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NEW MODALITIES OF DIABETES MANAGEMENT

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Abstract:

Introduction: *Diabetes mellitus (DM) is becoming more common at an alarming rate around the world. Diabetes's standing has shifted over the last three generations; previously considered a minor disease of the elderly, it is now one of the main causes of morbidity and mortality among middle-aged and young individuals. Chronic diseases such as Type 1 and Type 2 diabetes are caused by high blood glucose levels, insulin sensitivity, and insulin shortage. Traditional diabetes treatments, such as insulin sensitization and insulin secretion, have unfavorable side effects, resulting in patient noncompliance and medication discontinuation. Nanotechnology in diabetes research has stimulated the development of innovative methods for monitoring glucose and delivering insulin, which have the potential to improve the quality of life for diabetic patients. In addition to insulin and oral hypoglycemic medications, other therapies such as -cell regeneration and gene therapy are presently used to control diabetes.*

Aim of the Study: *The current review focuses on nanocarrier-based medication delivery technologies and new diabetes treatment options.*

Methodology: *The review is comprehensive research of PUBMED since the year 2002 to 2022*

Conclusion: *Diabetes care is in serious need of improvement. Diabetes is becoming more common at an unprecedented rate, putting enormous economic strain on healthcare spending and the cost of treating diabetic complications. While there are numerous relevant new treatment medications, none (save insulin or insulin analogs) are successful alone in achieving appropriate glycemic control. As a result, combinations of complimentary medications are becoming increasingly significant in illness therapy. Furthermore, the development of novel medications that target other targets will improve our ability to successfully treat this crucial disease.*

Keywords: *diabetes mellitus, insulin, blood glucose level, nanocarrier, treatment strategies.*

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INTRODUCTION:

Diabetes mellitus is a common chronic metabolic condition where there is a defect with insulin secretion, action, or both resulting in persistent hyperglycemia. As of 2019, an estimated 463 million adults worldwide are thought to have diabetes with an 8.3% prevalence rate and 46.3% of cases going untreated; by 2045, that number is predicted to rise to 700 million Diabetes is one of the leading causes of death globally, and its sharp increase in prevalence threatens mankind. Additionally, the age group of 40–59 makes up the largest percentage of 463 million individuals who reside in low- and middle-income nations.[1]

The IDF Western Pacific region has the greatest age-adjusted prevalence of diabetes in adults, with 163 million, 197 million, and 212 million in 2019, 2030, and 2045, respectively, according to geographical study. In contrast, the IDF Africa (AFR) region had the lowest age-adjusted rates for the same predicted years (19 million, 29 million, and 47 million). This is partly because of urbanization, low levels of obesity, and malnutrition. However, by 2045, there would be 143% more diabetics in this region than there were in any other, making it the location with the largest increase in diabetes cases during that period.[2]

Diabetes arises from either insufficient insulin production by the pancreas or improper insulin utilization by the body. Diabetes is brought on by lifestyle choices and metabolic abnormalities. [3] There are three primary types of diabetes: An autoimmune reaction in which the body's immune system destroys the pancreatic β-cells responsible for making insulin is the cause of type 1 diabetes. Type 2 Diabetes Mellitus is the most common type of diabetes. The main cause of hyperglycemia, or high blood glucose levels (BGL), is insulin resistance, which is the body's cells' partial inability to respond to insulin. Elevated blood glucose levels are a feature of gestational diabetes mellitus (GDM), which can develop throughout pregnancy (though most frequently after week 24) and usually ends after delivery.[4]

Currently Available Oral Antidiabetics Therapy

1. Biguanides:
   The best choice for antidiabetic monotherapy is metformin (MET). It reduces hepatic glucose synthesis and raises insulin sensitivity. This medication helps to reduce serum LDL cholesterol and triglycerides, both of which are sensible decreases. It also activates the mitochondrial complex 1, glycerophosphate dehydrogenase (GPDH) in the mitochondria, obstructing enzymes, and adenosine monophosphate-activated protein kinase (AMPK), which is linked to the expression of hepatic gluconeogene genes.[5]

2. Sulfonylureas:
   The sulfonylurea class of antidiabetic medications stimulates pancreatic β-cells' natural production of insulin. First-generation tolbutamide and second-generation Glibenclamide, Glyburide, Glipizide, Gliclazide, and Glimepiride are typical examples of this category. Their primary targets are β-cells' adenosine triphosphate-sensitive potassium channels (KATP), and they only show promise in pancreatic β-cells that are still present.[6]

