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Scientific Paper Entitled: Review Of Recent Drugs of Diabetes Mellitus Type 2

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Abstract

Diabetes mellitus (DM) is a metabolic disorder that occurs when the body has reduced insulin activity or insufficient insulin secretion. As the disease progresses, it leads to various complications such as nephropathy, retinopathy, and cardiovascular problems. There are two main subtypes of DM: type 1 DM and type 2 DM. Type 1 DM is typically treated with insulin replacement therapy, while type 2 DM is managed with oral medications for lowering blood sugar levels.

The primary drug therapy for type 2 DM includes insulin secretagogues, biguanides, insulin sensitizers, alpha-glucosidase inhibitors, incretin mimetics, amylin antagonists, and sodium-glucose co-transporter-2 (SGLT2) inhibitors. In cases where patients are unable to achieve their target blood sugar levels with a single oral medication, combination therapy involving two drugs may be recommended. However, conventional dosage forms of these drugs often have issues with inconsistent absorption and a short duration of action. This necessitates frequent dosing and can result in more side effects, leading to ineffective treatment and patient non-compliance.

Given the complex nature of the disease, nanotechnology-based approaches have gained attention for the treatment of type 2 DM. These approaches offer advantages such as targeted drug delivery to specific sites, improved drug absorption, and reduced dosing frequency. In this review article, we explore the underlying mechanisms of type 2 DM,

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current conventional treatment strategies (both single and combination therapy), and the use of nanotechnology for drug delivery in the management of type 2 DM.

Key words: *Type II Diabetes mellitus, monotherapy, combination therapy.*

Introduction

Diabetes mellitus (DM) is a significant global health concern, affecting over 400 million individuals worldwide (Khursheed et al., 2019). This metabolic disorder progressively leads to severe complications affecting various aspects of the body, including microvascular, macrovascular, and neuropathic complications. DM can be caused by insufficient insulin secretion, damage to pancreatic β cells, or insulin resistance resulting from the non-utilization of insulin. The increasing prevalence of sedentary lifestyles is a major contributing factor to the rising number of diabetic patients globally, with projections estimating that the elderly population (over 65 years) will be impacted by DM, reaching 366 million cases by 2030(Wild et al., 2004).

DM is associated with a range of complications, including nephropathy, neuropathy, cardiovascular and renal complications, retinopathy, and food-related disorders, among others. There are two main types of DM: type 1 DM and type 2 DM. Type 1 DM is an autoimmune disorder that specifically affects the pancreatic cells responsible for insulin production, leading to a reduction or impairment in insulin production. On the other hand, type 2 DM arises from the impairment of pancreatic beta cells, which hinders an individual's ability to effectively utilize insulin(Wong et al., 2017).

The primary conventional drug classes for treating hyperglycemia in diabetes include sulfonylureas (stimulate insulin release), biguanides (reduce glucose production by the liver), peroxisome proliferator-activated receptor-γ (PPARγ) agonists (enhance insulin action), and α-glucosidase inhibitors (inhibit glucose absorption in the gut)(Chaudhury et al., 2017). These drugs can be used as monotherapy or in combination with other hypoglycemic agents. However, their use is associated with drawbacks such as severe hypoglycemia, weight gain, suboptimal dosing regimens leading to lower therapeutic efficacy, decreased potency, altered side effects due to drug metabolism, lack of target specificity, and solubility and permeability issues(Oral and Injectable (Non-Insulin) Pharmacological Agents for the Treatment of Type 2 Diabetes - Endotext - NCBI Bookshelf, n.d.).

Despite the development of promising anti-hyperglycemic agents, optimizing existing therapies to achieve balanced glucose levels and reduce long-term diabetes-related complications remains a major challenge(Tan et al., 2019). In this context, nanoformulations have emerged as a potential solution to overcome the limitations of conventional drugs(Souto et al., 2019). Nanoformulations improve drug solubility and offer several advantages, including reduced dosage requirements, rapid onset of action, controlled drug release, minimized side effects, optimized drug delivery, extended drug half-life, reduced patient variability, enhanced bioavailability, and improved pharmacokinetics and pharmacodynamics(Uppal et al., 2018). Moreover, nanoformulations can work at the molecular level to enhance cellular drug uptake, disrupt efflux mechanisms like the P-glycoprotein pump, or target specific receptors, further enhancing the therapeutic profile of anti-diabetic drugs(Kobori et al., 2013).

This review article examines the current conventional drugs used in the treatment of type 2 DM, discusses their limitations, and explores novel nanoformulations that are being actively researched to address the drawbacks associated with conventional drug use.

Pathophysiology of diabetes

The homeostasis of glucose in the body is maintained by a number of hormones. However two hormones namely, insulin and glucagon play a dominant role in the regulation of glucose homeostasis(Okur et al., 2017). Insulin is secreted by β cells when the concentration of glucose rises. Insulin decreases the level of blood glucose either:
a) By inhibiting the production of glucose from liver by glycogenolysis and gluconeogenesis(Mayorov, 2011), or
b) By increasing the uptake of glucose by liver, muscle and fat tissue.
Glucagon is secreted by α cells of pancreas when the concentration of glucose is low. Glucagon acts by
a) Antagonizing the effect of insulin by enhancing the processes like glycogenolysis and gluconeogenesis in liver(Ojha et al., 2019).
b) In addition to glucagon, cortisol and catecholamines also increases the plasma glucose levels.

