IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

Nanoparticles And The New Era Of Advanced Delayed Drug Delivery System In Diabetes Management

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ABSTRACT

Diabetes mellitus (DM) has been known to mankind for over 2000 years. DM is a group of metabolic disorders characterized by total insulin deficiency, relative insulin deficiency, or insulin resistance. The increase in DM prevalence is due to three influences including lifestyle, ethnicity and age. Current challenges in diabetes management include Optimize the use of existing therapies to ensure adequate glycemic, blood pressure and lipid control and reduce complications. Several studies are currently focusing on new treatment options for diabetes mellitus. Among these options, the use of nano-medicine has emerged as one of the most prominent and promising methods.Worldwide, a significant scientific effort has been made to develop a less intrusive, more precise alternative to the traditional subcutaneous approach. Transdermal insulin, an artificial pancreas with a closed-loop system, as well as buccal, oral, pulmonary, nasal, ophthalmic, and rectal channels are some of the more recent techniques being investigated. The usage of insulin inhalers, transdermal patches, tablets, pumps, etc. is among the future trends. Polymeric hydrogels and insulin-loaded bioadhesive poly D,L-lactide-co-glycolide are some examples of non-invasive delivery systems. Nanoparticles for oral administration, aerosolized liposomes with dipalmitoyl phosphatidylcholine for pulmonary administration, cyclodextrins for nasal administration, microneedle arrays made of hyaluronic acid, and iontophoresis for transdermal delivery,Therefore supply of insulin therapy through various advance drug delivery system is essential to lower blood glucose level in DM patients. in this retrospective study we are emphasizing on currently trending as well as novel advanced drug delivery system which are far more efficient than previously used conventional insulin delivery systems Therapy

Keywords: Diabetes mellitus, Transdermal, Insulin Pump, Nanotechnology, antidiabetic drugs.

Introduction

Diabetes mellitus (DM) has been known to mankind for over 2000 years. DM is a group of metabolic disorders characterized by total insulin deficiency, relative insulin deficiency, or insulin resistance. Type 1 DM and type 2 DM are two types of DM. Type 1 DM is an autoimmune disease that affects pancreatic cells and reduces or impairs insulin production, whereas type 2 DM is caused by impaired pancreatic beta cells. result and ability to use a person's insulin**.** The increase in DM prevalence is due to three influences including lifestyle, ethnicity and age. Current challenges in diabetes management include Optimize the use of existing therapies to ensure adequate glycemic, blood pressure and lipid control and reduce complications. Several studies are currently focusing on new treatment options for diabetes. Among these options, the use of nano-medicine has emerged as one of the most prominent and promising methods. A hallmark of DM is the long latency, chronicity, Multi-organ involvement and need for care Managing chronic illness is difficult Diabetes (DM) is a major health problem affecting over 400 million people worldwide. This metabolic disorder gradually leads to life-threatening chronic microvascular, macrovascular, and neuropathic complications. DM is caused by either lack of insulin secretion, damage to pancreatic β-cells, or insulin resistance associated with insulin nonuse. The trend towards a sedentary lifestyle may be a major reason why the number of people with diabetes continues to rise worldwide, and in 2030 in the elderly population will reach 366 million Type 1 DM and type 2 DM are two types of DM. Type 1 DM is an autoimmune disease that affects pancreatic cells and reduces or impairs insulin production, whereas type 2 DM is caused by impaired pancreatic beta cells. result and ability to use a person's insulin(1) Since the early discovery of insulin, many hypoglycemic drug therapies used to treat diabetes have been approved and discontinued by the US Food and Drug Administration (FDA). To provide an up-to-date overview of current trends in antidiabetic drugs, this review article provides a comprehensive analysis of major classes of antihyperglycemic compounds and their mechanisms Types of insulin, biguanides, sulfonylureas, meglitinides (glinides), alpha-glucosidase inhibitors (AGIs), thiazolidinediones (TZDs), incretin-dependent therapies, sodium glucose cotransporter 2 (SGLT2) inhibitors, and combinations thereof . The number of alternative therapies to treat T2DM is growing, with nearly 60 agents currently approved by the FDA. In addition, nearly 100 other antidiabetic drugs have been evaluated in clinical studies. In addition to the standard treatment of insulin therapy and metformin, there are new drug combinations. B. Metformin, SGLT2 inhibitors, and dipeptidyl peptidase-4 (DPP4) inhibitors have found important applications in the last decade. In addition, several interesting alternatives such as roveglitazone, efpeglenatide, and tirzepatide have entered ongoing clinical trials. Newer drugs such as glucagon-like peptide-1 (GLP-1) receptor agonists, DPP4 inhibitors and SGLT2 inhibitors are gaining popularity in the pharmaceutical market, while low-cost over-the-counter drugs are on the rise in developing countries doing. The great heterogeneity of type 2 diabetes is also creating a drive towards more individualized and accessible treatments. We describe some interesting alternatives that could help us achieve this in the near future with ongoing clinical trials(2) Over the last decade, the field of transdermal drug delivery has gained prominence due to its advantages over traditional oral dosage forms. The global transdermal drug delivery market is expected to grow and reach approximately $95.57 billion by 2025. Overdose is problematic due to fluctuations in peak plasma concentrations after oral and parenteral administration, making effective plasma concentration monitoring difficult. Transdermal drug delivery systems offer several advantages because the administered drug can bypass factors that alter hepatic first-pass metabolism and gastrointestinal pharmacokinetics. This significantly increases systemic bioavailability and reduces the risk of concentration-related side effects. This generally improves patient compliance because the drug is released at a predetermined rate over an extended period of time, making it easier and more convenient to use at lower dosing frequencies.[3] Development of oral insulin remains under research. Administration of insulin via oral route causes the avoidance of pain all through the injection (in subcutaneous administration), anxiety because of needle, and infections which may be developed. Oral insulin delivery is useful due to its direct delivery to liver. Dynamics of subcutaneous delivery of insulin isn't similar to the normal endogenous insulin release . A very low permeability of insulin happens throughout epithelium of intestine due to two reasons, first is due to its excessive molecular weight and the fact that it is degraded very rapidly through enzyme Insulinase. Oral bioavailability of proteins like insulin is under 1%. So there's a goal to enhance it to approximately 30%–50%. Metabolism or degradation of insulin takes region through sure enzymes like pepsin, trypsin, chymotrypsin, so the insulin is degraded through acidic environment of stomach[4] Tzield binds to certain immune system cells and delays progression to stage 3 type 1 diabetes. Tzield may deactivate the immune cells that attack insulin-producing cells, while increasing the proportion of cells that help moderate the immune response. Tzield is administered by intravenous infusion once daily for 14 consecutive days. Tzield's safety and efficacy were evaluated in a randomized, double-blind, event-driven, placebo-controlled trial with 76 patients with stage 2 type 1 diabetes. In the trial, patients randomly received Tzield or a placebo once daily via intravenous infusion for 14 days.[3]

