insulin in the body is to reduce the high glucose level (Blood sugar level) . Insulin is a hormone produced by the pancreas, specifically by the beta cells in the islets of Langerhans. It plays a vital role in regulating blood sugar (glucose) levels in the body. Here's a closer look at its functions, regulation, and significance:

Functions of Insulin

1)Glucose Regulation:

Insulin facilitates the uptake of glucose into cells, particularly in muscle and fat tissues, helping to lower blood sugar levels after meals.

2)Glycogen Storage:

It promotes the conversion of glucose to glycogen in the liver and muscles, serving as a stored form of energy that can be used when needed.

3)Fat Storage:

Insulin encourages the storage of fat in adipose tissue and inhibits the breakdown of fat, helping to regulate fat metabolism.

4)Protein Synthesis:

Insulin aids in the synthesis of proteins and inhibits protein breakdown, supporting tissue growth and repair.

But in case of diabetes the level of blood glucose is generally high due to low concentration of the hormone insulin . There are different reasons for the resistance to produce the insulin by pancreas . On the basis of different reasons there are different types of diabetes mellitus .

Type 1 D.M (Insulin Dependent Diabetes Mellitus)

In case of the Type 1 Diabetes mellitus the BETA cell of the pancreas loss there ability to produce the enough insulin which will further enable to maintain the blood glucose level. When beta cells in the pancreas do not produce enough insulin, it can lead to elevated blood sugar levels, a condition known as hyperglycemia . This type of diabetes is characterized by the body's inability to produce insulin due to the autoimmune destruction of the insulin-producing beta cells in the pancreas

Etiological Factor :-

The etiology of Type 1 diabetes mellitus (T1DM) involves a combination of genetic, autoimmune, and environmental factors

1)Genetic Factors

i.Family History: While not directly inherited, having a family history of Type 1 diabetes increases the risk. Certain genes, particularly those related to the immune system (such as the HLA gene complex), are associated with a higher susceptibility.

ii.Genetic Markers: Specific genetic markers have been identified that indicate a higher risk for developing T1DM, but not everyone with these markers will develop the condition.

2. Autoimmune Response

i.Immune System Attack: Type 1 diabetes is primarily an autoimmune disease. The body's immune system mistakenly targets and destroys insulin-producing beta cells in the pancreas.

ii.Autoantibodies: The presence of autoantibodies (such as GAD65, ICA, and IAA) in the blood indicates an autoimmune response against pancreatic cells. These can sometimes be detected even years before the onset of diabetes.

3. Environmental Factors

i.Viral Infections: Certain viral infections (e.g., coxsackievirus, mumps, rubella) have been implicated as potential triggers for the autoimmune process that destroys beta cells.

ii.Dietary Factors: Some studies suggest that dietary factors, such as early exposure to cow's milk or low levels of vitamin D, might influence the risk of developing T1DM, although evidence is still being explored.

iii.Geographic and Seasonal Variability: Incidence rates vary by geography and season, suggesting that environmental factors may play a role in triggering the disease.

4. Other Factors

i.Stress: Physical or emotional stress may influence the onset of T1DM in genetically predisposed individuals.

ii.Other Autoimmune Conditions: Individuals with other autoimmune diseases (such as thyroid disease or celiac disease) may have an increased risk of developing T1DM.

Symptoms:-

1)Increased Thirst (Polydipsia):-

Individuals may feel excessively thirsty due to the body's attempt to dilute high blood sugar levels.

2)Frequent Urination (Polyuria):-

High blood sugar levels lead to increased urine production, causing more frequent trips to the bathroom.

3)Extreme Fatigue:-

A lack of insulin means that glucose cannot enter the cells for energy, leading to persistent tiredness.

4)Blurred Vision:-

High glucose levels can cause swelling in the lenses of the eyes, leading to temporary blurred vision.