Other hormones which are involved in maintenance of normal glucose level are amylin (a 37 amino acid peptide), glucagon like Pep- tide – 1 (GLP-1) (a 30 amino acid peptide) and Glucose dependent insulinotropic polypeptide (GIP) (a 42 amino acid peptide).

Amylin is secreted along with insulin. It decreases gastric emptying, which enhances glucose absorption after a meal intake. GLP and GIP are incretin or peptide derived from the gut. These incretins facilitate the synthesis and secretion of insulin from β cells of pancreas(Hieronymus & Griffin, 2015).
Glucose is not absorbed from intestine or by cells requiring energy freely. So the distribution of glucose to the cells is done by glucose transporters. The Glucose transporters are a family of membrane bound glycoproteins and are classified into two types(Stringer et al., 2015).
i) Sodium glucose co-transporter (SGLT)

ii) Facilitative glucose transporter (GLUT)

Diabetes mellitus is categorized into two major sub-types and the causes associated remains differential.

1- Type – I DM (T1DM): The immune system mistakenly attacks the β cells of pancreas where genes play a vital role.

2- Type – II DM (T2DM): Interplay of genetics and lifestyle factors plays a vital role. Being obese or overweight increases the associated risks.
Pathophysiology of T2DM may include any one or combination of any mechanisms of "ominous octet" as outlined below:(DeFronzo, 2009)

i) Reduced insulin secretion from β cells of the islets of Langerhans.
ii) Elevated glucagon secretion from α cells of the islets of Langerhans.
iii) Increased production of glucose in the liver.
iv) Dysfunction of neurotransmitters and insulin resistance in the brain.
v) Increase in lipolysis (breakdown of fats).
vi) Increase in the reabsorption of glucose by the kidneys.
vii) Reduction in the effect of incretin hormones in the small intestine.
viii) Impairment or decreased uptake of glucose by peripheral tissues such as skeletal muscle, liver, and adipose tissue.

3- Gestational diabetes occurs during pregnancy due to hormonal changes that make cells less sensitive to insulin(McIntyre et al., 2019).

4- Genetic mutations can lead to monogenic diabetes, which is caused by mutations in a single gene. Neonatal diabetes and maturity-onset diabetes of the young (MODY) are examples of monogenic diabetes(Sun et al., 2014).

3- Cystic fibrosis can affect insulin production due to scarring in the pancreas caused by thick mucus.

4- Hemochromatosis, a condition where the body stores too much iron, can lead to damage to the pancreas and impair insulin production.

5- Certain hormonal diseases, such as Cushing's syndrome, acromegaly, and hyperthyroidism, can cause insulin resistance and contribute to the development of diabetes.

6- Damage or removal of the pancreas, such as in cases of pancreatitis, pancreatic cancer, or trauma, can result in the loss or dysfunction of beta cells, leading to diabetes.

7- Certain medications, including niacin, diuretics, anti-seizure drugs, psychiatric drugs, HIV medications, pentamidine, glucocorticoids, anti-rejection medicines, and statins, can affect beta cell function or disrupt insulin production.

In summary, the pathophysiology of T2DM involves a combination of factors related to insulin secretion, glucagon secretion, glucose production, insulin resistance, and other underlying conditions or medications that can impact glucose metabolism in the body.

Risk factors

In the case of type 1 diabetes mellitus (T1DM), the risk of developing diabetes is higher in children and teenagers if their parent or sibling has diabetes(Streisand & Monaghan, 2014).

For type 2 diabetes mellitus (T2DM), the risk factors include:

- Being overweight or obese.
- Unhealthy dietary habits.
- Age over 45 years.
- Having a family history of diabetes.
- Leading a sedentary lifestyle.
- Having pre-diabetes or gestational diabetes.
- Having high cholesterol or triglyceride levels.

The risk of gestational diabetes increases if the person:

- Is overweight, especially with a body mass index (BMI) over 25.
- Is over 25 years of age.
- Has had gestational diabetes in a previous pregnancy.
- Has given birth to a baby weighing more than 9 pounds.
- Has a family history of type 2 diabetes.
- Has polycystic ovary syndrome (PCOS).

Complication

Diabetes is associated with a wide range of complications due to the damage caused by high blood sugar levels to organs and tissues in the body. The longer the body is exposed to high blood sugar levels, the higher the risk of developing additional complications. These complications can be categorized into microvascular and macrovascular complications:

1. Microvascular complications: These involve damage to small blood vessels. Examples include:

- Nephropathy: Kidney damage that can progress to kidney failure.
- Retinopathy: Damage to the blood vessels in the retina, leading to vision loss.

- Neuropathy: Nerve damage that can result in numbness, tingling, pain, or loss of sensation, particularly in the extremities.