Discussion

Immune-focused treatments for type 1 diabetes aim to stop or postpone the loss of functional beta cell mass. The conventional theory of type 1 autoimmunity The focus of diabetes has been on systemic immune dysregulation and autoreactive T cells that have moved to the periphery and destroyed islets despite thymic selection. This theory of type 1 diabetes development is known as T cell-mediated "homicide" Due to their efficacy in treating other autoimmune disorders, subsequent studies have focused on cell- or cytokine-directed treatments Many medicines are now being developed, and efforts to target T cells or proinflammatory cytokines are still worthwhile. However, so far, these strategies have only been partially successful This can be a sign that we need to refocus.[5] According to Herold, the medication particularly binds to a molecule known as CD3, the "cognate" part of the T cell that, when activated, is responsible for the T cell's function. Teplizumab inhibits autoimmunity and prolongs the pancreas' capacity to produce insulin by attaching to the CD3 molecule in immune cells.[6]

MODERN INSULIN DELIVERY SYSTEMS

Insulin Pen Injectors

These significant improvements in insulin delivery have made self-injection more simple and practical. These are more compact devices that use smaller gauge needles and a syringe and insulin cartridge, which may make injections less unpleasant Both prefilled and durable pens are available. A refillable insulin cartridge is used in a sturdy pen. A prefilled pen is completely throwaway. Types of prefilled insulin syringes are depicted . Insulin pens have a number of benefits, including the ability to achieve consistently more exact dosages and being more portable and convenient than standard vial and syringe. The drawback of an insulin pen is that, unlike a regular syringe, it is impossible to mix two distinct types of insulin.(7)

External insulin pumps

External insulin pumps are compact gadgets around the size of a pager that you can carry around in your pocket or fastened to your belt. They consist of a cannula or catheter that is placed beneath the skin of your belly and attached to an insulin reservoir It is demonstrated how an insulin pump operates. They can be programmed to release bigger doses of insulin during meals or when blood sugar levels are high, or to release it slowly and continuously throughout the day. The fundamental benefit of a pump is that it closely resembles the pancreas' gradual, regular release of insulin. The danger of experiencing low blood sugar episodes is the downside (hypoglycaemia)(7)

Implantable insulin pumps

An implantable insulin pump is implanted just under the skin, usually in the abdomen .External insulin pump. Insulin is delivered to the peritoneal cavity rather than subcutaneously Tissues, supplemented with specialized high-strength insulin every 2-3 months as needed Patient insulin requirements(7)

Insulin inhalers

Inhaled insulin is not the newest method of insulin delivery since it was taken off the market in October 2007 due to lung cancer. However, it was recorded here for educational purposes only(7)

Insulin spray

Another promising alternative to insulin delivery is buccal route. delivery of acid-labile insulin and Elimination of insulin destruction by first-pass metabolism is an advantage of the oral region.abundant blood supply; Patients do not inhale with a buccal spray device like the formulation. Spray finely on the cheek mucosa as shown in the illustration.[3] . Rapid inclusion Blood flow is allowed with high velocity spray. Inhaled insulin formulations reveal risks to lung tissue Can be avoided because the drug is deposited on the oral mucosa(7)

Insulin pill

Multiple insulin injections daily are required to control postprandial blood sugar. treatment with insulin Subcutaneous or other parenteral administration causes peripheral hyperinsulinemia, which can also occur coronary artery disease, hypertension, dyslipidemia, weight gain, and hypoglycemia. Oral insulin products have been shown to properly insulinize the liver to provide insulin. In a more physiological manner, it results in a decrease in peripheral insulin researcher Discovered that insulin can be protected with a chemical coating known as a novel polymer Oral insulin, an insulin capsule, is on the horizon. coating is insulin When taken in tablet form, it is not broken down by enzymes and becomes useless before it enters the bloodstream. Azopolymer-coated pellets trap therapeutic agents until the pellet reaches the colon and is used. Delivery of insulin to the colonic region. Bacteria that live in the colon secrete enzymes that can do this Degradation of the azopolymer initiates release of insulin from the pellet insulin is Microencapsulated using a pH-responsive polymer. Alginate is one of the polymers whose coating is protective. The acidic pH of the stomach breaks them down, but dissolves and releases insulin trapped in the gut Pilot trials are underway to develop insulin tablets as a potential alternative Insulin injection or pump infusion. This endeavor requires new delivery techniques(7)