5)Unexplained Weight Loss:-

The body begins to break down fat and muscle for energy when it cannot utilize glucose, leading to weight loss despite normal or increased eating.

6)Increased Hunger (Polyphagia):-

Despite eating more, individuals may feel hungry due to the body's inability to use glucose effectively.

7)Irritability and Mood Changes:-

Fluctuating blood sugar levels can affect mood and behavior.

Type 2 D.M (insulin independent Diabetes Mellitus)

In case of type 2 diabetes mellitus , the insulin is keep produced through the pancreatic Beta cell but the cell , tissue , organ , system , in order to say that the human body oppose to the insulin resultant in the failure of reduce the level of glucose in the blood , due to this the high level of blood glucose occur and we can seen Type 2 D.M. Type 2 diabetes mellitus (T2DM) is a chronic condition that affects how the body metabolizes glucose (sugar). It is characterized by insulin resistance and, over time, a relative deficiency in insulin production.

High blood glucose level occurs for the prolonged period this will be responsible for the great sign and symptoms of the type 2 Diabetes mellitus .

Etiology:-

1)Genetic Factors

i.Family History: A family history of diabetes increases the risk of developing T2DM, suggesting a genetic predisposition.

ii.Specific Genes: Certain genetic variations have been associated with insulin resistance and beta-cell dysfunction.

2. Environmental Factors

i.Obesity: Excess body fat, particularly visceral fat around the abdomen, is one of the strongest risk factors. It contributes to insulin resistance.

ii.Sedentary Lifestyle: Lack of physical activity increases the risk of developing insulin resistance and obesity.

iii.Dietary Habits: Diets high in refined carbohydrates, sugars, and unhealthy fats can contribute to weight gain and increased blood sugar levels.

3. Metabolic Factors

i.Insulin Resistance: The primary issue in T2DM is the body's inability to respond effectively to insulin, which prevents glucose from entering cells.

ii.Beta-Cell Dysfunction: Over time, the pancreas may struggle to produce enough insulin to overcome insulin resistance, leading to higher blood sugar levels.

4. Hormonal Factors

i.Hormonal Imbalances: Conditions such as polycystic ovary syndrome (PCOS) and other endocrine disorders can increase the risk of T2DM due to their impact on insulin sensitivity.

5. Age

i.Increased Risk with Age: The risk of developing T2DM increases with age, particularly after 45, due to a combination of increased insulin resistance and reduced physical activity.

6. Ethnicity

i.Certain ethnic groups (such as African Americans, Hispanic Americans, Native Americans, and some Asian Americans) have a higher risk of developing T2DM.

7. Other Medical Conditions

i.Conditions like hypertension and dyslipidemia (abnormal lipid levels) are often associated with T2DM and can contribute to its development.

8. Psychosocial Factors

i.Stress: Chronic stress can lead to increased blood sugar levels due to hormonal changes (e.g., cortisol).

ii.Sleep Patterns: Poor sleep quality and sleep disorders, such as sleep apnea, can also increase the risk of developing T2DM.

Epidemiology :-

The epidemiology of diabetes mellitus (DM) focuses on the patterns, causes, and effects of this chronic disease within populations. Here's a concise overview In 2017, 425 million people had diabetes worldwide, up from an estimated 382 million people in 2013 and from 108 million in 1980. Accounting for the shifting age structure of the global population, the prevalence of diabetes is 8.8% among adults, nearly double the rate of 4.7% in 1980. Type 2 makes up about 90% of the cases. Some data indicate rates are roughly equal in women and men, but male excess in diabetes has been found in many populations with higher type 2 incidence, possibly due to sex-related differences in insulin sensitivity, consequences of obesity and regional body fat deposition, and other contributing factors such as high blood pressure, tobacco smoking, and alcohol intake. Diabetes occurs throughout the world but is more common (especially type 2) in more developed countries. The greatest increase in rates has, however, been seen in low- and middle-income countries, where more than 80% of diabetic deaths occur. The fastest prevalence increase is expected to occur in Asia and Africa, where most people with diabetes will probably live in 2030. The increase in rates in developing countries follows the trend of urbanization and lifestyle changes, including increasingly sedentary lifestyles, less physically demanding work and the global nutrition transition, marked by increased intake of foods that are high energy-dense but nutrient-poor (often high in sugar and saturated fats, sometimes referred to as the "Western-style" diet). The global number of diabetes cases might increase by 48% between 2017 and 2045. Among young and middle aged adults the prevalence of diabetes is 6.7% and prediabetes is 5.6% according to the National Family Health Survey-4. The average age on onset is 42.5 years. Nearly 1 million Indians die due to diabetes every year.