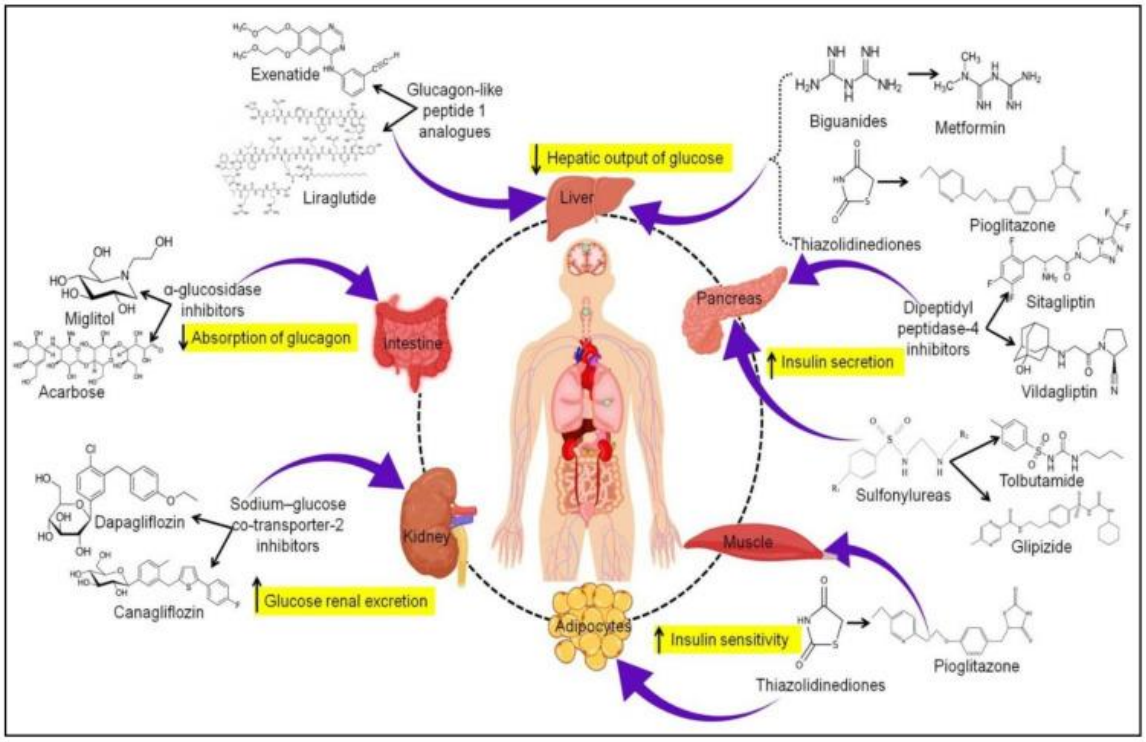

Fig.2 Different categories and modes of action of antidiabetic drugs. [3]

3. Thiazolidinediones:
Thiazolidinediones (TZDs) are activators of peroxisome proliferator-enacted receptor γ (PPR-γ) that enhance insulin affectability in liver adipocytes and heart muscles.[3]

4. Dipeptidyl Peptidase-4 Inhibitors:
Gliptins, or dipeptidyl peptidase-4 (DPP4) inhibitors, are modern therapeutic agents that work by inhibiting the DPP4 enzyme. Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin, and Linagliptin are typical examples in this category. The inactivation of incretin hormones is overlooked due to the inhibition of enzymes.[3]

5. Glucagon-like Peptide 1 Analog:
GLP-1 analogs are incretin-based therapies that decrease glucagon secretion, lower hepatic glucose production, and increase insulin secretion in a glucose-dependent manner. These substances are intolerable as DPP4 inhibitors in spite of this. Studies indicated a drop in HbA1c levels and promoted weight loss.[7]

6. Sodium-Glucose Co-Transporter-2 Inhibitors:
Gliflozins, sodium-glucose co-transporter-2 (SGLT2) inhibitors inhibit the uptake of sodium, which lowers the amount of glucose that is taken up by the kidneys through the proximal tubules of the renal nephron. Canagliflozin, Empagliflozin, and Dapagliflozin are members of this class. Because these agents act freely on insulin, they are used in patients with diabetes.[3]