Transdermal Patch

A transdermal patch is a medicated patch that is applied to the skin to deliver a specific dose of medicine through the skin into the bloodstream. It delivers insulin through a patch of skin. The patch is placed on the skin and ensures painless insulin administration. This allows rapid and controlled drug delivery without the pain of injection and the potential complications associated with inhaled drugs. It also avoids the first-pass gastrointestinal and liver metabolism that occurs often after oral administration it is effective Economical, patient-friendly insulin delivery As well as the supply of various drugs, condition . However, transdermal patch systems include: Limits on drugs needed High blood concentrations cannot be administered, can even cause irritation and sensitization skin. Adhesive may not stick well to everyone Some skin types and wearability may be poor. In addition to these restrictions, The product is also a major drawback for a wide range of people Approval of this product(7)

Iontophoresis

A low-level electrical current carries drug ions across the skin, causing vasodilation and increased blood flow Iontophoretic Patches for Transdermal Delivery Iontophoresis differs from transdermal medication patches in that it uses a weak electrical current in the process. This improves the delivery of drug ions to the skin and surrounding tissues. Depending on the net charge of the insulin molecule, the applied potential has been shown to increase the speed of insulin translocation across the skin. Gels are considered the best delivery vehicles for iontophoresis because they can be easily fused with iontophoresis delivery systems and conform to skin contours(7)

Islet cell transplant

Insulin-producing beta cells are taken from a donor's pancreas and transplanted into a diabetic patient. After transplantation, donor islets begin to produce and release insulin, which positively regulates blood glucose levels. The Process of Islet Cell Transplantation for the Treatment of Diabetes Islets from Exocrine Tissue Portal Infusion and Transplantation of Islets into the Liver(7)

Gene therapy

Adenoviruses are used to introduce new genes into cells. If the treatment is successful, the new gene will produce a functional protein to treat the disease. A gene called SHIP2, which regulates insulin, has been identified as a potential gene therapy target for the treatment of type 2 diabetes.More than 1,700 clinical trials have been conducted using a variety of gene therapy techniques.(7)

Insulin analogues

Insulin analogues are modified forms of insulin that the human body uses to control glucose levels like insulin. To change her ADME (Absorption, Distribution, Metabolism and Excretion) properties that The amino acid sequence of insulin can be altered by genetically manipulating the underlying DNA produce insulin analogues(7)

Rapid-acting insulin analogue

They are the fastest acting insulins. fast-acting insulin analog include: Aspart, Glulysine, Lyspro. It is important to inject because they enter the bloodstream within minutes and it is important to inject them within 5 to 10 minutes of eating. Peak duration is 60-120 minutes and fades away Completed in about 4 hours.(7)

Long-acting injected insulin analogue

Long-acting insulin is the longest acting and provides a relatively constant level of insulin that remains stable for hours after injection. They are also called "peakless" insulin. They begin to act within 60-90 minutes, have maximum effect in about 5 hours, and then gradually become ineffective in the next 12-24 hours. They include insulin detemir insulin glargine(7)

Premixed analogue

Fast-acting insulin acts immediately upon injection, and long-acting insulin has no peak activity. These are the main advantages of analogue insulin. Fast-acting insulin helps people who are insulin dependent by minimizing the rapid rise (spike) in blood sugar levels after meals. Some are confident that because there are no periods of peak activity, they can avoid the nocturnal hypotension that long-acting analogue insulin is so prevalent. Loss of subconsciousness, lethargy and weight gain are side effects of analogue insulin, animal insulin has no such side effects(7)

Newer injectable insulins

Insulin degludec: Insulin degludec is the last amino acid removed from the B chain and hexadecanedioic acid from LysB29. An ultra-long-acting profile with a half-life of more than 24 hours can be achieved by subcutaneous injection that converts insulin to soluble multi-hexamers.[7]

NON-INVASIVE INSULIN DRUG DELIVERY SYSTEMS

Insulin-loaded bioadhesive PLGA nanoparticles for oral drug delivery

The chitosan-PLGA nanoparticles are positively charged, Mucoadhesion and enhanced absorption that increase the residence time of insulin in vitro Improving in vivo bioavailability for oral administration. Toxicity of nanoparticle drug delivery systems was a big concern. Related studies show nanoparticles enhance therapeutic efficacy effects, but can also increase toxicity. However, the positive properties of CS-PLGA-NPs do not enhance this. Cytotoxicity as chitosan is biocompatible and biodegradable with low cytotoxicity. that's why it has Widely used in fields such as tissue engineering, gene therapy and drug delivery[7]

Polymeric hydrogels for oral insulin delivery

polymer The hydrogel protects insulin from enzymatic degradation in the acidic stomach and effectively delivers it to the stomach. colon. Mechanisms of hydrogel swelling and hyperemia under varying body pH conditions control insulin secretion. The combination of enzyme inhibitors within the polymer system is It may increase the potency of orally administered insulin. some insulin derivatives increased Physicochemical and biological stability such as alkylated/acylated insulin, PEGylation and polysialylation Insulin is the most promising candidate for oral administration In one study, polyelectrolyte-crosslinked hydrogels were synthesized using gamma radiation induced Copolymerization of methacrylic acid (MAA) and N,N-dimethylaminoethyl methacrylate (DMAEMA) Aqueous solution used for oral administration of insulin. Drug release studies showed an increase in The MAA content of the copolymer increases, shapes and enhances its release into the simulated intestinal fluid Insulin release behavior from these Carriers[7]