2. Macrovascular complications: These involve damage to large blood vessels. Examples include:

- Heart diseases: Diabetes increases the risk of developing cardiovascular diseases such as coronary artery disease and heart failure.

- Stroke: Increased risk of stroke due to the narrowing or blockage of blood vessels in the brain.

Other complications associated with diabetes include:

- Infections and slow-healing sores: High blood sugar levels can impair the immune system, making individuals more susceptible to infections and leading to slow wound healing.

- Depression and dementia: There are an increased risk of mental health conditions like depression and cognitive decline, including dementia, in individuals with diabetes.

Diabetes diagnosis

To diagnose prediabetes or diabetes, various blood tests can be performed, including:

- Fasting plasma glucose (FPG) test: Measures blood glucose levels after an 8-hour fasting period.

- HbA1C test: Measures average blood sugar levels over the previous three months.

For diagnosing gestational diabetes, blood tests are typically conducted between the 24th and 28th week of pregnancy. These may include a glucose challenge test and a three-hour glucose tolerance test [20,40]. Regular testing is essential for individuals with symptoms of diabetes or those at risk of developing the condition(Mirghani Dirar & Doupis, 2017).

Therapeutic approaches in non-insulin treatment for type 2 diabetes mellitus

A number of non-insulin based oral therapies have emerged for the treatment of type 2 DM. These are categorized under the following sub-headings:

4- Insulin Secretagogues

5- Biguanides

6- Insulin Sensitizers

7- Alpha Glucosidase Inhibitors

8- Incretin mimetics

9- Amylin antagonists

10- SGLT2 inhibitors

- Insulin secretagogues

Insulin Secretagogues, particularly sulfonylureas and meglitinides, work by increasing insulin secretion from the pancreas. They achieve this by binding to the sulfonylurea receptor (SUR) on the ATP-sensitive potassium channels of pancreatic β cells(Seino et al., 2017). First-generation sulfonylureas include Tolbutamide, Chlorpropamide, Tolazamide, and Acetohexamide, while second-generation sulfonylureas include Glibenclamide, Glipizide, and Glimepiride. The development of second-generation sulfonylureas was aimed at enhancing their potency, providing a more rapid onset of action, shorter plasma half-lives, and longer duration of action. Common side effects of sulfonylureas include symptoms of low blood sugar levels, such as dizziness, sweating, confusion, and nervousness. Other potential side effects may include hunger, weight gain, skin reactions,

stomach upset, and dark-colored urine. Metiglinides, represented by the prototype molecule derived from the non-sulfonylurea moiety of Glibenclamide, exert their effect by closing the ATP-sensitive potassium channels on the plasma membrane of pancreatic β cells. Repaglinide and Nateglinide are additional drugs used in this category(Hemmingsen et al., 2016).

- Biguanides

Biguanides, such as Metformin, improve the body's response to natural insulin by increasing insulin receptor activity. They work by reducing the absorption of glucose from the intestine, decreasing glucose production by the liver, and lowering hepatic glucose output through a decrease in gluconeogenesis and an increase in glycolysis(Quillen et al., 1999). Unlike insulin secretagogues, biguanides do not directly influence insulin secretion. Phenformin and Buformin were previously used in this category but were withdrawn from clinical use due to a high risk of associated lactic acidosis. Metformin, on the other hand, has a much lower risk of lactic acidosis and is widely used. Biguanides do not cause hypoglycemia or induce weight gain. They also have anti-hypertriglyceridemic effects and vasoprotective properties. By activating AMP-dependent protein kinase, biguanides block the breakdown of fatty acids. However, common adverse effects of biguanides include gastrointestinal distress such as diarrhea, cramps, nausea, vomiting, and increased flatulence. Long-term use of biguanides is associated with decreased absorption of vitamin B12(Sanchez-Rangel & Inzucchi, 2017).

- Insulin sensitizers

Insulin sensitizers, also known as Peroxisome Proliferator-Activated Receptor (PPAR) agonists, are a class of drugs that regulate protein and carbohydrate metabolism and maintain glucose homeostasis. PPARs are nuclear hormone receptors and ligand-activated transcription factors. There are three subtypes of PPARs: PPARα, PPARδ, and PPARγ. PPARγ is specifically involved in glucose homeostasis. PPARγ agonists, commonly known as thiazolidinediones or "glitazones," increase cellular sensitivity to insulin, decrease systemic fatty acid production and uptake, enhance glucose uptake by skeletal muscles, and reduce glucose production by inhibiting gluconeogenesis(Greenfield & Chisholm, 2004).

The first-generation PPARγ agonists include Pioglitazone, Rosiglitazone, and Ciglitazone. However, they are associated with common side effects such as edema, weight gain, macular edema, and heart failure. When combined with other antidiabetic drugs, they may also increase the risk of hypoglycemia. Additionally, they can cause a decrease in hematocrit and hemoglobin levels and an increased risk of bone fractures(Lebovitz, 2019).