New Treatment Strategies

The Closed-Loop Technology

Diabetes treatment has seen a surge in interest in closed-loop systems, particularly in the form of sophisticated insulin delivery systems. Closed-loop systems, also known as artificial pancreas systems, automate glucose regulation through the combination of insulin infusion and continuous glucose monitoring (CGM) technology. In an attempt to mimic the physiological insulin response, these systems alter the amount of insulin delivered based on the glucose levels that are being measured. Closed-loop technology offers several advantages over traditional insulin delivery methods. It makes it possible to administer insulin more precisely and individually, reducing the risk of hypo- and hyperglycemia. Closed-loop systems continuously monitor glucose levels and alter the insulin supply to

improve glycemic control and extend duration in the target range.[8]

Oral Hypoglycemics Nanocarrier

Ideal uses of nanotechnology exist in the development of drug delivery systems (DDS). Most biological activities depend on nanoscale entities like viruses and ribosomes. Through direct interactions with subcellular entities, nanoparticles (NPs) can trigger intracellular events. The promising applications of therapeutic DDS based on nanocarriers are drawing more attention to them than traditional DDS. More of the drug surface can come into contact with the body at the same drug concentration because nanocarriers have a higher surface-to-volume ratio. [9]

Because pharmacological therapy has limitations and nanocarriers have advantages in drug administration and imaging, researchers are heavily involved in the treatment and management of diabetes mellitus using NPs. In the management of diabetes, liposomes, polymer-based NPs, and inorganic NPs are the most widely used nano-based drug delivery systems. Various polymer-based nanoparticles (NPs) such as micelles, nanospheres, dendrimers, and nanocapsules have been identified as effective drug carriers. These nanocarriers have the potential to be beneficial in a variety of ways, including enhancing stability through the circumvention of various biological barriers in vivo, boosting bioavailability, and shielding medications from enzymatic degradation. Additionally, by acting as a non-linear response to an external signal and acting as an adaptive automated system to mimic endogenous insulin supply, they can reduce the risk of hypoglycemia and improve patient compliance.[9]