Acrylic polymers for oral insulin delivery

Recent studies have demonstrated the potential of polyalkylcyanoacrylates (PACA) as colloidal carriers for drugs. PACA not only improves oral absorption of insulin, but also prolongs its action in the presence of protease inhibitors. Capric acid and glycyrrhizic acid can be used as oral absorption enhancers. A pH-sensitive copolymer hydrogel prepared from N-vinylcaprolactam and methacrylic acid monomers by free radical polymerization provided an encapsulation efficiency of 52% and was evaluated for oral delivery of insulin in humans. The formulation in this study is a promising carrier for oral delivery of insulin. Poly(ethylene glycol)-grafted methacrylic acid and poly(ethylene glycol) nanosphere-grafted acrylic acid crosslinked network nanospheres were developed for use as oral insulin delivery devices. Radical precipitation/dispersion was used for the synthesis of copolymer nanospheres. By isolating the concentrated insulin solution, insulin was loaded into the copolymer at concentrations of 9.33 mg and 9.54 mg per 140 mg solid sample. An in vitro study was performed to examine the passage of insulin-loaded copolymer samples through the gastrointestinal tract. In a study with diabetic rats, serum glucose levels in animals administered insulin-loaded copolymers were lower than control values and persisted for at least 6 hours. caused a significant decrease[7]

Aerosolized liposomes for pulmonary delivery of insulin

The lungs provide a good blood supply, a large absorptive area with a very thin absorptive mucosa. The anatomy of the human respiratory system and the nature of influences brought about by the respiratory process complicates the delivery of peptides and proteins to the lung. Aerosolized liposomes containing phosphatidylcholine improve pulmonary insulin delivery by opening the epithelial cell spaces of the pulmonary mucosa rather than through mucosal cell damage, and smaller liposome particle sizes are also beneficial for improving pulmonary delivery.[7]

β-Cyclodextrin grafting hyperbranched polyglycerols as carriers for nasal insulin deliver

CDs are believed to enhance nasal absorption of peptides and proteins by inhibiting their enzymatic degradation, disrupting the epithelial membrane by extraction of phospholipids and proteins, and/or opening tight junctions and the positive charge of the nanoparticles might also play an important role, since the interaction of positively charged material with the negatively charged epithelium membrane would be helpful for opening the tight junction and facilitating the absorption of drugs across the paracellular pathway[7]

INVASIVE INSULIN DRUG DELIVERY SYSTEMS

Novel microneedle arrays fabricated from hyaluronic acid for the transdermal delivery of insulin

Microneedles are a promising technology for delivering drugs to the skin, as microneedles inserted into human skin are said to be painless. Microneedle arrays, use a system to push drugs through tiny needles that do not reach under the skin enough to trigger pain receptors. The stratum corneum barrier is destroyed. An alternative method is to deliver insulin through the skin into the systemic circulation using novel insulin-loaded microneedles that use hyaluronic acid to generate a morphology that does not cause skin damage. Complete absorption of insulin from the skin into the systemic circulation when administered via microneedles was demonstrated by pharmacodynamic and pharmacokinetic data. The hypoglycemic effect is almost the same for insulin-loaded microneedles and subcutaneous insulin injections. Hygroscopicity, stability, drug release profile and dissolution properties are key properties of insulin-loaded hyaluronic acid microneedles.[7]

Transdermal Delivery of Insulin by Amidated Pectin Hydrogel Matrix Patch

PI dermal matrix patches were made by dissolving pectin/insulin in deionized water and solidifying with CaCl2. Oral glucose test responses from diabetic rats showed lower blood glucose levels. Non-diabetic control rats showed higher plasma insulin concentrations than untreated diabetic rats[7]

Dissolving polymer microneedle patches for rapid and efficient transdermal delivery of insulin

The hypoglycemic effect was found to be similar in rats receiving insulin-loaded microneedles and subcutaneous insulin injections.Both the relative pharmacological availability and relative bioavailability of insulin were approximately 92%. Therefore, the pharmacological activity is retained even after insulin encapsulation. Microneedles retain his 90% of insulin even after 1 month of storage at 25 or 37°C. Results confirm the stable encapsulation of bioactive molecules using starch/gelatin and is thus a relatively painless, rapid and convenient method for transdermal administration of protein drugs.[7]

Nanotechnology in medicine

The term "nanotechnology" is used to describe the manipulation of matter at the atomic, molecular and supramolecular level, resulting in unique quantum mechanical effects. Therefore, the reduction of at least one dimension at the nanoscale (1–100 nm) has the potential to provide new technological advances in the design, fabrication, characterization and development of various nanomaterials in various fields. Includes apply. Nanoparticles (NPs) have many excellent properties. Compared to bulk structures, nanomaterials tend to be more dependent on shape and size, making interfaces more accessible. For example, metallic nanoparticles (NPs) exhibit characteristic colors depending on their nanosize and shape and can be widely used in bioimaging applications.[8]

The use of nanomaterials and nanodevices in the field of health and medicine, has open the door to the establishment of a new nanoscience area, this of nanomedicine. The advancements of nanotechnology in medicine can be summarised into three categories[8]

A. Drug delivery/therapeutics

Nanotechnology is also used in drug design to enhance absorption. For example, many drugs are readily soluble in water, whereas others are rapidly absorbed and eliminated from the body as waste products before the active substances reaches its optical Concentration, and may not be therapeutically effective. In addition, nanotechnology is gaining attention due to its ability to create particles that are attracted to specific cell types, especially diseased cells for direct therapy such as cancer cells[8]

B. Diagnosis/imaging

Nanomedicine can improve early detection, diagnosis, and prevention of disease by using specific nanoparticles as diagnostic tools and labels for high-resolution imaging, or as substrates for biosensor development. Applications of nanosensors will ultimately lead to the production of highly sensitive sensors Biomedical devices for rapid and high-throughput detection of disease biomarkers magnetic, chemical, structural properties) and those for diagnostic imaging (tumor detection, imaging of atherosclerotic plaques, etc.[8]

C. Tissue repairing/biomaterials

Nanotechnology enables the development of biocompatible scaffolds that mimic the complexity and function of extracellular matrices (ECMs) used for tissue regeneration. Furthermore, scaffolds with nanofeatures are designed to encapsulate and control the spatiotemporal release of drugs (such as growth factors). Nanotechnology-based biomaterials (nancoatings or nanostructured surfaces) are also used to overcome various problems of implant materials such as: B. Bacterial adhesion or corrosion resistance, e.g. orthopedics For diabetes, one of the most important contributions of nanotechnology is the development of new nanosensors for simple, accurate and sensitive blood glucose measurement. Nanotechnology has enabled the development of robust insulin delivery vehicles that bypass the acid environment of the stomach and facilitate direct transfer of insulin molecules to the bloodstream, thus providing an alternative to daily subcutaneous injections.[(8)]