Prevalence

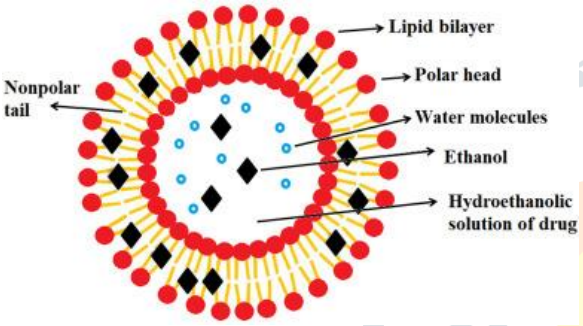
1)Global Estimates: Over 500 million adults worldwide have diabetes, with projections suggesting this could reach 700 million by 2045.

2)Types of Diabetes:

Type 1 Diabetes: Accounts for about 5-10% of cases, typically diagnosed in children and young adults.

Type 2 Diabetes: Represents approximately 90-95% of cases, often linked to obesity and lifestyle factors.

Ethosome :- Ethosomes are a type of lipid-based drug delivery system designed for transdermal (through the skin) delivery of therapeutic agents. They consist of phospholipids, ethanol, and water, and are characterized by their ability to enhance skin permeability. novel lipid carriers composed of ethanol, phospholipids, and water. They are reported to improve the skin delivery of various drugs. Ethanol is an efficient permeation enhancer that is believed to act by affecting the intercellular region of the stratum corneum. Ethosomes are soft malleable vesicles composed mainly of phospholipids, ethanol (relatively high concentration), and water. These soft vesicles represent novel vesicles carriers for enhanced delivery through the skin. The size of the ethosomes vesicles can be modulated from tens of nanometers to microns.



Ethosome

Composition:-

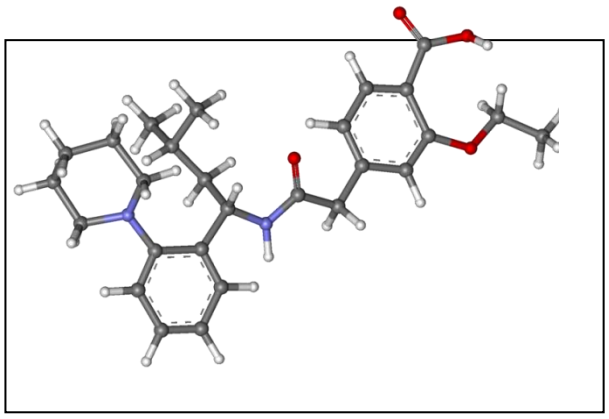
1) Phospholipids: Form the lipid bilayer, providing structural integrity.

2)Ethanol: Increases fluidity of the lipid membrane and disrupts the skin barrier, allowing for enhanced penetration of the drug.

3)Water: Serves as a solvent and helps in the formulation process.

Repaglinide :-

Repaglinide is an oral antidiabetic medication used to manage Type 2 diabetes Repaglinide is an antidiabetic drug in the class of medications known as meglitinides, and was invented in 1983. Repaglinide is a medication used in addition to diet and exercise for blood sugar control in type 2 diabetes. The mechanism of action of repaglinide involves promoting insulin release from β-islet cells of the pancreas.