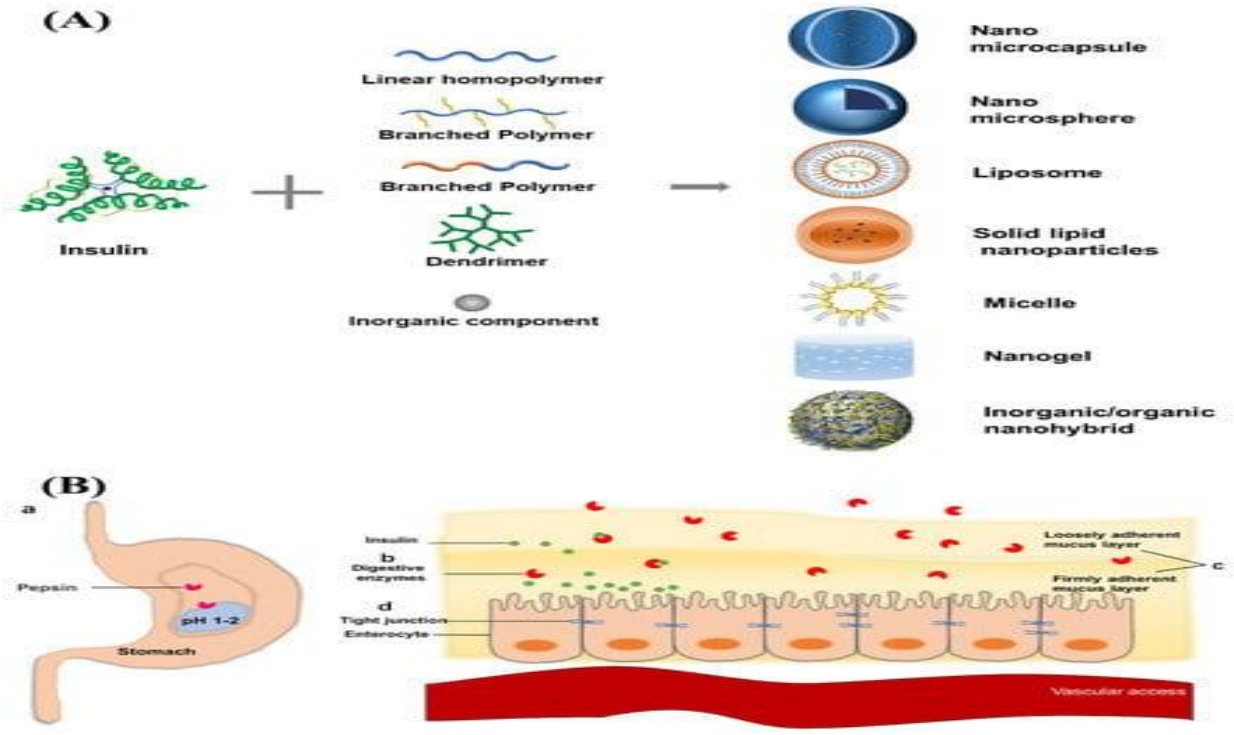

Fig. 3 (A)Nanostructure Delivery System of Oral Insulin
(B) Absorption barrier or Oral Insulin [10]

Nanocarriers-based therapy of diabetes:[3]

1. Phyto-NPs (Selenium cleome droserifolia NPs)
2. Zinc oxide NPs (Costus igneus-loaded ZnO NPs)
3. Dendrimer (G4 PAMAM)
4. Solid lipid nanoparticles (Valsartan (Val)-loaded SLN (Val-SLN))
5. Polymeric NPs (Metformin (MET)-loaded polymeric NPs)
6. Bovine serum albumin NPs (BSA-NPs) (Apatinib-loaded BSA-NPs coated hyaluronic acid (HA)

Liposomes

Lipid bilayer structure and an aqueous core make up liposomes. When combined with the lipid bilayer, the aqueous core creates a liposome that can carry both hydrophilic and hydrophobic medications into the body. In stored conditions, liposomes prevent chemical and biological drug degradation and improve drug solubility. The presence of MET in the aqueous phase causes a concentration gradient to occur throughout the lipid layer, which causes the lipid membrane to break. These two characteristics produce better and more synchronized drug release, which leads to synergistic activity. Liposomes do have certain drawbacks, though, including limited biological and physical stability brought on by phospholipid hydrolysis, oxidation, fusion sedimentation, and conglomeration. Liposomes have the ability to trigger defense reactions that include complement process-based pseudo-allergy initiation and opsonization. Moreover, difficulties with large-scale liposome production and sterilization prevent liposomes from being commercialized.[11]

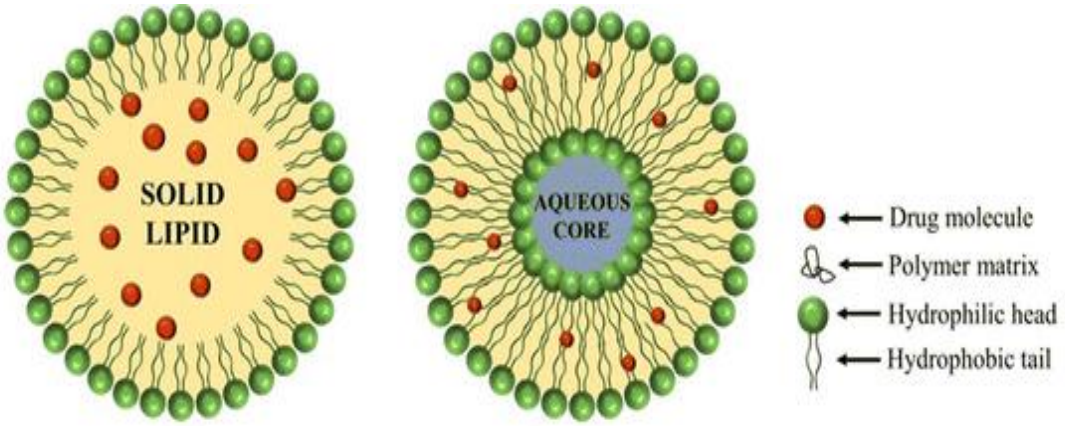

Fig.4 Solid Lipid Nanoparticle and Liposome loaded with drug molecule.[12]

The development of liposomes as oral drug carriers with low bioavailability has been aided by the promising precedents offered by injectable liposomes and their biocompatibility. The enhanced permeation through the intestinal epithelium may be attributed to the structural and compositional similarities between liposomes and cell membranes. Furthermore, liposomes' surface can be altered to help them get past potential physicochemical obstacles and alter how they behave in the gastrointestinal tract. This can be done, for example, by adding cationic surfactants, bile salts, or targeting ligands.[12]

Solid Lipid Nanoparticle

A lipid core and a monolayer surfactant shell stabilize solid lipid nanoparticles, allowing them to form aqueous dispersions at the nanoscale. Triglycerides, fatty acids, waxes, and phospholipids are frequently utilized lipids in the synthesis of solid lipid nanoparticles; surfactants include poloxamers, lecithin, polysorbates, and derivatives of bile salts. Furthermore, solid lipid nanoparticles may acquire muco adhesion qualities through surface modification.