Aims of nanotechnology in prediabetes/T2DM treatment

Nanotechnology is applied to address major treatment-hindering drawbacks of modern commercial drugs, such as Limited bioavailability and rapid drug release into the bloodstream, resulting in unwanted side effects To this purpose nanostructured-biomolecules and nanomaterials are synthesized to **1**. Increase bioavailability by protecting oral drugs and ensuring safe reach to blood circulation from initial absorption in the gastrointestinal tract **2** Prolong drug release: (a) Maintain constant drug concentration; (b) Reduce frequency of dosing and therefore; (c) Improve patient compliance **3** Reduce drug's potential side effects (combination of 1 + 2) such as hyperglycemia, weight gain, increase in insulin resistance, β-cells destruction, renal and cardiovascular complications[(8)]

Nano-drug carriers

Drug encapsulation in NPs aims to prolong drug release and presence in the systemic circulation. In addition, sustained release improves drug uptake from target tissues and reduces toxicity. Sulfonylureas are a class of antidiabetic drugs that work by increasing insulin release from pancreatic beta cells. One of the most commonly used sulfonylureas is gliclazide, which must be dosed twice daily. Entrapment of gliclazide in biodegradable and biocompatible carriers may enable sustained release of the drug into circulation. Although gliclazide lowered glucose levels rapidly (45%, 2 hours after administration), the effect of gliclazidniosomes on blood glucose was slow, reaching a maximum after 6 hours (~48%). Normalization of glucose levels 8-10 hours after administration of gliclazide Glipizide, a secondary sulfonylurea that stimulates the release of insulin from the pancreas, has a biological half-life of approximately 3.5 hours and extends it. It is administered 2 to 3 times daily for Encapsulated in poly-E-caprolactone (PCL), a biodegradable and biocompatible polymer, this difference tends to decrease over time (50 mg/dl to 30 mg/dl 1 day after treatment). mg/dl). Day 7) The dose of glipizide was 800 µg/kg (three times a day) for 7 days. In vitro release kinetic evaluation showed slow dissolution of the formulation. Nearly 25% cumulative release in first 24 hours to 65% in 168 hours[(8)]

Metal NPs as indirect antidiabetic drugs

Various trace elements are associated with glucose homeostasis, including zinc, vanadium, chromium, selenium and lithium. These metals have been implicated as cofactors in many biochemical enzymatic reactions, and several studies have highlighted their biological effects in impaired glucose metabolism. Both NPs act by increasing insulin secretion (the effect of ZnONP was stronger than SNP), insulin receptor α gene expression and glucokinase activity in the liver of diabetic animals. ZnONP in combination with vildagliptin (a DPP4 inhibitor) provides synergistic effects that enhance positive therapeutic outcomes[8]

Oral Nano Drug Delivery Systems of Antidiabetic Phytocompounds

Polymeric NPs

NPs are colloidal drug delivery systems covering particles ranging from 10 nm to 1000 nm in diameter. They may be reservoir systems, in which the drug is encapsulated in cavities surrounded by a polymer membrane called nanocapsules, or matrix systems, in which the drug is dispersed in particles called nanospheres. Due to their design flexibility, polymers have attracted much attention for their functionalization, polymer versatility and macromolecular synthesis methods in therapeutic applications. Polymer-based delivery systems can be divided into synthetic polymer NPs and non-artificial polymer NPs.[10]

NPs Based Upon Inartificial Polymers

Non-toxicity and biocompatibility are the main advantages of inartificial polymers compared to synthetic polymers. Sodium alginate, chitosan, gum arabic, rosin, and dextran are inartificial polymers designed to deliver anti-diabetic botanical compounds.[10]

Chitosan-Based NPs

Due to its simple surface modification, ability to blend with several polymers, non-immunogenicity, non-toxicity, and significant compatibility with cells and tissues, chitosan is the material that delivers antidiabetic phytocompounds the most widely. ferrous acid In comparison to free ferulic acid, chitosan NPs had four times the oral bioavailability in vivo, and they had superior antidiabetic potential in streptozotocin (STZ)-induced diabetic rats. This might be explained by chitosan's special capacity to momentarily loosen the tight junctions that connect epithelial cells. Additionally, chitosan's high positive charge makes it ideal for oral medication administration because it improves adherence to negatively charged mucosal surfaces, enhancing cell absorption. Additionally, the chitosan's active groups OH and NH2[10]

Alginate/Chitosan-Based NPs

In the cell walls of brown algae, alginate is a hydrophilic anionic copolymer that is widely distributed. Alginate has a broad range of medicinal applications because of its exceptional capacity to gel in aqueous medium or at low pH in the presence of divalent cations like calcium ions. By interacting electrostatically with other oppositely charged groups, alginate and chitosan can create polyelectrolyte complexes. While chitosan, which is more soluble at high pH, stabilises alginate, which is more soluble at low pH, the poor solubility of the alginate network at low pH reduces the high solubility of chitosan at low pH. In contrast to chitosan or alginate alone, the alginate/chitosan complex efficiently inhibits the release of the phytocompounds it has been used to encapsulate. Alginate and succinyl chitosan exhibit excellent pH sensitivity.[10]

Gum-Based NPs and Gum/Chitosan-Based NPs

Guar gum, gellan gum, karaya gum, gum acacia, locust bean gum, konjac gel, and xanthan gums are examples of natural gums that have been widely used to create safe drug delivery systems. They exhibit great stability across a wide pH range and the ability to form hydrogels when in contact with water. An organic anionic polymer formed from pine trees is gum rosin.(10)