Dual PPARα/γ agonists have been developed to provide synergistic action in lipid metabolism, insulin sensitivity, and inflammation control. These agents activate both PPARα and PPARγ receptors and help reduce the side effects associated with PPARγ agonists. Examples of dual PPARα/γ agonists include Muraglitazar, Tesaglitazar, Aleglitazar, Ragaglitazar, Naveglitazar, and Saroglitazar. However, the use of Muraglitazar was withdrawn from clinical trials due to cardiotoxicity.

The use of second-line drugs has become more prevalent in the treatment of diabetes mellitus due to the side effects associated with first-line drugs(Asif, 2014).

New classes of drugs included in advanced therapy

Now a days the newer classes of drugs used for T2DM are as following:

1- Alpha glucosidase inhibitor

2- Amylin agonists

3- Incretin mimetics (GLP – 1 Agonists and DPP – IV inhibitors)

4- SGLT2 antagonists/ inhibitors

a) Alpha-glucosidase inhibitors (AGIs)

Alpha-amylase and alpha-glucosidase are important enzymes involved in carbohydrate metabolism. Alpha-glucosidase inhibitors (AGIs) are oral medications commonly used to treat type 2 diabetes mellitus (T2DM). These drugs work by slowing down the absorption of carbohydrates in the gastrointestinal tract, thereby reducing postprandial hyperglycemia (high blood sugar levels after a meal). AGIs act as competitive inhibitors for the enzymes in the small intestine, delaying the digestion of carbohydrates such as starch and resulting in a slower release of glucose into the bloodstream. The first AGI, acarbose, was derived from Actinomyces utahensis and inhibits the enzyme alpha-glucosidase. Other AGIs used for managing T2DM include voglibose and miglitol(Narita et al., 2012).

AGIs have several benefits, including lowering post-meal blood sugar levels and reducing HbA1c (a measure of long-term blood sugar control). They can also increase the levels of GLP-1, a hormone that helps delay digestion and decrease appetite. However, AGIs may have side effects such as bloating, flatulence, and gastrointestinal irritation, although these symptoms usually improve over time.

It is important to note that AGIs are not recommended for individuals with certain conditions, including inflammatory bowel disease (such as ulcerative colitis or Crohn's disease), intestinal blockage, digestive disorders in the intestines, or diabetic ketoacidosis (a condition where the body burns fat instead of carbohydrates for energy). Acarbose should not be used by patients with an ulcer in the large intestine, cirrhosis of the liver, or pregnant women(Derosa & Maffioli, 2012).

b) Amylin analogues

Amylin is a hormone composed of a single chain of 37 amino acids. It is produced and released together with insulin by the beta cells of the pancreas. Its primary functions include slowing down gastric emptying, suppressing the secretion of glucagon (a hormone that raises blood sugar levels), and regulating food intake by influencing the appetite center in the brain(Adeghate & Kalász, 2011). In individuals with both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), there is a deficiency of amylin. To address this, researchers have developed analogues of amylin that can mimic its actions and help maintain glucose homeostasis.

Amylin itself is not suitable as a therapeutic drug because it tends to aggregate and become insoluble in solution. Therefore, chemical analogues have been created to replicate the actions of amylin. These analogues are available in injectable form and are used in the treatment of both T1DM and T2DM. They are typically administered before meals and exert similar effects to natural amylin. One example of an amylin analogue is pramlintide acetate, which is marketed under the brand name Symlin® and is given via subcutaneous injection(Schmitz et al., 2004).

The most common side effects of amylin analogues include nausea, vomiting, headache, and hypoglycemia when used in combination with insulin. However, these side effects generally diminish as patients adjust to the medication(Schmitz et al., 2004).

c) Incretin mimetics (GLP-1 agonists and DPP-IV inhibitors)

GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide) are incretin hormones derived from the gut. Incretins are natural metabolic hormones that contribute to a decrease in blood glucose levels. They are released after a meal. GLP-1, which consists of 36 amino acids, is secreted by L cells in the gut in a manner similar to insulin secretion from pancreatic beta cells. GLP-1 stimulates the synthesis and secretion of insulin from pancreatic beta cells. The metabolism of carbohydrates in the L cells of the intestine leads to the closure of ATP-sensitive potassium channels, depolarization of the cell membrane, and entry of calcium ions (Ca2+), resulting in the secretion of GLP-1. However, the half-life of GLP-1 is short (about 1-2 minutes) due to rapid metabolism by

dipeptidyl peptidase-IV (DPP-IV) enzymes. Therefore, the development of GLP-1 analogues with longer half-lives has been explored as a potential treatment for both type 1 and type 2 diabetes mellitus. DPP-IV inhibitors also act as incretin mimetics(Hinnen, 2017).

GLP-1 agonists or analogues are a new class of injectable drugs used for the treatment of type 2 diabetes mellitus. To enhance stability and resistance to DPP-IV metabolism, GLP-1 analogues have been designed by substituting the alanine residue at the N-terminal with other amino acids such as threonine, glycine, and serine. These analogues are more stable in vitro and have twice the potency of GLP-1. Exenatide was the first GLP-1 analogue developed, and it has an N-terminal glycine residue, making it resistant to DPP-IV. Other GLP-1 analogues include lixisenatide, dulaglutide, and liraglutide. GLP-1 analogues increase insulin secretion and inhibit glucagon release, leading to lower blood glucose levels and reduced HbA1c levels. Common side effects of incretin mimetics include nausea, vomiting, headaches, dizziness, increased sweating, indigestion, constipation, and loss of appetite(Holst, 2019).