1) Repaglinide

↓

2) Depolarization (open Ca++ channels) in Beta inslet cell

↓

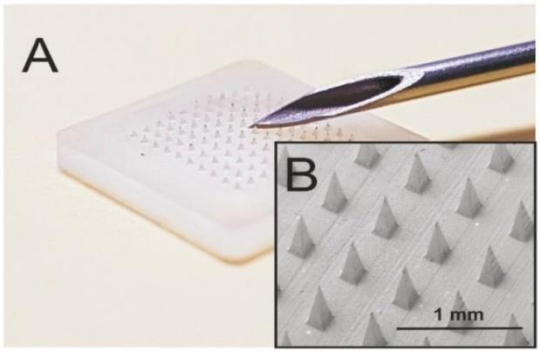
3) Insulin stimulate

The repaglinide causing the depolarization in the beta islet of pancreas resulting in the stimulation in the secration of insulin can be seen .

Microneedle :-

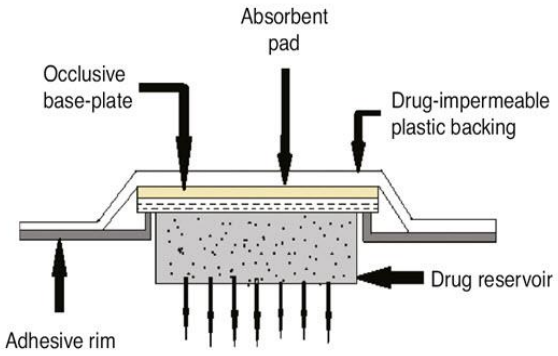
Microneedling is a minimally invasive cosmetic procedure that involves the use of fine needles to create micro-injuries in the skin. This technique stimulates the body's natural healing processes, promoting collagen and elastin production. The microneedle is a device which is basically used in skin therapy , for the purpose of the natural glowing of skin or to reduce the pimples , dark spots flashes on the skin.But in the drug delivery system the microneedle is very small device which may be electrical or non. Having top level of velocity (high frequency) through which the drug have delivered and it does not cause any pain or mark unlike the needle or syringe. Microneedles are of 150–1500 μm size in length, 50–250 μm in width, and 1–25 μm in diameter . Microneedles cause micron-sized pore formation due to skin puncturing, and these channels act as a direct route of drug delivery. It basically favers the transdermaldrug delivery route .In regular life the patients takes their medicine by needle or syringe directly as per the direction of the physician. But in case of advanced drug technique e.g MN technique it has more benefits than using syringe or needles but some are disadvantages also there. If the drug is taken through the MN technique it is non irritable or non damageable and

causes safety of the skin. It is not painful and too much comfortable



Ethosome Loaded Repaglinide and microneedling :-

Ethosome-loaded repaglinide refers to the formulation of repaglinide using ethosomes to enhance its transdermal delivery. This approach aims to improve the drug's absorption and efficacy while minimizing side effects. Ethanol Effect- The presence of ethanol in ethosomes disrupts the skin barrier, facilitating better penetration of repaglinide through the stratum corneum. By delivering repaglinide directly through the skin, ethosomes can increase the bioavailability of the drug compared to oral administration.Ethosome formulations can provide a sustained release of repaglinide, helping to maintain stable blood glucose levels over time. Transdermal delivery may decrease gastrointestinal side effects associated with oral dosing, such as nausea or digestive disturbances.



Microneedle with ethosome loaded Repaglinide .

Combining ethosome-loaded repaglinide with microneedling represents an innovative approach to managing diabetes mellitus (DM), particularly for improving drug delivery and enhancing skin health. Here's an overview of how this combination can work:

Conceptual Framework

Enhanced Drug Delivery:

i.Ethosomes: Utilizing ethosomes for repaglinide allows for transdermal delivery, improving the absorption and bioavailability of the drug while minimizing gastrointestinal side effects.

ii.Microneedling: The microneedling procedure creates microchannels in the skin, enhancing the permeation of ethosome-loaded repaglinide into the systemic circulation.