Dextran-Based NPs

Negatively charged and highly water soluble carbohydrate is dextran. It primarily includes 1.3-branching and linear -1,6-linked glucopyranose units. Dextran is mostly produced by Lactobacillus, Streptococcus, and Leuconostoc in environments high in sucrose. Drug encapsulation is challenging due to the low affinity between lipophilic medicines and hydrophilic polymeric matrix.(10)

NPs Based Upon Synthetic Polymers

The FDA has approved the biodegradability and biocompatibility of synthetic polymer NPs, which are typically made of poly (vinyl alcohol) (PVA), poly (-caprolactone) (PCL), poly (lactic acid) (PLA), poly (lactic-co-glycolic acid) (PLGA), and poly (methyl methacrylate) (PMMA). Polyesters are used in amphiphilic diblock copolymers, where their adaptability allows for changes in drug loading capacity, carrier size, and drug release by altering the compositions and modifying the block lengths.(10)

Lipid-Based Nano Systems

Lipid-based nanodelivery systems are composed of biocompatible/biodegradable lipid moieties (GRAS), which are generally recognized as safe, and can improve the oral bioavailability of poorly water-soluble drugs while the lipids are compatible with water. It is an absorption enhancer because it can increase the oral bioavailability of poorly soluble drugs in a number of ways. Structural and chemical abundance of lipids form delivery systems with different properties, offering multiple opportunities to include different active agents(10)

Inorganic Nanocarriers

Inorganic materials have been used to explore nanocarriers with controlled morphology and size. Recent breakthroughs in surface functionalization and structural control of inorganic nanocarriers have brought more possibilities for drug delivery.(10)

Nano-DDS of MET for efficient diabetes treatment

MET, a biguanide drug for diabetes, is widely used to treat type II diabetes because of its mild side effects. However, MET still has some drawbacks that severely limit its therapeutic efficacy, such as poor intestinal absorption, high doses, and the need for frequent dosing due to its short half-life. , several nano-DDS are rationally designed, developed and efficiently delivered by MET. Drug-encapsulated nano-DDSs exhibit more properties of nanocarriers than the intrinsic properties of drugs. Therefore, nano-DDS may significantly change the mode of drug delivery. Various MET-encapsulated nano-DDSs have been contrasted by non-covalently loading MET into polymeric NPs, and various new polymers have been designed and synthesized to efficiently deliver MET.[9]

MET-encapsulated nano-DDS for oral delivery

A hydrophilic molecule with high solubility and low absorption properties, MET belongs to the biopharmaceutical classification system 'BCS'. Class III drugs Poor oral absorption efficiency and short half-life of MET lead to frequent dosing of high doses, even in grams per day. Therefore, great efforts have been made to improve this situation, and several nano-DDSs loaded with MET, including alginate NPs, have been developed to achieve controlled drug release and improved oral absorption. Rationally designed. For example, MET-loaded alginate NPs were developed through emulsion cross-linking technology for diabetes treatment. Gastrointestinal absorption and intestinal permeability of MET were significantly improved compared to free drug[9]

ESTABLISHED DRUG CLASSES FOR THE TREATMENT OF DIABETES

Types of Insulin

Various types of insulin make up a significant portion of the FDA-approved antidiabetic drugs, with at least 14 unique analogues and combination therapies. Insulin is perhaps one of the best-studied proteins and an essential component of type 2 diabetes treatment. Recombinant insulin analogues have been developed that function in a variety of ways. Fast-acting insulin analogues provide the required bolus insulin levels at meals (prandial insulin) and include insulin lispro, aspart, and gluticine. Long-acting insulins, such as detemir, glargine, and long-acting degludec, are released slowly over an extended period of time to provide the basal insulin levels (basal insulin) you need throughout the day and night. Such a spectrum of insulin analogues enables the combination of different forms of insulin, thereby providing an effective basal bolus regimen that better reflects physiological insulin secretion.[2]

Sulfonylureas (SU)

Two SU plus metformin combination regimens have been approved by the FDA and are currently on the market. glyburide/metformin, glipizide/metformin. Combinations of glimepiride and metformin exist and SU agents are associated with increased prevalence of hypoglycemia[2]

Biguanides

Metformin selectively inhibits the mitochondrial isoform of glycerophosphate dehydrogenase, indirectly activates adenosine monophosphate-activated protein kinase (AMPK), and reduces cytosolic dihydroxyacetone phosphate, secretion of the NADH/NAD ratio and endogenous glucose production. In addition, metformin may increase insulin sensitivity in muscle tissue. [2]

Alpha-Glucosidase Inhibitors

Inhibition of α-glycosidase prevents complex carbohydrates from being digested into simple sugars in the small intestine. These active ingredients therefore act as pseudo-carbohydrates (substrate analogues) where they inhibit digestive enzymes and prevent oligo- and polysaccharides from being catabolized into monomers. It lowers postprandial blood glucose levels and reduces hyperglycemia .AGIs have been shown to be as effective as metformin, so they are prescribed as first-line treatment or in combination with other antidiabetic agents often Side effects of AGI include bloating, bloating, discomfort, and diarrhea.(2)

Thiazolidinediones

There are currently two of his TZDs on the market, rosiglitazone and pioglitazone, which were approved by the FDA in 1999. The use of TZDs was previously limited due to safety concerns and side effects. TZD drugs are effective as monotherapy or combination therapy. Combination therapy of pioglitazone and metformin is currently on the market. Four TZD monotherapies and one combination therapy with a dipeptidyl peptidase 4 (DPP4) inhibitor are in clinical development studies. The most clinically advanced is robeglitazone, which has already been approved in South Korea and is currently undergoing Phase III trials with additional combinations. TZD molecules can interact with PPAR-α and PPAR-γ isoforms, which are predominantly expressed in adipose tissue and skeletal muscle. This activates these receptors and stimulates complex formation with another essential component, the retinoid X receptor. The ternary complex specifically binds to DNA via the peroxisome proliferation response element (PPRE) and functions as a target gene promoter to stimulate gene expression. (2)