GLP-1 receptor agonists are recommended as add-on therapy for patients who do not achieve their target HbA1c levels after three months of metformin therapy. They can also be used as first-line therapy for patients who cannot tolerate or are contraindicated for metformin. GLP-1 receptor agonists are well-suited for early use in type 2 diabetes because they stimulate insulin release and suppress glucagon secretion only when blood glucose levels are elevated, reducing the risk of hypoglycemia. GLP-1 receptor agonists can be used in combination with metformin or in triple therapy with metformin and a sodium-glucose co-transporter 2 (SGLT-2) inhibitor for patients with persistent hyperglycemia. Combining incretins with basal insulin may delay the need for mealtime insulin and reduce the risk of hypoglycemia. DPP-IV is an enzyme that deactivates GLP-1, and DPP-IV inhibitors increase the activity of GLP-1 by inhibiting its degradation. Currently available DPP-IV inhibitors include sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, gemigliptin, anagliptin, teneligliptin, trelagliptin, and omarigliptin. These inhibitors have high oral bioavailability(Gallwitz, 2019).

d) Sodium glucose co-transporter 2 antagonists/ inhibitors

The reabsorption of glucose in the proximal convoluted tubule (PCT) of the kidney involves two types of transporters: the facilitative glucose transporter (GLUT), which operates through passive transport, and the sodium-glucose co-transporter (SGLT), which functions through active co-transport with sodium. SGLT2 inhibitors specifically target and inhibit the SGLT2 protein present in the PCT. By inhibiting SGLT2, these drugs prevent the reabsorption of glucose in the kidney, leading to increased glucose excretion in the urine. This mechanism helps maintain glucose levels in the blood and improves other glycemic parameters(Scheen, 2015).

There are several SGLT2 inhibitors available, including canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin. These inhibitors can be used as monotherapy or in combination with other antidiabetic medications such as metformin, sulfonylureas, thiazolidinediones, or insulin(Kalra et al., 2018).

Monotherapy for the treatment of T2DM

When treating type 2 diabetes mellitus (T2DM) with a single medication (monotherapy), the goal is to reduce glycosylated hemoglobin (HbA1c) levels by approximately 0.5% to 1.5%. Once HbA1c levels have reached the recommended target of less than 7%, it becomes important to focus on controlling postprandial (after-meal) glucose levels in order to further improve HbA1c.

Metformin is the preferred first-line medication for the initial treatment of T2DM. However, in cases where metformin is contraindicated for certain patients or if patients

experience complications while using metformin, alternative hypoglycemic agents are chosen as the primary treatment option for the condition.

In summary, monotherapy for T2DM aims to reduce HbA1c levels by 0.5% to 1.5%. Once HbA1c levels are below 7%, controlling postprandial glucose levels becomes more important. Metformin is the first-line drug of choice, but other hypoglycemic agents are used when metformin is contraindicated or associated complications arise(Rhee et al., 2017).

Combination therapy for treatment of T2DM

When monotherapy fails to adequately control glycemic parameters in patients with type 2 diabetes mellitus (T2DM), combination therapy is recommended to achieve better glycemic control and delay the deterioration of beta-cells. Combination therapy can involve the use of two or more drugs, and in some cases, oral hypoglycemic agents can be combined with insulin therapy(Cahn & Cefalu, 2016).

When considering initial combination therapy for a T2DM patient, several factors need to be taken into account. These include assessing whether the combination therapy will effectively reduce the clinical intensification of diabetes, as maintaining glycemic control becomes more challenging with diet and exercise alone. Additionally, the combination of different medications may improve the function of beta-cells and the underlying pathophysiology of diabetes. Patient compliance is crucial, considering factors such as the patient's acceptance of the therapy, dosing frequency, and safety. The cost of the combination therapy should also be considered in terms of affordability for the patient. Evaluating the risk-to-benefit ratio is important to ensure that the potential benefits outweigh the risks associated with the combined medications. Furthermore, assessing primary and secondary endpoints can help determine if combination therapy is able to address issues associated with single therapy or the addition of insulin, such as weight gain and hypoglycemia.

In summary, combination therapy, either dual or triple drug therapy, is recommended when monotherapy fails to control glycemic parameters in T2DM. Factors such as effectiveness, improvement of beta-cell function, patient compliance, cost, risk-to-benefit ratio, and achievement of treatment goals should be considered when selecting the appropriate combination therapy.

Novel drug delivery system for antidiabetic drugs for T2DM

Conventional drug delivery systems have limitations such as ineffective dosage, decreased potency due to drug metabolism, and lack of target specificity. However, Novel Drug Delivery Systems (NDDSs) have emerged as a promising field in recent years due to their advantages, including reduced dosing frequency, enhanced bioavailability, protection from degradation in the acidic gastric environment, and targeted therapeutic efficacy with fewer side effects(DiSanto et al., 2015).