Niosomes

Niosomes are self-assembled and composed of two-layered nanostructures made of cholesterol and non-ionic surfactants. This bilayered framework is made up of a hydrophilic head (directed towards the aqueous solvent) and a hydrophobic tail (oriented far from the solvent). The structure helps to engulf hydrophobic drugs inside the lipid bilayer and hydrophilic drugs inside the aqueous core. Their main point of interest is their sustained drug release, which prompts a reduction in the dose frequency and toxicity. In an investigation, metformin-loaded niosomes showed extended hypoglycaemic activity for 6–8 h compared to MET solution, reducing the BGL for only 2–4 h. The constant drug release is due to the hydrophobic phospholipid obstacles of niosomes. Glimepiride in niosomes made up of sorbitan monostearate, Span 60, and cholesterol can increase the therapeutic efficacy of the medicine.[13]

Micelles

Micelles are groups of amphiphilic molecules that have the ability to solubilize hydrophobic medications. Additionally, when the attained concentration matches the critical micelle concentration (CMC), clusters may form. Micelles are used to stabilize the straightforward drug solution

manufacturing process, and their assembling nature and molecular structure are clearly defined. RG-PLC-Ms showed an improved lipid profile and raised serum levels of malondialdehyde and insulin. Phospholipid in the formulation reduced the surface tension between the artificial compound and the fluid of the gastrointestinal tract (GIT), which resulted in longer drug transfer and penetration across the cell membrane. The last several decades have seen a widespread implementation of insulin delivery mechanisms for the treatment of diabetes. Polymeric micelles that respond to both glucose and hydrogen peroxide were studied by Liu et al. in relation to the transmission of insulin.[14]

Stem Cell Technology

It is well known that β cell deficiency in the pancreatic cells causes insufficient insulin secretion, which is the cause of both type 1 and type 2 diabetes. Stem cell technology ought to focus on eliminating the defects present in the pancreatic β cell or improving the body cells' susceptibility to the effects of insulin. It can be used for replacing β cells presents a new avenue, whereas existing approaches focused on islet cell and pancreas transplantation are constrained by the lack of available donor organs. Unlike type 1 diabetes, which is brought on by an autoimmune response that destroys pancreatic β cells, type 2 diabetes is brought on by abnormalities in the function of β cells in addition to insulin resistance in peripheral organs.[15]

Mesenchymal stem cell (MSC) therapy suppresses the immune system, therefore, it has become a promising treatment option for type 1 diabetes. Hematopoietic stem cells are multipotent stem cells with the ability to differentiate into every type of blood cell and the ability to modulate the immune system. Therefore, hematopoietic stem cell transplantation has shown to be a promising therapeutic, improving β cell function in patients recently diagnosed with type 1 diabetes. [15,16]