Meglitinides

Two meglitinides have been approved by the FDA. Nateglinide in 2009 and Repaglinide in 2013 Meglitinides have a mechanism of action similar to sulfonylureas in that they increase insulin secretion in the pancreas. They bind to SUR in pancreatic beta cells, but at a different binding site than SU, inducing the same cascade of responses leading to insulin secretion. In contrast to SU, meglitinides, especially nateglinide, show glucose-sensitive effects, increasing potency at higher glucose concentrations. Meglitinides are short-acting and are associated with lower risks of hypoglycemia, weight gain, and chronic hyperinsulinemia than sulfonylureas. There are currently no meglitinides. In clinical studies, meglitinides are associated with an increased risk of hypoglycemia in diabetic patients with advanced chronic kidney disease.(2)

Oral Delivery of Insulin

Any medicine can be administered orally, and this is the most practical method. Insulin that can be taken orally is still being developed. When insulin is administered orally, needle anxiety, potential infections, and pain from the injection (when administered subcutaneously) are all avoided. Due to its direct distribution to the liver, oral insulin administration is advantageous. A very low permeability of insulin occurs across the epithelium of the intestine for two reasons: first, because of its high molecular weight and the fact that it is broken down by the enzyme Insulinase very quickly. This means that the dynamics of subcutaneous insulin delivery are not similar to the normal endogenous insulin release. Proteins like insulin have a very poor oral bioavailability of just 1%. There is a target, then. Surfactants (ethylenediaminetetraacetic acid) have been used as an excipient to improve the absorption of protein-based medications like insulin. In some studies, mucoadhesive polymers, which increase intestinal penetration, have been utilised to deliver insulin to the mucosa. Using nanoparticles to administer insulin is a far more recent method of doing so. The therapeutic effectiveness of insulin is significantly influenced by the quantity of insulin and polymer. Studies conducted in vitro revealed that nanoparticles shield insulin from enzymatic breakdown. Polyalkylcyanoacrylate, polymethacrylic acid, and polylactic-co-glycolic acids are the primary polymers utilised in the formulation of nanoparticles (PLGA). Additionally, naturally occurring polymers including chitosan, alginate, gelatin, albumin, lectin, and others are employed. Chitosan among them has a good penetration property.(4)

Buccal Route of Insulin Administration

Buccal mucosa refers to the lining of the inner cheek, and buccal insulin is the term used when insulin is absorbed by this buccal mucosa and transported to the systemic circulation by inserting buccal formulation inside the mouth, specifically between the upper gingiva and cheek. The molecular weight, hydrophilicity, conformation stereo specificity, solubility, electrostatic charge, and partition coefficient of proteins and peptides are factors that affect the absorption potential. Through the use of a device that sprays the insulin, the insulin is absorbed in the mouth and throat in this manner of delivery. Because the blood supply to the buccal mucosa is so high because to the reticulated veins, absorption is likewise quite high. This inhibits hepatic first pass metabolism. delivery using a high-powered inhaler Due to their 3D (three-dimensional) structural conformance and coherence and ability to assist buccal application and adhesion, pelted nanoparticles have been employed for the buccal delivery of insulin. In order to distribute insulin buccally, buccoadhesive tablets using compression of powder mixtures (carbopol 934, hydroxyl propyl methylcellulose, and a few absorption boosters) have been employed; nevertheless, patches, which are thin and flexible, are thought to be preferable to tablets. Additionally, it has a drug reservoir, impermeable backings, a bioadhesive surface, and other components.(4)

Sustained Release Strategy Designed for Lixisenatide

MATERIALS

Sigma-Aldrich provided PEG with a molecular weight (MW) of 1500, -caprolactone (CL), and stannous 2-ethyl-hexanoate (stannous octoate, 95%). It was decided to buy D,L-lactide (LA) and glycolide (GA) from Hangzhou Medzone Biotech Ltd. (Zhejiang, China). The supplier of Lixi was GL Biochem Ltd. (Shanghai, China). The Nanjing Jiancheng Bioengineering Institute sold triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) assay kits.(11)

Interactions between Lixi and the Copolymers

DLS was used to investigate the interaction of Lixi with copolymers in aqueous media. Micelle size of the mixture in water with the two copolymers before and after Lixi loading. All three polymer systems formed uniform micelles at low concentrations with sizes of 35, 35, and 38 nm.The addition of Lixi did not affect the unimodal pattern of the polymer micelles. , the particle size increased to some extent. The surface charge of the micelles was measured by ζ potential analysis to determine whether the introduction of Lixi altered the surface charge. Pure copolymer micelles have a slightly negative surface charge at neutral pH. In contrast, Lixi is positively charged (+34 mV) due to the presence of positively charged amine groups on the peptide backbone. For example, looking at the micellar mixture, Lixi complexed with the micellar mixture reduced the negative surface charge. The surface charge of micelles approached electroneutrality with increasing Lixi concentration CD is the most widely used tool for detecting secondary structures such as folding and binding properties of low-abundance proteins/peptides. As shown in Fig. 5c, native Lixi exhibits negative bimodal bands at approximately 208 nm and 222 nm, indicating the typical α-helical secondary structure of the peptide. After introducing Lixi into the aqueous copolymer solution, the secondary structure of Lixi changed significantly. Negative signals at 208 and 222 nm were significantly reduced in magnitude and exhibited a red shift with the introduction of the copolymer. Increasing the amount of PLGA-PEG-PLGA in the polymer produced greater changes. Combined with the above measurements, we speculated that electrostatic interactions between Lixi and copolymers facilitate drug loading into polymeric micelles, resulting in increased micelle size and Lixi conformational transitions.(11)