NDDSs for the treatment of type 2 diabetes mellitus (T2DM) can be classified into several categories. Particulate systems, including microparticulate and nanoparticulate systems, are miniaturized structures that can transport drugs intracellularly and can be coupled with ligands to target specific receptors. Microparticles allow targeted drug release at specific sites and maintain drug concentration in the plasma by controlling the release rate. They have a larger surface-to-volume ratio, which aids in the dissolution of insoluble drugs. Microparticles are transported through transcellular transport via carrier or receptor-mediated endocytosis. On the other hand, nanoparticles, such as polymeric, metallic, lipid-based, and biological nanoparticles, have higher intracellular uptake compared to microparticles. They can be taken up by cells through transcellular and paracellular pathways. Nanoparticles also exhibit increased mucoadhesion, as they are retained in the gastrointestinal tract through interactions with the mucus and endothelial layers(Jeevanandam et al., 2018).

Vesicular systems, such as liposomes and niosomes, have the potential for effective drug delivery due to their proximity to the cell membrane's lipid bilayer-like structure. These systems provide controlled release patterns, improve stability, and maintain therapeutic drug concentrations in the biological system. Liposomes can be unilamellar or multilamellar vesicular systems, and various formulation strategies are being developed to prolong drug delivery, improve drug loading efficiency, and achieve triggered release at the desired site of action. Niosomes, which are self-assembled lamellar structures containing non-ionic surfactants, enhance the oral bioavailability of poorly water-soluble drugs, reduce dosing frequency, and mitigate dose-dependent toxicity(Kesharwani et al., 2018).

The self-nano-emulsifying drug delivery system (SNEDDS) is an anhydrous liquid mixture that encapsulates insoluble drugs in a dissolved form with particle sizes of 200 nm or less. It improves drug solubility, enhances absorption rates, and provides better enzymatic and chemical stability. SNEDDS also enhances the oral bioavailability of poorly water-soluble drugs(Nasr et al., 2016).

Transdermal drug delivery systems (TDS) provide an alternative mode of drug administration that is non-invasive, self-administrable, and patient-compliant. TDS can overcome the problem of first-pass metabolism and can be an option for delivering hydrophilic drugs, macromolecules, and vaccines using permeation enhancers.

In summary, NDDSs offer advantages over conventional drug delivery systems for the treatment of T2DM. Particulate systems, vesicular systems, SNEDDS, and transdermal delivery systems are among the NDDSs being explored for their potential in improving drug efficacy, bioavailability, and targeting, while minimizing side effects.

Conclusion

The increasing prevalence of a sedentary lifestyle and obesity has led to a higher number of diabetes patients, creating a significant demand for anti-diabetic medications. This has driven companies to invest more in research and development to develop targeted formulations. Nanotechnology holds the promise of bringing revolutionary advancements in the field of therapeutics. Extensive research on nanoformulations has made significant progress in nanoparticulate drug delivery systems for anti-diabetic drugs.

However, it is important to address long-term safety concerns and ethical issues associated with nanoformulations. Adhering to the latest FDA guidelines for regulating such products is essential to ensure their safety and enhance efficacy. Active targeting strategies, such as functionalizing suitable ligands or employing combination drug therapy with multiple anti-diabetic drugs, have the potential to regulate glucose levels for extended periods. These ongoing technological advancements in nanotechnology offer promising prospects for the development of efficient therapeutic approaches to lower glucose levels in the future.

References:

Adeghate, E., & Kalász, H. (2011). Amylin Analogues in the Treatment of Diabetes Mellitus: Medicinal Chemistry and Structural Basis of its Function. The Open Medicinal Chemistry Journal, 5(Suppl 2), 78–81. https://doi.org/10.2174/1874104501105010078

Asif, M. (2014). The prevention and control the type-2 diabetes by changing lifestyle and dietary pattern. Journal of Education and Health Promotion, 3(1), 1. https://doi.org/10.4103/2277-9531.127541

Cahn, A., & Cefalu, W. T. (2016). Clinical Considerations for Use of Initial Combination Therapy in Type 2 Diabetes. Diabetes Care, 39(Supplement_2), S137–S145. https://doi.org/10.2337/dcS15-3007

Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., Marco, A., Shekhawat, N. S., Montales, M. T., Kuriakose, K., Sasapu, A., Beebe, A., Patil, N., Musham,

C. K., Lohani, G. P., & Mirza, W. (2017). Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Frontiers in Endocrinology, 8. https://doi.org/10.3389/fendo.2017.00006

DeFronzo, R. A. (2009). From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes, 58(4), 773–795. https://doi.org/10.2337/db09-9028

Derosa, G., & Maffioli, P. (2012). Mini-Special Issue paper Management of diabetic patients with hypoglycemic agents α-Glucosidase inhibitors and their use in clinical practice. Archives of Medical Science, 5, 899–906. https://doi.org/10.5114/aoms.2012.31621