2)Synergistic Effects:

i.The micro-injuries from microneedling can increase the skin's permeability, allowing the ethosomal formulation to penetrate more effectively. This can lead to improved therapeutic outcomes in blood glucose control.

Potential Benefits

i.Improved Glycemic Control:

Enhanced delivery of repaglinide through this combination may lead to more effective blood glucose management, particularly for postprandial spikes.

ii.Reduced Side Effects:

By avoiding the gastrointestinal route, patients may experience fewer side effects associated with oral administration of repaglinide.

Skin Health Improvement:

Microneedling can improve skin texture and promote healing, which is particularly beneficial for diabetic patients who may face skin complications.

Personalized Treatment:

This approach allows for a more tailored treatment plan, addressing both systemic and dermatological needs in diabetic patients.

Consideration

1)Patient Assessment:

It's essential to evaluate the patient's overall health, blood glucose control, and any existing skin conditions before initiating treatment.

2)Professional Administration:

Both microneedling and ethosome formulation should be performed by qualified professionals to ensure safety and efficacy.

3)Post-Treatment Care:

After microneedling, patients should follow a specific skincare regimen to promote healing and enhance the effects of ethosome-loaded repaglinide.

Advantages:

1)Enhanced Drug Delivery:

Ethosomes are lipid-based carriers that facilitate improved penetration through the skin. By loading repaglinide, an oral hypoglycemic agent, into ethosomes, the drug can be delivered more effectively into the systemic circulation via the transdermal route.

2)Minimized Side Effects:

Transdermal delivery can reduce gastrointestinal side effects commonly associated with oral medications, offering a more tolerable option for patients.

3)Controlled Release:

Ethosomes can provide a controlled release of repaglinide, potentially leading to more stable blood glucose levels and fewer peaks and troughs in drug concentration.

4)Improved Patient Compliance:

A non-invasive delivery method like microneedling may enhance patient compliance compared to daily oral medications or injections.

5)Potential for Localized Treatment:

While repaglinide is primarily a systemic drug, the localized effect of microneedling could potentially improve metabolic function in specific areas, complementing overall glycemic control.

Future Aspects:

1)Research and Development:

Further studies are needed to optimize ethosome formulations, focusing on the stability and release kinetics of repaglinide.

2)Clinical Trials:

Conducting clinical trials will be essential to evaluate the efficacy, safety, and long-term outcomes of this combined approach in diverse populations.

3)Personalized Medicine:

Future developments could include tailoring the formulation and treatment regimen based on individual patient profiles, including their specific type of diabetes and metabolic conditions.

4)Integration with Technology:

Combining this approach with wearable technology for real-time glucose monitoring could enhance diabetes management, allowing for adjustments in medication delivery based on glucose levels.

5)Broader Applications:

Exploring ethosome delivery for other antidiabetic agents could expand treatment options and improve outcomes for patients with diabetes.

Conclusion ;- The innovative approach of using ethosome-loaded repaglinide in conjunction with microneedling represents a significant advancement in diabetes mellitus treatment. By leveraging the enhanced transdermal delivery capabilities of ethosomes, this method not only improves the bioavailability of repaglinide but also minimizes side effects typically associated with oral medications. The potential for controlled drug release and improved patient compliance adds to its appeal, making it a promising alternative for managing blood glucose levels.As research progresses, clinical trials will be crucial to validate the efficacy and safety of this

combined approach. The future holds exciting possibilities for personalized medicine, integrating technology for real-time monitoring and potentially expanding this delivery system to other antidiabetic agents. Overall, this innovative strategy could reshape diabetes management, offering patients a more effective and convenient therapeutic option while paving the way for enhanced quality of life.

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