Long-Term Blood Sugar Control

To further confirm the long-term glycemic control efficacy of the Lixi/Gel system, mice received two consecutive injections of the Lixi/Gel system on days 10 and 20 after the first dose. After 30 days, animals were euthanized and blood samples taken from the eyes. As can be seen from the plasma insulin concentration, compared with the PBS-treated group, two consecutive daily injections of free Lixi for 1 month significantly increased the plasma insulin concentration. Interestingly, there were higher insulin levels in the Lixi/Gel group, indicating that the slow and steady release of Lixi promoted insulin secretion more effectively. HbA1c, which is formed by nonenzymatic, irreversible glycosylation of hemoglobin and can effectively reflect blood glucose levels over the past 1–3 months, is considered a long-term control indicator, in contrast to highly variable blood glucose concentrations. is done. glycemic control period. Therefore, plasma HbA1c levels were also detected, and compared to the PBS group, the group receiving Lixi/gel formulations three times within one month and free Lixi twice daily for 30 days had no significant HbA1c showed a decrease. Furthermore, he found no significant difference in HbA1c between the Lixi/Gel and Free Lixi groups. The results demonstrate that the efficacy of the Lixi/Gel system on long-term glycemic control is comparable to twice-daily injections of free Lixi.(11)

Future Perspectives

Although hopeful results from type 1 diabetes preventive and disease modification studies continue to be found, none of the strategies mentioned above seem to be adequately successful. by themselves in controlling or avoiding type 1 diabetes. Therefore, future efforts will need to have a fresh perspective, building on previous knowledge of the immunopathophysiology of type 1 diabetes while also examining the potential of combination therapies that combine tried-and-true or novel therapeutic modalities. Additionally, type 1 diabetes may benefit from the knowledge gained about the positive impact of specific medications on factors like body weight and cardiorenal risk from type 2 diabetes [6]

Conclusion

The use of cutting-edge insulin delivery systems can lessen the long-term effects of diabetes mellitus. A noninvasive approach has been attempted to take the place of the invasive subcutaneous route. Significant advancements have been made in the delivery of insulin orally, buccally, and intravenously. Each route has a unique set of benefits and drawbacks. The oral route appears to be the most promising non-invasive option since nanotechnology enables the various encapsulations to pass through the acidic environment of the stomach. Patient compliance is increased by the oral route's enhanced absorption rates and simplicity of administration. Even Phytocompounds are prospective candidates for antidiabetic drugs due to their plentiful sources, considerable therapeutic effects, and few adverse effects. In general, phytocompounds have four hypoglycemic mechanisms: decreasing carbohydrate breakdown and glucose absorption; promoting glucose uptake and metabolism; improving insulin action and sensitivity; and acting as an antioxidant and anti-inflammatory. As we mentioned above the delivery systems for effective insulin therapy teplizumab is found to be one of the most prominent and effective compared to conventionally pre-existing insulin drug delivery therapies. Teplizumab reduces autoimmune destruction of pancreatic B-cells by increasing Foxp 3+, CD8+, CD25+ T-cells While maintaining CD4+ T-cells thus leading to a reduction in the ratio of CD4+ to CD8+ Cells.

References

1. Santwana Padhi, Amit Kumar Nayak and Anindita Behera, *Biomedicine & Pharmacotherapy*, 2020, **131,** 1
2. Amelia D. Dahlén, Giovanna Dashi, Ivan Maslov, Misty M. Attwood, Jörgen Jonsson, Vladimir Trukhan, and Helgi B. Schiöth, *Frontiers In pharmacology*, 2022 **12** 1
3. Li Ching Ng, Manish Gupta, *Asian. J. Pharmaceutical Science. Science Direct*, 2019, **22,** 12
4. Arun Verma, Nitin Kumar, Rishabha Malviya, and Pramod Kumar Sharma, Hindawi Publishing Corporation J. of Pharmaceutics, **2014**, 1 & 2
5. Ana Luisa Perdigoto, Paula Preston-Hurlburt, Pamela Clark, S. Alice Long, Peter S. Linsley, Kristina M Harris, Steven E, Gitelman, Carla J. Greenbaum, Peter A, Gottlieb, William Hagopian, Alyssa Woodwyk, James Dziura, Kevan C, Herold, *Diabetologia, Springer*, 2018
6. Bernt Johan von Scholten, Frederik F. Kreiner, Stephen C. L. Gough, Matthias von Herrath, *Diabetologia, Springer*, 2021, **64,** 1037–1048
7. Yasmeen, T. Mamatha, Md. Zubair, Sana Begum, Tayyaba Muneera, *British J. of Pharmaceutical Research*, 2015, **5(5),** 294-308

8. Yannis V. Simos, Konstantinos Spyroub, Michaela Patilac, Niki Karoutab, Haralambos Stamatisc, Dimitrios Gournis, Evangelia Dounousi, Dimitrios Peschos, *Asian. J. Pharmaceutical Science. Science Direct*, 2020, **15,** 33, 2 & 3
9. Yao Chen, Xinzhu Shan, Cong Luo, Zhonggui He, *J. of Pharmaceutical Investigation*, 2020,
10. Xin Nie, Zhejie Chen, Lan Pang, Lin Wang, Huajuan Jiang, Yi Chen, Zhen Zhang, Chaomei Fu, Bo Ren, Jinming Zhang, *Int. J. Nanomedicine* 2020, **15,** 10215–10240
11. Yaping Zhuang, Xiaowei Yang, Yamin Li, Yipei Chen, Xiaochun Peng, Lin Yu, Jiandong Ding, *American Chemical Society Publication*, 2019, **11**, 29604−29618