DiSanto, R. M., Subramanian, V., & Gu, Z. (2015). Recent advances in nanotechnology for diabetes treatment. WIREs Nanomedicine and Nanobiotechnology, 7(4), 548–564. https://doi.org/10.1002/wnan.1329

Gallwitz, B. (2019). Clinical Use of DPP-4 Inhibitors. Frontiers in Endocrinology, 10, 389. https://doi.org/10.3389/fendo.2019.00389

Greenfield, J. R., & Chisholm, D. J. (2004). Experimental and clinical pharmacology: Thiazolidinediones - mechanisms of action. Australian Prescriber, 27(3), 67–70. https://doi.org/10.18773/austprescr.2004.059

Hemmingsen, B., Sonne, D. P., Metzendorf, M.-I., & Richter, B. (2016). Insulin secretagogues for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus. Cochrane Database of Systematic Reviews, 2016(10). https://doi.org/10.1002/14651858.CD012151.pub2

Hieronymus, L., & Griffin, S. (2015). Role of Amylin in Type 1 and Type 2 Diabetes. The Diabetes Educator, 41(1_suppl), 47S-56S. https://doi.org/10.1177/0145721715607642

Hinnen, D. (2017). Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. Diabetes Spectrum, 30(3), 202–210. https://doi.org/10.2337/ds16-0026

Holst, J. J. (2019). From the Incretin Concept and the Discovery of GLP-1 to Today's Diabetes Therapy. Frontiers in Endocrinology, 10, 260. https://doi.org/10.3389/fendo.2019.00260

Jeevanandam, J., Barhoum, A., Chan, Y. S., Dufresne, A., & Danquah, M. K. (2018). Review on nanoparticles and nanostructured materials: History, sources, toxicity and regulations. Beilstein Journal of Nanotechnology, 9, 1050–1074. https://doi.org/10.3762/bjnano.9.98

Kalra, S., Kesavadev, J., Chadha, M., & Kumar, Gv. (2018). Sodium-glucose cotransporter-2 inhibitors in combination with other glucose-lowering agents for the treatment of type 2 diabetes mellitus. Indian Journal of Endocrinology and Metabolism, 22(6), 827. https://doi.org/10.4103/ijem.IJEM_162_17

Kesharwani, P., Gorain, B., Low, S. Y., Tan, S. A., Ling, E. C. S., Lim, Y. K., Chin, C. M., Lee, P. Y., Lee, C. M., Ooi, C. H., Choudhury, H., & Pandey, M. (2018). Nanotechnology based approaches for anti-diabetic drugs delivery. Diabetes Research and Clinical Practice, 136, 52–77. https://doi.org/10.1016/j.diabres.2017.11.018

Khursheed, R., Singh, S. K., Wadhwa, S., Kapoor, B., Gulati, M., Kumar, R., Ramanunny, A. K., Awasthi, A., & Dua, K. (2019). Treatment strategies against diabetes: Success so far and challenges ahead. European Journal of Pharmacology, 862, 172625. https://doi.org/10.1016/j.ejphar.2019.172625

Kobori, T., Harada, S., Nakamoto, K., & Tokuyama, S. (2013). Functional Alterations of Intestinal P-Glycoprotein under Diabetic Conditions. Biological and Pharmaceutical Bulletin, 36(9), 1381–1390. https://doi.org/10.1248/bpb.b13-00369

Lebovitz, H. E. (2019). Thiazolidinediones: The Forgotten Diabetes Medications. Current Diabetes Reports, 19(12), 151. https://doi.org/10.1007/s11892-019-1270-y

Mayorov, A. Y. (2011). Insulin resistance in pathogenesis of type 2 diabetes mellitus. Diabetes Mellitus, 14(1), 35–45. https://doi.org/10.14341/2072-0351-6248

McIntyre, H. D., Catalano, P., Zhang, C., Desoye, G., Mathiesen, E. R., & Damm, P. (2019). Gestational diabetes mellitus. Nature Reviews Disease Primers, 5(1), 47. https://doi.org/10.1038/s41572-019-0098-8

Mirghani Dirar, A., & Doupis, J. (2017). Gestational diabetes from A to Z. World Journal of Diabetes, 8(12), 489–511. https://doi.org/10.4239/wjd.v8.i12.489

Narita, T., Yokoyama, H., Yamashita, R., Sato, T., Hosoba, M., Morii, T., Fujita, H., Tsukiyama, K., & Yamada, Y. (2012). Comparisons of the effects of 12-week administration of miglitol and voglibose on the responses of plasma incretins after a mixed meal in Japanese type 2 diabetic patients. Diabetes, Obesity and Metabolism, 14(3), 283–287. https://doi.org/10.1111/j.1463-1326.2011.01526.x

Nasr, A., Gardouh, A., & Ghorab, M. (2016). Novel Solid Self-Nanoemulsifying Drug Delivery System (S-SNEDDS) for Oral Delivery of Olmesartan Medoxomil: Design, Formulation, Pharmacokinetic and Bioavailability Evaluation. Pharmaceutics, 8(3), 20. https://doi.org/10.3390/pharmaceutics8030020