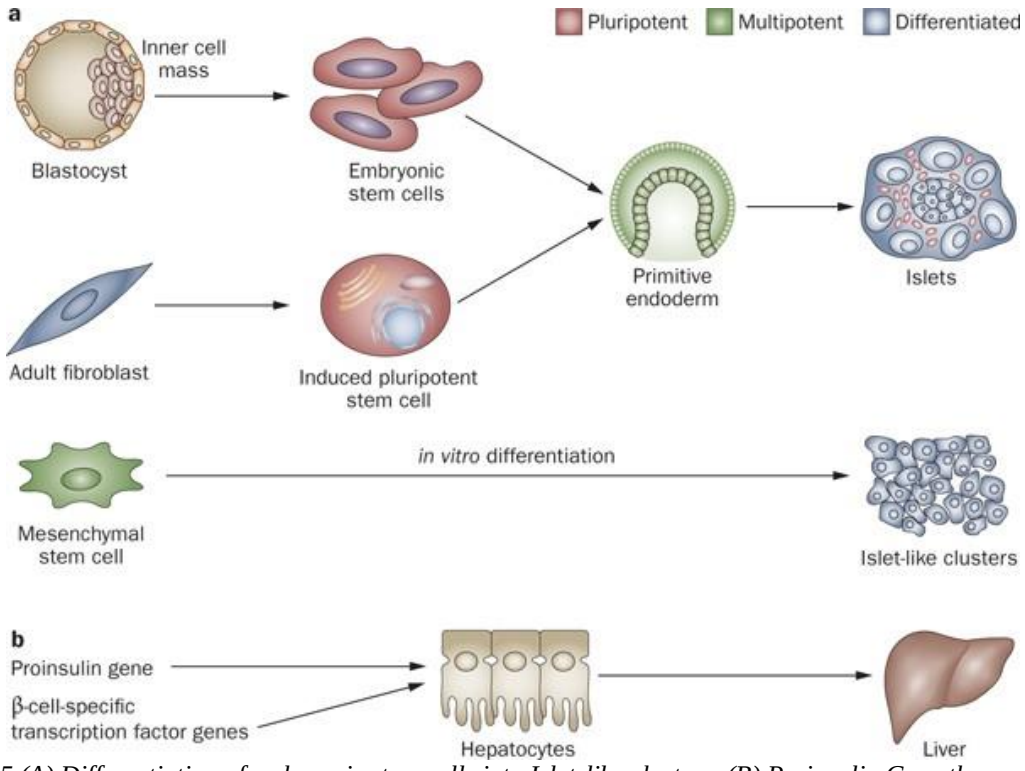

Fig.5 (A) Differentiation of embryonic stem cells into Islet-like clusters. (B) Proinsulin Gene therapy. [16]

Gene Therapy

The most crucial part of the treatment, which reduces the complications associated with diabetes is controlling blood sugar levels. There are two ways to deliver genes during somatic gene therapy, which uses the somatic cells from the body. In vivo, gene therapy involves injecting gene therapy vectors directly into patients via subcutaneous, intravenous, intrabronchial, or local injection, whereas ex vivo gene therapy involves removing tissues from the body, inserting the therapeutic gene in vitro, and then reintroducing it into the body. The goal of ex vivo

therapy is to create cells that have characteristics, such as the ability to produce insulin. Moreover, this treatment has been used to produce β cells for transplantation. The process of surgically extracting the tissue from the body and then reintroducing the genetically altered tissues into the patient's body, however, raises concerns. Moreover, the autoimmune destruction of pancreatic β cells that synthesize insulin causes type 1 diabetes, and islet transplantation has been investigated as a potential treatment option.[15,16]

Insulin Pump Therapy

Insulin pump therapy uses prandial boluses to augment small amounts of basal rate insulin continuously in an attempt to mimic physiologic insulin secretion. Much more accurate insulin delivery is made possible by the ability to modify basal insulin and boluses in response to daily changes in each person's insulin sensitivity and needs. Insulin pumps are getting easier to use and smaller. With numerous extra features that make diabetes treatment easier, the accessible pumps available today are considered "smart," thanks to the quick development of technology. The flexibility to adjust multiple daily basal and intermittent rates takes care of momentary variations in insulin sensitivity, like those that occur during exercise or related illnesses. The patterns of insulin requirement throughout the day depend on an individual's age and pubertal stage. The patterns of insulin requirement throughout the day depend on the age and pubertal stage of an individual. Insulin pump therapy enables more circadian-specific, nearly physiologic basal rate delivery.[17]

CONCLUSION:

Clinical progress has been made in the areas of disease development, prevention, and treatment, but as of yet, no therapeutic approach has proven to be entirely effective. The search for a successful drug is not far off, as new technologies are transforming the options for treatment. The field of diabetes research has undergone a significant revolution thanks to the comprehensive study that identified the genes involved in the disease's development and the sequencing of entire genomes. Lipid-based nanocarriers have been the subject of extensive and increased research over the past 20 years as potential oral drug delivery systems. Their potential to enhance intestinal permeability, solubility, and stability of oral drugs, along with their low toxicity profile, have contributed to this. The gastrointestinal tract contains physicochemical obstacles to the delivery of oral drugs, including mucus, enzymes, and extremely high and low pH. If lipid-based nanocarriers are designed to anticipate the biological behavior of the systems, they may be able to withstand these harsh conditions that currently pose challenges.

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