Ojha, A., Ojha, U., Mohammed, R., Chandrashekar, A., & Ojha, H. (2019). Current perspective on the role of insulin and glucagon in the pathogenesis and treatment of type 2 diabetes mellitus. Clinical Pharmacology: Advances and Applications, Volume 11, 57–65. https://doi.org/10.2147/CPAA.S202614

Okur, M. E., Karantas, I. D., & Siafaka, P. I. (2017). Diabetes Mellitus: A Review on Pathophysiology, Current Status of Oral Pathophysiology, Current Status of Oral Medications and Future Perspectives. ACTA Pharmaceutica Sciencia, 55(1), 61. https://doi.org/10.23893/1307-2080.APS.0555

Oral and Injectable (Non-Insulin) Pharmacological Agents for the Treatment of Type 2 Diabetes—Endotext—NCBI Bookshelf. (n.d.). Retrieved April 20, 2022, from ttps://www.ncbi.nlm.nih.gov/books/NBK279141/

Quillen, D. M., Samraj, G., & Kuritzky, L. (1999). Improving Management of Type 2 Diabetes Mellitus: 2. Biguanides. Hospital Practice, 34(11), 41–44. https://doi.org/10.1080/21548331.1999.11443925

Rhee, S. Y., Kim, H. J., Ko, S.-H., Hur, K.-Y., Kim, N.-H., Moon, M. K., Park, S.-O., Lee, B.-W., Choi, K. M., Kim, J. H., & Committee of Clinical Practice Guideline of Korean Diabetes Association. (2017). Monotherapy in Patients with Type 2 Diabetes Mellitus. Diabetes & Metabolism Journal, 41(5), 349. https://doi.org/10.4093/dmj.2017.41.5.349

Sanchez-Rangel, E., & Inzucchi, S. E. (2017). Metformin: Clinical use in type 2 diabetes. Diabetologia, 60(9), 1586–1593. https://doi.org/10.1007/s00125-017-4336-x

Scheen, A. J. (2015). Pharmacodynamics, Efficacy and Safety of Sodium–Glucose Co-Transporter Type 2 (SGLT2) Inhibitors for the Treatment of Type 2 Diabetes Mellitus. Drugs, 75(1), 33–59. https://doi.org/10.1007/s40265-014-0337-y

Schmitz, O., Brock, B., & Rungby, J. (2004). Amylin Agonists: A Novel Approach in the Treatment of Diabetes. Diabetes, 53(suppl_3), S233–S238. https://doi.org/10.2337/diabetes.53.suppl_3.S233

Seino, S., Sugawara, K., Yokoi, N., & Takahashi, H. (2017). β-Cell signalling and insulin secretagogues: A path for improved diabetes therapy. Diabetes, Obesity and Metabolism, 19(S1), 22–29. https://doi.org/10.1111/dom.12995

Souto, E. B., Souto, S. B., Campos, J. R., Severino, P., Pashirova, T. N., Zakharova, L. Y., Silva, A. M., Durazzo, A., Lucarini, M., Izzo, A. A., & Santini, A. (2019). Nanoparticle Delivery Systems in the Treatment of Diabetes Complications. Molecules, 24(23), 4209. https://doi.org/10.3390/molecules24234209

Streisand, R., & Monaghan, M. (2014). Young Children with Type 1 Diabetes: Challenges, Research, and Future Directions. Current Diabetes Reports, 14(9), 520. https://doi.org/10.1007/s11892-014-0520-2

Stringer, D. M., Zahradka, P., & Taylor, C. G. (2015). Glucose transporters: Cellular links to hyperglycemia in insulin resistance and diabetes. Nutrition Reviews, 73(3), 140–154. https://doi.org/10.1093/nutrit/nuu012

Sun, X., Yu, W., & Hu, C. (2014). Genetics of Type 2 Diabetes: Insights into the Pathogenesis and Its Clinical Application. BioMed Research International, 2014, 1–15. https://doi.org/10.1155/2014/926713

Tan, S. Y., Mei Wong, J. L., Sim, Y. J., Wong, S. S., Mohamed Elhassan, S. A., Tan, S. H., Ling Lim, G. P., Rong Tay, N. W., Annan, N. C., Bhattamisra, S. K., & Candasamy, M. (2019). Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 13(1), 364–372. https://doi.org/10.1016/j.dsx.2018.10.008

Uppal, S., Italiya, K. S., Chitkara, D., & Mittal, A. (2018). Nanoparticulate-based drug delivery systems for small molecule anti-diabetic drugs: An emerging paradigm for effective therapy. Acta Biomaterialia, 81, 20–42. https://doi.org/10.1016/j.actbio.2018.09.049

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global Prevalence of Diabetes. Diabetes Care, 27(5), 1047–1053. https://doi.org/10.2337/diacare.27.5.1047

Wong, C. Y., Al-Salami, H., & Dass, C. R. (2017). Potential of insulin nanoparticle formulations for oral delivery and diabetes treatment. Journal of Controlled Release, 264, 247–275. https://doi.org/10.1016/j.jconrel.2017.09.003